Protocol B1971017

A PHASE 2, RANDOMIZED, CONTROLLED, OBSERVER-BLINDED STUDY TO DESCRIBE THE IMMUNOGENICITY, SAFETY, AND TOLERABILITY OF *NEISSERIA MENINGITIDIS* SEROGROUP B BIVALENT RECOMBINANT LIPOPROTEIN 2086 VACCINE (BIVALENT rLP2086) IN HEALTHY SUBJECTS AGED ≥24 MONTHS TO <10 YEARS

Statistical Analysis Plan (SAP)

Version: 2.0 (Final)

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ABBREVIATIONS

AE	adverse event
CI	confidence interval
CRF	case report form
e-diary	electronic diary
EDMC	external data monitoring committee
GMT	geometric mean titer
HAV	hepatitis A virus
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
ISC	independent statistical center
LLOQ	lower limit of quantitation
LP2086	lipoprotein 2086
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measurement
MnB	Neisseria meningitidis serogroup B
PRP-OMP	polyribosylribitol phosphate oligosaccharide of Haemophilus influenzae type b conjugated to outer membrane protein
rLP2086	recombinant lipoprotein 2086
SAE	serious adverse event
SAP	statistical analysis plan

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	July 16, 2014	PPD	Initial Version
Version 2.0	June 16, 2016	PPD	• Modified evaluable population to be consistent with other bivalent rLP2086 protocols. • Removed references to 'Group 1' specific immunogenicity analyses • CCI [redacted] • Clarified the extent of sub group analyses for key endpoints • Provided details of when p-values and other between-group comparison statistics will be provided for safety endpoints. • Removed multiple imputation analyses • Removed ZINB model for incidence rates. • Added section about research-related injuries following Visit 7.

2. INTRODUCTION

The purpose of this document is to provide further details about the statistical analysis methods specified in the study protocol B1971017. A brief description of the study design and the study objectives are given. Subsequent sections include analysis populations, and the definitions of immunological and safety endpoints, followed by details of statistical methods. The windowing specifications, list of tables/figures/listings, mock-up tables, listings, figures, and programming rules are prepared separately based on the methods described in this document. Any major deviations from the methods specified in this document and the protocol will be discussed in the clinical study report.

2.1. Study Design

This is a Phase 2, randomized, controlled, observer-blinded, multicenter study in which approximately 400 healthy subjects will be randomized in a 3:1 ratio to receive either bivalent rLP2086 at Months 0, 2, and 6, or HAV vaccine at Months 0 and 6 and saline at Month 2. Subjects will be stratified equally into 2 age groups: ≥24 months to <4 years or ≥4 years to <10 years.

Table 1. Study Design

	Vaccination (Vax) 1	Post–Vax 1 Follow-up	Vax 2	Post–Vax 2 Blood Draw	Vax 3	Post–Vax 3 Blood Draw	Month 12 Follow-up and Blood Draw
Visit number	1	2	3	4	5	6	7
Approx - month	0	1	2	3	6	7	12
Group 1 (300)	Bivalent rLP2086		Bivalent rLP2086		Bivalent rLP2086		

Table 1. Study Design

	Vaccination (Vax) 1	Post–Vax 1 Follow-up	Vax 2	Post–Vax 2 Blood Draw	Vax 3	Post–Vax 3 Blood Draw	Month 12 Follow-up and Blood Draw
Group 2 (100)	HAV vaccine		Saline		HAV vaccine		
Blood draw	5-10 mL			5-10 mL		5-10 mL	5-10 mL

Abbreviations: HAV = hepatitis A virus; Vax = vaccination.

2.1.1. Sample Size and Power

The study sample size is not based on hypothesis-testing criteria. This study will enroll approximately 400 subjects with a randomization ratio of 3:1 (bivalent rLP2086 group : control).

2.1.2. Assessments

Subjects will receive investigational products at Visit 1, 3, and 5. All of the subjects will have a blood draw for immunogenicity assessment at Visits 1, 4, 6 and 7, which is at baseline, 1 month post-vaccination 2, 1 month post-vaccination 3 and 6 months post-vaccination 3 respectively.

Reactogenicity data, including local reactions, systemic events (including fever), and use of antipyretics will be collected via an electronic diary (e-diary) completed for each subject for 7 days following each vaccination.

Adverse events (AE) will be collected from the signing of the informed consent document (ICD) to Visit 6 (1 month post-vaccination 3 blood draw). Serious Adverse Events (SAE), medically attended (non-serious) adverse events, and newly diagnosed chronic medical conditions will be collected throughout the study. In addition, AE within 30 minutes after investigational product administration will be documented.

2.1.3. Number of Immunogenicity Assays

Sera from subjects will be tested in serum bactericidal assay using human complement (hSBAs) with the 4 primary MnB test strains. *Two (2) of the primary strains (*CCI [redacted] *[A22] and* CCI [redacted] *[B24]) will be tested at each blood sampling time point for half of the subjects (in both groups), and the other 2 primary strains (*CCI [redacted] *[A56] and* CCI [redacted] *[B44]) will be tested at each blood sampling time point for the remaining half of the subjects*. This would yield a total number of approximately 3,200 hSBA results from the 4 primary strains.

Table 2. Number of Immunogenicity Assays

Visit	Baseline (Visit 1)	1 Month Postvaccination 2 (Visit 4)	1 Month Postvaccination 3 (Visit 6)	6 Months Postvaccination 3 (Visit 7)
Assay	hSBA	hSBA	hSBA	hSBA
hSBA for A22/B24 among 50% subjects	200*2	200*2	200*2	200*2
hSBA for A56/B44 among the other 50% subjects	200*2	200*2	200*2	200*2
Total	800	800	800	800

Volume of serum permitting, additional assays will be run on samples to test the 2 alternate primary strains not originally tested. If all 4 primary strains are tested on all subjects, the total number of hSBA results would be approximately 6,400.

2.2. Study Objectives

2.2.1. Primary 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 <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.*

The primary immunogenicity objectives and analyses will be descriptive; no formal statistical tests will be used.

2.2.2. 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 both age strata combined).*

- *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, ≥4 years to <10 years at study entry, and in both age strata combined.

The secondary immunogenicity objectives and analyses will be descriptive; no formal statistical tests will be used.

2.2.3. Exploratory Objective

- CCI [redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

3.1. Final Analysis

No interim analysis is planned for this study.

This study will use an external data monitoring committee (EDMC). The EDMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The Independent Statistical Center (ISC) will provide the safety reports to the EDMC. Unblinded safety data will be reviewed by the EDMC throughout the study and no type I error will be adjusted for the multiple looks at the safety *data.*

3.2. Unblinding

The study database will be unblinded after all of the data are cleaned. The analyses will then be performed to include all of the data summaries.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There are no formal statistical hypotheses in this study.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Full Analysis Set

The intent-to-treat (ITT) population includes all subjects who are randomized. All randomized subjects who have at least 1 valid and determinate assay result related to a proposed analysis will be included in the modified intent-to-treat (mITT) population. This analysis set is for the immunogenicity analysis. Subjects will be analyzed according to the investigational product to which they were randomized.

5.2. 'Per Protocol' Analysis Set

The evaluable population will be the primary population for the immunogenicity analyses. To be included in the evaluable population for the primary immunogenicity endpoint, subjects will have to meet all the following criteria:

1. Randomized into the study,

2. Were eligible, ie, satisfied all inclusion/exclusion criteria, through 1 month post vaccination 3,

3. Received all the scheduled investigational products at study visits 1, 3 and 5 as randomized,

4. Have baseline blood drawn prior to the first dose of vaccine and have post-vaccination 3 blood draw (Visit 6) within 28-42 days after vaccination 3 (Visit 5). (The interval day will be calculated as blood draw date – vaccination date),

5. Had a valid and determinate assay results for the proposed analysis, and

6. Had no important protocol deviations.

An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, subject receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's global medical monitor will identify those subjects with an important protocol deviation before any immunogenicity analysis is carried out.

Subjects will be analyzed according to the investigational product to which they were randomized.

5.3. Safety Analysis Set

All subjects who received at least 1 dose of the investigational product (rLP2086, HAV vaccine or saline) and with safety data available will be included in the safety population. The safety population will be used for all of the safety analyses. The following separate safety populations will be defined: vaccination 1, vaccination 2, vaccination 3, and follow-up.

1. Vaccination 1 Safety Population: This population will include all subjects who received the first dose of the investigational products (rLP2086 or HAV vaccine) at visit 1.

2. Vaccination 2 Safety Population: This population will include all subjects who received the investigational product (rLP2086 or saline) at visit 3.

3. Vaccination 3 Safety Population: This population will include all subjects who received the investigational product (rLP2086 or HAV vaccine) at visit 5.

4. Follow-up Safety Population: This population will include all subjects who received at least 1 dose of investigational product (rLP2086, HAV vaccine or Saline) and for whom safety information is available from after visit 6 to visit 7, or from the time of subject withdrawal to visit 7.

In the safety analysis set, subjects will be analyzed according to the investigational product received.

5.4. Treatment Misallocations

If a subject was:

- Randomized but not treated, then they will be reported under their randomized treatment group for immunogenicity analyses, where assay results are available. However, they are by definition excluded from the evaluable immunogenicity and safety analyses as actual treatment is missing.

- Treated but not randomized, then by definition they will be excluded from the immunogenicity analyses since randomized treatment is missing, but will be reported under the treatment they actually received for all safety analyses.

- Randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all immunogenicity analyses where assay results are available, but will reported under the treatment they actually received for all safety analyses.

5.5. Protocol Deviations

The following describes any protocol deviations that relate to the statistical analyses or populations:

5.5.1. Deviations Assessed Prior to Randomization

Any subjects who do not meet the inclusion / exclusion criteria will not be included in the evaluable immunogenicity population.

5.5.2. Deviations Assessed Post-Randomization

The full list of protocol deviations for the study report will be compiled prior to database closure. The subjects with **important** protocol deviations (iPD) will be excluded from the evaluable immunogenicity population as described in Section 5.2.

6. ENDPOINTS AND COVARIATES

6.1. Immunogenicity Endpoint(s)

6.1.1. Primary Immunogenicity Endpoint

- *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 LLOQ for CCI (A22) is 1:16. The LLOQ for the other 3 primary test strains is 1:8.

6.1.2. Secondary Immunogenicity Endpoints

In healthy subjects aged ≥24 months to <10 years at study entry:

- *Proportion of subjects 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 vaccine.*

In healthy subjects aged ≥24 months to <4 years at study entry, ≥4 years to <10 years at study entry, and in both age strata combined:

- *Proportion of subjects with hSBA titer ≥ lower limit of quantitation (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 vaccine.*

- *Proportions of subjects achieving hSBA titers 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 vaccine.*

- *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 vaccine.*

6.1.3. Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

6.2. Safety Endpoints

6.2.1. Primary Safety Endpoints

In healthy subjects aged ≥24 months to <4 years and in healthy subjects aged ≥4 years to <10 years at study entry and in both age strata combined:

- *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, diarrhea, 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 following time periods:*
  - *30 Days after each vaccination.*
  - *30 Days after any vaccination.*
  - *During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).*

- *During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).*
- *Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).*

- *Percentage of subjects with at least 1 medically attended AE occurring during the following time periods:*
  - *30 Days after each vaccination.*
  - *30 Days after any vaccination.*
  - *During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).*
  - *During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).*
  - *Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).*
- *Percentage of subjects with at least 1 newly diagnosed chronic medical condition occurring during the following time periods:*
  - *30 Days after each vaccination.*
  - *30 Days after any vaccination.*
  - *During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).*
  - *During the follow-up phase (from 1 month after the last study vaccination [Visit 6] through 6 months after the third study vaccination [Visit 7]).*
  - *Throughout the study period (from the first study vaccination [Visit 1] through 6 months after the third study vaccination [Visit 7]).*
- *Percentage of subjects with at least 1 AE occurring during the following time periods:*
  - *30 Days after each vaccination.*
  - *30 Days after any vaccination.*
  - *During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the last study vaccination [Visit 6]).*

- *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 though Visit 6).*

6.2.2. E-Diary Safety Data

The reactogenicity data are prompted adverse events (AEs) collected from an e-diary. The prompted events are: local reactions (redness, swelling, and pain at injection site); systemic events (vomiting, diarrhea, headache, fatigue, muscle pain other than muscle pain at any injection site, and joint pain); temperature; and use of antipyretic medication.

The e-Diary will record reactogenicity data from day 1 to day 7 for each vaccination. The analysis interval for reactogenicity data after each vaccination will be 'any day 1-7' which will include data from day 1 to day 7. The day of vaccination is considered as day 1.

6.2.2.1. Local Reaction Endpoints

The local reactions prompted by the e-diary will be: pain, redness, and swelling.

6.2.2.1.1. Local Reaction Presence

For each local reaction, the derivation of whether or not the specific reaction occurred on 'any day 1-7' will be made. The variable will be calculated for each vaccination as well as for any vaccination. The derivation of this variable is given in the table below.

Table 3. Derived Variables for Local Reactions

Variable	Yes (1)[a]	No (0)	Missing (.)
Any day 1-7	Subject reports the reaction as 'mild' 'moderate' or 'severe' on any day 1-7	Subject reports the reaction as 'none' on all 7 days or as a combination of 'none' and missing on all 7 days.	Subject reports the reaction as missing on all 7 days.

a. For redness and swelling, 'mild', moderate', and 'severe' categories are based on the caliper measurement reported from eDiary.

6.2.2.1.2. Maximum Severity for Local Reaction

A caliper is used to measure the diameter of any redness or swelling. Caliper units are converted to centimeters according to 1 caliper unit = 0.5 centimeters. See tables below for the grading of local reactions.

Table 4. Grading of Redness and Swelling

Grades	Measurement
Mild	0.5 to 2.0 cm (1 to 4 caliper units)
Moderate	2.5 to 7.0 cm (5 to 14 caliper units)
Severe	>7.0 cm (>14 caliper units)

Table 5. Grading of Pain

Grades	
Mild	Does not interfere with activity
Moderate	Interferes with activity
Severe	Prevents daily activity

The maximum severity (highest grading) of each local reaction within 7 days of vaccination will be derived for each vaccination as well as any vaccinations. The maximum severity will be derived as follows:

= missing, if values are missing for all days 1-7;

= 0, if the subject reports all reactions as 'None' for all days 1-7

= highest grade (maximum severity) within 7 days of vaccination, if the answer is not 'None' for at least 1 day;

6.2.2.1.3. Duration of Each Local Reaction

For subjects experiencing any local reactions (or those with derived reaction presence in Table 3), the maximum duration (last day of reaction –first day of reaction +1) will be derived for each vaccination. Resolution of the event is the last day in which the event is recorded in the e-diary or the date the event ends if it is unresolved during the subject diary-recording period, unless chronicity is established.

6.2.2.1.4. Onset Day of Each Local Reaction

For subjects experiencing any local reaction, the onset day will be the first day that the reaction is present via the e-Diary, relative to the vaccination. The day of vaccination is considered as Day 1.

In summary, the following variables will be derived for local reactions:

1. Each local reaction on each day (up to day 7) after each vaccination.
2. Each local reaction on 'any day 1-7' after each vaccination and any vaccination.
3. Maximum severity of each local reaction on 'any day 1-7' after each vaccination and any vaccination.
4. Maximum duration of each local reaction after each vaccination.
5. Onset day of each local reaction relative to each vaccination.
6. Any local reaction on 'any day 1-7' after each vaccination and after any vaccination.

6.2.2.2. Systemic Events Endpoints

The systemic events reported via e-diary will be: vomiting, diarrhea, headache, fatigue, muscle pain other than muscle pain at any injection site, and joint pain. See the table below for the severity scales of each systemic event.

Table 6. Grading of Other Systemic Events

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires IV hydration
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 stools in 24 hours	6 or more loose stools in 24 hours
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Fatigue	Does not interfere with activity	Some interference With activity	Prevents daily routine activity
Muscle pain (other than muscle pain at the injection site)	Does not interfere with activity	Some interference With activity	Prevents daily routine activity
Joint pain	Does not interfere with activity	Some interference With activity	Prevents daily routine activity

Abbreviation: IV =intravenous

For systemic events, the following variables will be available similar to local reaction

1. Each systemic event on each day (up to day 7) after each vaccination
2. Each systemic event on 'any day 1-7' after each vaccination and any vaccination
3. Maximum severity of each systemic event on 'any day 1-7' after each vaccination and any vaccination
4. Maximum duration of each systemic event after each vaccination
5. Onset day of each systemic event relative to each vaccination
6. Any systemic event (including fever) on 'any day 1-7' after each vaccination and after any vaccination

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 6.2.2.1).

6.2.2.3. Temperature

Oral temperature will be collected in the e-Diary for 7 days (day 1 to day 7) after each vaccination. The highest temperature for each day will be recorded in the e-Diary. The

protocol defines fever as an oral temperature ≥38.0°C. Fever will be scaled as 38.0°C to ≤38.4°C, 38.5°C to ≤38.9°C, 39.0°C to ≤39.4°C, 39.5°C to ≤40°C, and >40°C for a given day per Protocol.

Similar to the derivations of systemic events and local reactions, fever will be derived for:

1. Fever on each day (up to day 7) after each vaccination.
2. Fever on 'any day 1-7' after each vaccination and any vaccination.
3. Highest Fever (maximum severity) on 'any day 1-7' after each vaccination and any vaccination.
4. Maximum duration of fever after each vaccination.
5. Onset day of fever relative to each vaccination.

Temperatures <35.0°C and >42.0°C will be excluded from the analysis.

Summary tables presenting temperature results will include the proportion of subjects utilizing each route of temperature measurement as a footnote.

6.2.2.4. Use of Antipyretic Medication

The use of antipyretic medication will be recorded in the e-Diary for 7 days (day 1 to day 7) after each vaccination.

The following variables will be derived:

1. Use of antipyretic medication on each day (up to day 7) after each vaccination.
2. Type of antipyretic medication on each day (up to day 7) after each vaccination.
3. Use of antipyretic medication on 'any day 1-7' after each vaccination and any vaccination.
4. Type of antipyretic medication on 'any day 1-7' after each vaccination and any vaccination.
5. Maximum duration of use of antipyretic medication after each vaccination.
6. Onset day of antipyretic use relative to each vaccination.

6.2.2.5. Correlation Between Fever and Use of Antipyretic Medication

A separate aggregated endpoint by combining the use of antipyretics and fever presence will be derived. This aggregate variable will include the following:

1. Antipyretic use with fever presence.

2. Antipyretic use without fever presence.

3. Fever presence without antipyretic use.

4. No fever and no use of antipyretics.

The variable will be derived for on 'any day 1-7' after each vaccination and any vaccination.

6.2.2.6. Severity Increase and Potentiation for Reactogenicity Across Doses

This derivation will be applied to each local reaction and each systemic event (including fever).

These endpoints will be derived as following:

Table 7. Derived Variables for Increasing Severity and Potentiation

Variable	Yes (1)	No (0)	Missing
Increasing Severity (days 1-7)	If the maximum severity is more severe in any following dose(s) compared with the previous dose(s)	If the maximum severity for the later dose(s) is at most the same severity as the previous dose(s)	If all data for the reaction is missing for all days 1-7 after dose 1, dose 2 and dose 3 or only 1 dose was received.
Potentiation (days 1-7)	If the maximum severity is more severe following dose 2 than dose 1, AND more severe following dose 3 than dose 2	If the maximum severity post dose 2 is at most the same severity as post dose 1, OR the maximum severity post dose 3 is at most the same severity as post dose 2	If all data for the reaction is missing for all days 1-7 after any dose, or less than 3 doses were received.

6.2.3. Safety Data Collected Through CRF

The CRF is designed to collect newly diagnosed chronic medical conditions and adverse events on 2 different pages. A medically-attended adverse event is defined as a non-serious adverse event that results in an evaluation at a medical facility. A newly diagnosed chronic medical condition is defined as a disease or condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects.

The relationship between (S)AEs and the investigational products (rLP2086 vaccine, HAV/saline vaccine) will be characterized as related or not related as described in the protocol. The severity of AEs will be characterized as mild, moderate, and severe, as shown in the table below.

Table 8. Grading of AE Severity

Grade	
Mild	Does not interfere with subject's usual function
Moderate	Interferes to some extent with subject's usual function
Severe	Interferes significantly with subject's usual function

Adverse events prior to first vaccination will be excluded from the AE analysis. These will be included in medical history summaries.

Adverse events will be categorized according to MedDRA.

6.2.3.1. Analysis Intervals

There will be up to 7 analysis intervals for safety data collected via CRF.

Table 9. Analysis Interval for AE, SAE, Medically Attended AE and Newly Diagnosed Chronic Medical Conditions

#	Analysis Interval	Analysis Population	Interval Start date (inclusive)	Interval Stop (inclusive)	Safety Data
1	Within 30 days after vaccination 1	Vax 1 Safety	Vax 1 date	Vax 1 date + 30 days	AE, SAE, MAE, NDCMC
2	Within 30 days after vaccination 2	Vax 2 Safety	Vax 2 date	Vax 2 date + 30 days	AE, SAE, MAE, NDCMC
3	Within 30 days after vaccination 3	Vax 3 Safety	Vax 3 date	Vax 3 date + 30 days	AE, SAE, MAE, NDCMC
4	Within 30 days after any vaccination	Safety	Vax 1, Vax 2, or Vax 3 date	Vax 1, Vax 2, or Vax 3 date + 30 days	AE, SAE, MAE, NDCMC
5	During the vaccination phase	Safety	Visit 1 date	Visit 6 date (or end of vaccination day)	AE, SAE, MAE, NDCMC, Days missed school due to AE
6	During the follow-up Phase	Follow-up Safety	Visit 6 date + 1 day, or end of vaccination date + 1 for early withdrawal subjects	Visit 7 date	SAE, MAE, NDCMC,
7	Throughout the study	Safety	Visit 1 date	Visit 7 date	SAE, MAE, NDCMC, Neuroinflammatory and autoimmune conditions

AE=Adverse events, SAE=Serious adverse events, MAE=Medically-attended AE, NDCMC=Newly diagnosed chronic medical conditions

6.2.3.2. Immediate Adverse Events

Any AE that occurred within the first 30 minutes after the investigational product administration will be classified as an immediate AE. Immediate AEs are a subset of AEs.

Any AE occurring on the day of vaccination will have AE onset time captured.

Four (4) analysis intervals will be applied to immediate AEs.

Table 10. Analysis Interval for Immediate AE

#	Analysis Interval	Analysis Population	Interval Start Date (inclusive)	Interval Stop (inclusive)
1	Vaccination 1	Vax 1 Safety	Vaccination 1 time	Vaccination 1 time + 30 minutes
2	Vaccination 2	Vax 2 Safety	Vaccination 2 time	Vaccination 2 time + 30 minutes
3	Vaccination 3	Vax 3 Safety	Vaccination 3 time	Vaccination 3 time + 30 minutes
4	Any vaccination	Safety	Vaccination 1, 2, or 3 time	Vaccination 1, 2, or 3 time + 30 minutes

6.2.3.3. Days of School Missed Due to AE

For each subject, the number of days of school missed because of AEs will be aggregated across the vaccination phase. Then summary statistics using mean (standard deviation), median, and range will be descriptively tabulated for the total days by each group.

The following variables will be derived:

1. Number of subjects reporting days missing school due to AE.

2. Percentage of subjects reporting days missing school due to AE among the safety population.

3. Percentage of subjects reporting days missing school due to AE among the subjects who report at least one AE during the vaccination phase.

4. Total number of days missing school due to AE during the vaccination phase.

Corresponding variables will be derived for absences from school due to related AEs only.

6.3. Other Endpoints

6.3.1. E-Diaries Completion

The following e-Diary compliance variables will be provided for each vaccination:

1. Compliance per day: the numerator is the number of subjects who completed (transmitted) the e-diary on a given day (day 1 to day 7) and the denominator is the total number of subjects who receive the vaccination.

2. At least *n* days: the numerator is the number of subjects who completed (transmitted) the e-diary on any *n* days and the dominator is the total number of subjects who received a vaccination. To be derived for $n = 1$ through 7.

6.3.2. Nonstudy Vaccination

Any *Haemophilus influenzae* type b conjugate vaccine (polyribosylribitol phosphate outer membrane protein: PRP-OMP) received prior to the signing of the ICD will be recorded in the case report form (CRF).

Any nonstudy vaccine given from the signing of the ICD to the blood draw at Visit 6 will be recorded in the CRF.

Nonstudy vaccines will be categorized according to the WHO Drug Dictionary (WHODRA).

6.3.3. Demographic, Medical History, and Baseline Characteristics Variables

The demographic variables are gender, race, ethnicity, and age (in years). Age at time of first vaccination and age at randomization will be derived based on calendar dates, ie, a subject is n years of age from their n^{th} birthday to the day before their $(n+1)^{th}$ birthday.

Medical history will be categorized according to the Medical Dictionary of Regulatory Activities (MedDRA).

Physical exam will be recorded as normal, abnormal, and not done.

6.4. Covariates

The following endpoints will further be summarized by race (White, Black, Asian and Other), by gender (Male, Female), and by country. Additionally, within each age stratum data will also be summarized by race, gender, and 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, AE, SAE, and MAE

Composite responses and 4-fold responses may additionally be summarized by age, race, gender, and country.

7. HANDLING OF MISSING VALUES

7.1. Immunogenicity Data

For the hSBA assay results, the following values will be set to missing: QNS (insufficient sera), indeterminate results, and Not Done. Subjects without a blood draw (eg, dropouts) will also have missing immunogenicity data.

The primary immunogenicity analyses will use only valid and determinate assay results with no imputation of missing values, which uses the assumption that data are missing completely at random (MCAR).[1] The approach to missing assay data depends on serology testing strategy, to be determined:

- If volume permits, subjects will have serum tested for all 4 primary strains by hSBA. In this case, descriptive summaries will explore the relationship between the missingness indicator and design variables or covariates (age, race, gender, site etc.). A sensitivity analysis using a mixed effects model with repeated measurement (MMRM) will be applied to the primary immunogenicity endpoints.

- If only 50% of subjects are tested for 2 of the 4 primary strains, and the other 50% of subjects tested for the other 2 primary strains, there will be no sensitivity analysis. Data will be assumed to be MCAR.

For the calculation of GMTs, hSBA values below LLOQ will be assigned a value of half the LLOQ. The LLOQ for CCI (A22) is 1:16, and for the other 3 primary test strains is 1:8.

7.2. Reactogenicity Endpoints

Subjects are excluded from the analysis of reactogenicity if they did not receive a particular vaccine dose or if the data are missing on all days of the interval.

Reactogenicity data will be collected through e-Diary, which does not allow subjects to skip individual questions. Therefore, for a specific day, as long as the e-Diary data is transferred for that day, all of the reactogenicity data for the subject on that day is considered complete. The e-Diary completion status will be summarized per Section 6.3.1. The e-diary completion summary will provide the missing data information on reactogenicity data.

Based on data from available studies, missing data on reactogenicity is minimal, which is consistent with Li et al. (2011).[2] No sensitivity analysis is planned for reactogenicity data.

7.3. CRF Safety Data

Subjects are excluded from the analysis if they do not receive a particular vaccine dose or if safety data are missing.

The sponsor is making every effort to follow up with subjects for safety data (6 months after the last vaccination). Data from previous studies showed a small proportion (5%) of subjects not being contacted via telephone or did not finish the full series of 3 doses of the vaccinations. The missing data rate on the safety data among each analysis interval will be summarized for each group. The numerator will be the # of subjects with missing CRF safety data information. The denominators vary with the analysis interval.

Table 11. Denominators for Safety Data Analysis Intervals

#	Analysis Interval	Denominator
1	Within 30 days of vaccination 1	# of subjects received vax 1
2	Within 30 days of vaccination 2	# of subjects received vax 2
3	Within 30 days of vaccination 3	# of subjects received vax 3
4	Within 30 days of any vaccination	# of subjects received any vax
5	During the vaccination phase	# of subjects received any vax
6	During the follow-up phase	# of subjects received any vax
7	Throughout the study	# of subjects received any vax

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Unless otherwise explicitly stated, descriptive statistics for continuous variables are: n, mean, median, standard deviation, minimum and maximum. Descriptive statistics for categorical variables are: n, percentage, and total (N).

8.1.1. Analyses for Continuous Data

For each of the 4 primary strains, hSBA titers will be logarithmically transformed for analysis and Geometric mean titers (GMTs) will be computed with 95% confidence intervals (CI) for each group. The 2-sided, 95% CI for the GMTs will be constructed by back transformation of the confidence intervals for the mean of the logarithmically transformed titers computed using the Student t distribution.

8.1.2. Analyses for Binary Data

8.1.2.1. Immunogenicity Data

All of the binary immunogenicity endpoints will be descriptively summarized along with the exact 2-sided 95% confidence interval (or Clopper-Pearson confidence limit) for the proportion.

The exact confidence interval for proportion will be computed using the F distribution. If *r* equals the number of responses and *n* equals the number of subjects, then it follows that $p = r / n$ is the estimate of the proportion of responses. An exact 95% confidence interval can be computed by solving the following 2 equations. For the lower limit p_L, use

$$p_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$ and for the upper limit p_U, use $$p_U = \frac{(r+1)F_U}{(n-r) + (r+1)F_U}$$

where F_L is the quantile from the F distribution for α=0.025, with numerator degrees of freedom equal to 2r and denominator degrees of freedom equal to 2(n-r+1). F_U is the quantile from the F distribution for α=0.975, with numerator degrees of freedom equal to 2(r+1) and denominator degrees of freedom equal to 2(n-r). When r equals 0, F_L should be set equal to 1.0 so p_L equals 0. When r equals n, F_U should be set equal to 1.0 so p_U equals 1. The confidence interval using the F distribution is described in Collett (1991).[3]

8.1.2.2. Safety Data

The proportion of subjects reporting immediate AEs and reporting reactogenicity events and by severity will be summarized and compared between Group 1 and Group 2. The difference in the percentages (Group 1- Group 2) and 2 sided 95% exact CIs for the difference will be provided with p-values. The exact CIs will be computed using the noninferiority procedure of Chan & Zhang,[4] using the standardized test statistic and gamma=0.000001.

Fisher's Exact test will be used to compare the endpoints of AE, SAE, medically attended AE and newly diagnosed medical conditions. The difference in the percentages (Group 1- Group 2) and 2 sided 95% CIs for the difference will be provided. The CIs of the

difference will be computed using the Miettinen-Nurminen[5] method. The confidence intervals and statistical tests presented for the safety data will not be used to test hypotheses but will be used to determine which events may need further clinical investigation. No adjustment for multiplicity is needed.

8.2. Statistical Analyses

8.2.1. Analysis of Primary Endpoints

The primary analysis for the primary objectives will be based on the evaluable immunogenicity population. 95% confidence intervals (CIs) for the percentage of subjects with hSBA titer ≥ LLOQ to each of the 4 primary strains at 1 month postdose 3 will be presented, along with the response rate. To address the two primary objectives, these data will be presented in the 2 age strata, ≥24 months to <4 years and ≥4 years to <10 years.

To support the interpretation of the primary analyses, an identical analysis based on the mITT population will be conducted.

As described in Section 7.1, depending on serology testing strategy, a further supportive analysis of the primary endpoints will be done using the MMRM model, in the evaluable population.

8.2.2. Analysis of Secondary Endpoints

The following analyses will address the secondary CCI immunogenicity objectives.

The primary endpoints (percentage of subjects with hSBA titer ≥ LLOQ to each of the 4 primary strains at 1 month postdose 3) will be analyzed in the 2 age strata combined. 95% confidence intervals (CIs) will be presented along with the response rate. This will be done for the evaluable and the mITT populations.

The proportions of subjects achieving hSBA titers >= LLOQ for each of the 4 primary strains at 1 month after the second vaccination and 6 months after the third vaccination will be analyzed in the 2 age strata separately and combined, in the evaluable and the mITT population. Analysis will be the same for the primary endpoints.

The proportions of subjects achieving hSBA titers 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 will be analyzed in the 2 age strata separately and combined, in the evaluable and the mITT population. Analysis will be the same for the primary endpoints.

The 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 will be analyzed in the 2 age strata separately and combined, in the evaluable and the mITT population. GMTs and 95% CI will be presented.

The empirical reverse cumulative distribution curves (RCDCs) will be presented graphically for each of the 4 primary strains and at each sampling time point, for the evaluable population.

8.2.3. Analysis of Exploratory Endpoints

CCI [redacted]

8.2.4. Additional Analyses of Immunogenicity

8.2.4.1. Assessing Missing hSBA with Other Variables

All of the subjects, for the combined age strata, will be dichotomized to 2 categories – with missing hSBA or non-missing hSBA. If a subject has missing data at any blood sampling visit for any strain, the subject will be categorized as 'Missing (1)'; if the subjects have hSBA data for all blood sampling visit for all strains, the subjects will be categorized as 'Non-missing (0)'. Then the summary statistics will be provided for the following variables by the missing indicator:

Age (mean, std), Race, Gender, Center, Vaccine Group, GMT on each strain for each group at each visit.

Additional summaries may be provided based on each primary strain, where the Missing (1) will be assigned to subject with missing data at any blood sampling visit for that strain and the non-Missing (0) will be assigned to subject with all 3 time points for that strain. The same variables will be summarized for each indicator.

8.2.4.2. Assessing Factors of Age, Race, Center, and Gender on GMT

A mixed-effect model with repeated measurement (MMRM)[6] will be utilized to assess the effect of age, race, center and gender, in which both baseline and the postvaccination titers (in logarithmic scale) are modeled 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 intrasubject correlation among the repeated measures, an unconstrured covariate matrix will be used. In case the model does not converge, further covariance structures will be explored (eg, autoregressive, compound symmetry).

Log (hSBA) = Group + center + race + gender + age at randomization +visit+ Group* visit.

The intercept will be set as a random effect.

Site may be used as centers. However, several sites maybe pooled to one center depending on geographic location (if size <5 within the site). In the case of non-convergence, country may be used as center.

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

This analysis 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.

8.2.5. Analysis of Safety Data

8.2.5.1. Reactogenicity Data

The presence of each local reaction, each systemic event, fever, use of antipyretic medication at each specific day (day 1, day 2, ….day 7) will be summarized with number and proportion of subjects reporting such event, for each vaccination. The presence and maximum severity of each local reaction, systemic events, and fever at 'any day 1-7' will be summarized with number and proportion of subjects reporting such event, by each vaccination as well as 'after any vaccination'. The summaries will include 95% Clopper-Pearson's CI.

Proportion differences (Group 1-Group 2), associated 95% CIs and p-values will only be provided, by each vaccination and after any vaccination for the following endpoints:

- any local reactions (overall and by type of event) and any severe local reactions (only overall)
- any systemic events (overall and by type of event) and severe systemic events (only overall)
- any use of anti-pyretics
- any fever and also any temperature above or equal to 39.0-39.9 and 40 degrees centigrade.

Also, the increasing severity and potentiation of local and systemic reactions across all 3 vaccinations will be summarized with number and proportion of subjects with such characteristics, along with 95% exact CI.

The aggregated variable for antipyretic use and fever will also be summarized with number and percentage, along with 95% exact CI (multinomial data),[a] for each vaccination.

For local reactions and systemic events, including fever and use of antipyretic medication, the maximum duration of the event will be summarized for each vaccination. The number of unknown durations will also be summarized. The onset day for each local reaction and systemic event will also be summarized.

All of these summaries will be summarized according to the vaccine received. The safety population at each corresponding dose will be used for the analyses for each vaccination. The data summaries will be descriptively presented by group.

[a] Goodman's Bonferroni based procedure, with Blyth-Still-Casella intervals as the basis for the Bonferroni procedure (StatXact 9 User Manual)

A listing will be provided for all of the severe reactogenicity data.

8.2.5.1.1. Unscheduled Visits (Unplanned Visits) for Severe Reactions

A listing will be generated for all of the subjects with unscheduled visits (or unplanned visits) for severe reactions.

8.2.5.2. Safety Data Collected Through CRF

8.2.5.2.1. SAE

The percentage of subjects reporting at least one SAE, and the number of episodes will be summarized for each group for each of the first 7 analysis intervals (see Table 9) with 95% Clopper-Pearson CI for the percentages. Proportion differences (Group 1-Group 2), associated 95% CIs and p-values from Fisher's exact test will be provided for analysis intervals 'During the vaccination phase' and 'Throughout the study'.

Similarly, the percentage of subjects reporting at least one related SAE, total # of related SAEs reported by each group. No between-group proportion differences, associated CIs or p-values for comparisons between groups will be generated for related SAEs.

In addition, for the analysis intervals of vaccination phase, follow-up phase, throughout the study, the SAEs will be summarized by each preferred term (MedDRA) with percentage and number of events for each group. Listings of related SAEs will be provided. All of the SAE will be listed with subject ID, event onset, the most recent vaccination, days of event relative to vaccination, duration of the event, and management and outcome.

8.2.5.2.2. Medically Attended AE

The Medically attended AE will be analyzed as per Section 8.2.5.2.1 in addition there will be:

- An analysis to include the summary of medically attended AE by severity for each analysis interval.
- An analysis to include 'moderate and severe' medically attended AE summary by preferred term for the analysis intervals 5 to 7.
- Proportion differences (Group 1-Group 2), associated 95% CIs and p-values from Fisher's exact test will be provided for analysis intervals 'During the vaccination phase' and 'Throughout the study' for any severe conditions and any severity.

8.2.5.2.3. Newly Diagnosed Chronic Medical Conditions

The percentage of subjects reporting at least one newly diagnosed chronic medical conditions, and the number of episodes will be summarized, by severity and overall, for each group for each of the first 7 analysis intervals (see Table 9) with 95% Clopper-Pearson CI for the percentages. Proportion differences (Group 1-Group 2), associated 95% CIs and p-values from Fisher's exact test will be provided for analysis intervals 'During the vaccination phase' and 'Throughout the study' for any severity. Similarly, the percentage of subjects reporting

at least one related newly diagnosed chronic medical condition, and total # of related newly diagnosed chronic medical conditions will be reported by each group. No between-group proportion differences, associated CIs or p-values will be generated for related newly diagnosed chronic medical conditions.

In addition, for the analysis intervals of vaccination phase, follow-up phase, throughout the study, the NDCMCs will be summarized by each preferred term (MedDRA) with percentage and number of events for each group.

8.2.5.2.4. Immediate AE

The number and percentage of subjects reporting adverse events during the protocol specified first 30-minute observation period will be summarized by group for each vaccination.

This immediate AE report will be summarized for each vaccination and any vaccination. These summaries will include 95% Clopper-Pearson's CI. Unconditional exact 95% CI on the proportion differences and p-value will also be provided.

The immediate AE categorized as SAE (defined as immediate AE and also meet the definition of SAE) will be summarized similarly.

Immediate AE will not be summarized by preferred term. Instead, these immediate AE will be listed.

8.2.5.2.5. AE

The AEs will be analyzed similar as per Section 8.2.5.2.1, except that only the first 5 intervals from Table 9 are applicable as regular (nonserious, not medically attended) AEs are only collected during the vaccination phase. However, if such AEs during the follow-up phase were recorded in the database, these data will be listed separately.

Note that for the analysis interval of vaccination phase the AEs will be summarized by each preferred term (MedDRA) with percentage and number of events for each group. Percentages and 95% CIs on the proportion differences will also be provided for adverse events with 1% or above.

In addition, related AEs will also be summarized by each preferred term with percentage and number of events for each group.

8.2.5.2.6. Days Missing School Due to AE's

Descriptive summary statistics will be provided (mean, std, median, and range for numbers of days, number and percentages of subjects) for each group.

8.2.5.2.7. Multiple Events per Subjects (Incidence Rates)

The frequency distribution on number of events reported by each subject will be summarized for each of the following safety variables:

1. Any AE during the vaccination phase.

2. Any SAE throughout the study.

3. Any Medically attended AE throughout the study.

4. Any newly diagnosed chronic medical conditions throughout the study.

5. Any newly diagnosed chronic medical conditions categorized as SAE throughout the study.

For each subject, the number of events reported per year will be estimated by summarizing the total number of events reported over the observation period and standardizing it to an annual rate by multiplying by 365 and dividing by days on study. The overall incidence rate for each of the safety variables will be reported by group.

8.2.5.2.8. Neuroinflammatory and Autoimmune Conditions

A list of preferred terms (MedDRA), to include all of the neuroinflammatory and autoimmune conditions, will be provided by the medical monitor prior to database lock. These events can be SAE, or AE.

A listing of neuroinflammatory and autoimmune conditions matching this preferred terms list will be provided.

8.2.5.3. RRIs Occurring Within 48 hours After Blood Draw

From Visit 7 research-related injuries (RRI) occurring within 48 hours of the blood draw will be collected. A medically important RRI is any untoward medical occurrence that, results in death, is life-threatening (immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in congenital anomaly/birth defect. Medical and scientific judgment is exercised in determining whether an injury is an important medical event. RRIs occurring within 48 hours of a blood draw will be listed in the CSR. Events with an onset equal to the date of Visit 7 will be reviewed by the study lead clinician; unless otherwise documented before the database release, any events with an onset equal to the date of Visit 7 will be included on the appropriate listing(s) of RRIs.

8.2.5.4. Death

Any cases of death will be listed separately.

8.2.6. Analyses of Study Conduct

8.2.6.1. Subject Disposition, Vaccination Administration, Blood Samples

The number and percentage of subjects who are randomized, take each dose of investigational product, are qualified in each analysis population, withdrew during the vaccination phase, complete the vaccination phase, complete the study (both vaccination phase and follow-up phase), complete all of the study procedures., and withdraw from the follow-up phase, completed the follow-up phase, and are major protocol violators (excluded from evaluable immunogenicity population), will be summarized. The reasons for

withdrawal will also be tabulated. The number of subjects who completed all procedures will be the number of subjects who complete all CRFs at each of the 7 visits.

In addition, the relationship of randomized vaccine group to actual vaccine group received will be presented as a cross tabulation of the actual sequence received versus the randomized vaccine administration regimen.

For each blood draw at Visit 1, Visit 4, Visit 6 and Visit 7, the number and percentage of subjects randomized, vaccinated, and providing blood samples within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated for each group.

Similarly, for each vaccination visit, the number and percentage of subjects who are randomized, vaccinated (visits 1, 3, 5), and vaccinated within the protocol-specified time frame, before and after the specified time frame will be tabulated for each group.

The ITT population will be used to generate these tables. All of the summary tables will be presented for each randomized group and total population.

A listing of non-compliant vaccine administration will be provided. The protocol violators will also be listed. Subjects receive the vaccine not as randomized will be listed as well. A full listing of subjects that withdrew and subjects that withdrew due to AEs will be provided.

Listings for the subjects with flags to be included or excluded in each analysis population will be provided. In addition, the reason for not included in a specific analysis population will be listed.

8.2.6.2. Demographic, Medical History, and Baseline Characteristics

Standard summary reports will be provided. Demographic summaries may also be generated for different analysis sets defined in Section 5.

8.2.6.3. E-Diary Completion

Variables defined in Section 6.3.1, will be summarized for each group using descriptive statistics. The denominators for the e-Dairy compliance rates will be the total number of subjects who receive the vaccination.

8.2.6.4. Nonstudy Vaccination and Concomitant Medication

Nonstudy vaccination summaries will be provided for the following analysis intervals: prior to the vaccination and during the vaccination phase. Concomitant medication will be summarized throughout the study. The denominator for the percentages will be the safety population.

8.2.7. Subgroup Analysis

Some immunogenicity and safety endpoints will be descriptively summarized by race, by gender , and by country as described in Section 6.4.

For the safety endpoints (AE, SAE, medically attended AE, newly diagnosed chronic medical conditions) collected, a separate summary table including analysis interval of 'Vaccination Phase', 'Follow-up Phase' (excluding AEs) and 'Throughout the study' (excluding AEs), will be provided for the subjects who completed the full series (3 doses) and those who only completed partial series (1 or 2 doses). Similar subgroup analysis will also be provided for those safety endpoints with relatedness of study vaccination.

All of the p-values and 95% CI provided for the subgroup analyses are considered as descriptive and no multiplicity adjustment will be made on these analyses. No formal inferences will be made between the subgroups.

9. REFERENCES

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