Title: A Phase 2, Multi-country, Randomized, Double-blind, Placebo-controlled Trial to Evaluate Safety and Immunogenicity when HIL-214 is Concomitantly Administered with Routine Pediatric Vaccines in Healthy Infants

Trial No. NOR-206

NCT: 05836012

STATISTICAL ANALYSIS PLAN

Protocol: NOR-206

Protocol Version: V2.0 09JUL2023

A Phase 2, Multi-country, Randomized, Double-blind, Placebo-controlled Trial to Evaluate Safety and Immunogenicity when HIL-214 is Concomitantly Administered with Routine Pediatric Vaccines in Healthy Infants

SAP/Amendment Number	**Date**
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1 Table of Contents

1.1 Table of Tables

1.2 Table of Figures

2 Abbreviations and Definitions

ADaM	Analysis Dataset Model
AE	Adverse Event
ANOVA	Analysis of Variance
BDRM	Blinded Data Review Meeting
CC	Complete Case
CI	Confidence Interval
CRF	Case Report Form
dp	Decimal Place
DPS	Data Point Set
DT	Diphtheria Toxoid
DTaP-Hib-IPV-HepB	Diphtheria, Tetanus, Acellular Pertussis Adsorbed, *Haemophilus influenzae* Type B, Poliovirus and Hepatitis B vaccine
FHA	Filamentous Hemagglutinin
GI.1/GII.4	Genotype GI.1/GII.4
GII.4c	GII.4 Consensus
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GMR	Geometric Mean Ratio
GSD	Geometric Standard Deviation
HBGA	Histo-Blood Group Antigen
HBsAg	Hepatitis B Surface Antigen
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig	Immunoglobulin
IMP	Investigational Medical Product
IRT	Interactive Response Technology
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantification
MAAE	Medically-Attended Adverse Event
MedDRA®	Medical Dictionary for Regulatory Activities
NAbs	Neutralizing Antibodies
PCV13	Pneumococcal Conjugate Vaccine
PRN	Pertactin
PRP	Unconjugated Capsular Polysaccharide
PT	Preferred Term
PTX	Pertussis Toxin
QC	Quality Control
RV1	Rotavirus Vaccine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SRR	Seroresponse Rate

TFLs	Tables Figures and Listings
TT	Tetanus Toxoid
ULOQ	Upper Limit of Quantification
WHODD	World Health Organization Drug Dictionary

3 Introduction

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analyses of study NOR-206. It also defines the summary tables, figures, and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol. The SAP is based upon, and assumes familiarity with the study protocol, version 2.0, dated 09JUL2023.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. The content of this SAP is compatible with the ICH E9 Guidance document.

4 Study Objectives, Endpoints and Estimands

4.1 Study Objectives

The primary immunogenicity objective of the study is:

- To evaluate the immune response to each licensed pediatric vaccine (DTaP-Hib-IPV-HepB, RV1, and PCV13) co-administered with a 2-dose regimen of HIL-214 at 4 and 6 months of age, compared to that of the routine pediatric vaccines co-administered with placebo.

The secondary immunogenicity objective of the study is:

- To evaluate the immunogenicity of a 2-dose regimen of HIL-214 co-administered with routine pediatric vaccines at 4 and 6 months of age, as measured 28 days post-dose 2 by histo-blood group antigen (HBGA) blocking antibody assay for norovirus GI.1 and GII.4 strains.

The safety objective of the study is:

- To evaluate the safety profile of a 2-dose regimen of HIL-214 co-administered with routine pediatric vaccines at 4 and 6 months of age, compared to that of the routine pediatric vaccines co-administered with placebo.

4.2 Study Endpoints and Estimands

4.2.1 Primary Endpoints and Estimands

Primary Immunogenicity Estimands:

Population:

Healthy infants 4 months of age, who meet all the trial eligibility criteria and who are to receive routine pediatric vaccines (DTaP-Hib-IPV-HepB, RV1, and PCV13) at 2, 4 and 6 months of age.

Treatment strategies to be compared:

- 2-dose series of HIL-214 at 4 and 6 months of age, with concomitant routine pediatric vaccines at 2, 4 and 6 months of age.

- 2-dose series of placebo at 4 and 6 months of age, with concomitant routine pediatric vaccines at 2, 4 and 6 months of age.

Primary immunogenicity endpoints (at 28 days post-dose 2 of HIL-214, administered at 6 months of age):

- Binary (yes/no) variable indicating anti-DT IgG concentration ≥0.1 IU/mL.
- Binary variable indicating anti-TT IgG concentration ≥0.1 IU/mL.
- Anti-FHA, PRN, and PTX IgG concentrations.
- Binary variable indicating anti-poliovirus neutralizing antibody titers ≥1:8, for poliovirus types 1, 2 and 3.
- Binary variable indicating anti-PRP IgG concentration ≥0.15 µg/mL.
- Binary variable indicating anti-HBsAg Ig concentration ≥10 mIU/mL.
- Anti-pneumococcal IgG concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F.
- Anti-RV1 IgA concentrations.

Population-level summaries:

The following will be estimated at 28 days post-dose 2 of HIL-214 (administered at 6 months of age), comparing routine vaccines co-administered with HIL-214 to routine vaccines co-administered with placebo:

- Difference in percentages of subjects with anti-DT IgG concentration ≥0.1 IU/mL.
- Difference in percentages of subjects with anti-TT IgG concentration ≥0.1 IU/mL.
- Ratios of:
    - Anti-pertussis (FHA) IgG geometric mean concentrations (GMCs).
    - Anti-pertactin (PRN) IgG GMCs, and
    - Anti-toxoid (PTX) IgG GMCs.
- Difference in percentages of subjects with anti-poliovirus neutralizing antibody titers ≥1:8, for poliovirus types 1, 2 and 3.
- Difference in percentages of subjects with PRP IgG concentration ≥0.15 µg/mL.
- Difference in percentages of subjects with HBsAg Ig concentration ≥10 mIU/mL.
- Ratios of anti-pneumococcal IgG GMCs for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F.
- Ratio of anti-RV1 IgA GMCs.

The analysis methods for the primary endpoints for the immunogenicity estimands are outlined in **Section 9.1.1.3**.

Intercurrent event strategies:

In the primary immunogenicity estimands, lack of compliance with vaccine administration schedule (missing dose of the routine pediatric vaccines, missing dose of the trial vaccine), and vaccine

administration outside the allowed window) will be handled using a principal stratum strategy, i.e., subjects who do not adhere to the schedule will be excluded from the analysis. Supplementary estimands will use the treatment policy strategy for lack of compliance with trial vaccine administration schedule.

Occurrence of death before Visit 4 (28 days post-dose 2) will be handled according to a principal stratum strategy (no data imputation).

Use of concomitant medications or other vaccines will be handled according to the treatment policy strategy (measurements from these subjects will be included in the primary immunogenicity analyses).

Rationale:

The primary immunogenicity estimands aim to evaluate the immune response to the routine childhood vaccines in pediatric subjects that receive all doses of childhood vaccines and HIL-214/placebo in the correct time window and compare responses to routine childhood vaccines co-administered with HIL-214 with responses to routine childhood vaccines alone.

The supplementary immunogenicity estimands aim to evaluate the immune response to the routine childhood vaccines in pediatric subjects that receive at least one dose of HIL-214 or placebo and compare responses to routine childhood vaccines co-administered with HIL-214 with responses to routine childhood vaccines alone.

4.2.2 Secondary Endpoints and Estimands

Secondary Immunogenicity Estimands:

Population:

Same as for the primary immunogenicity estimands.

Treatment strategy to be evaluated:

- 2-dose series of HIL-214 at 4 and 6 months of age, with concomitant routine pediatric vaccines at 2, 4 and 6 months of age.

Secondary immunogenicity endpoints (at 28 days post-dose 2, administered at 6 months of age):

- Anti-norovirus GI.1 and GII.4 HBGA-blocking titers.
- Anti-norovirus GI.1 and GII.4 HBGA-blocking titers fold rise from baseline.
- Binary variable indicating seroresponse to the HIL-214, where seroresponse is defined as at least a 4-fold increase from baseline in anti-norovirus GI.1 and GII.4 HBGA-blocking titers.

Population level summaries:

The following will be estimated at 28 days post-dose 2 (administered at 6 months of age):

- GI.1 and GII.4-specific geometric mean titers (GMTs) of HBGA-blocking titers.

- GI.1 and GII.4-specific geometric mean fold rise (GMFR) in HBGA-blocking titers.
- Seroresponse rates (SRR; i.e., percentage of subjects demonstrating seroresponse) for GI.1 and GII.4 serotypes.

The analysis methods for the secondary endpoints used in the immunogenicity estimands are outlined in **Section 9.2.1.3**.

Intercurrent event strategies:

Lack of compliance with the trial vaccine administration schedule, occurrence of death before Visit 4 (28 days post-dose 2), and use of concomitant medications or other vaccines will be handled using the same strategies as for the primary immunogenicity estimands.

Supplementary estimands will use the treatment policy strategy for lack of compliance with trial vaccine administration schedule.

Rationale:

The secondary immunogenicity estimands aim to evaluate the immune response for to HIL-214 in pediatric subjects that receive all doses of childhood vaccines and HIL-214 in the correct time window.

The supplementary immunogenicity estimands aim to evaluate the immune response for to HIL-214 in pediatric subjects receive at least one dose of HIL-214 or placebo.

4.2.3 Safety Endpoints and Estimands

Population:

Same as for the primary immunogenicity estimands.

Treatment strategies to be compared:

- At least one dose of HIL-214, with concomitant routine pediatric vaccines.
- At least one dose of placebo, with concomitant routine pediatric vaccines.

Safety endpoints:

- Occurrence (yes/no) of solicited local and systemic reactions during the first 7 days (including day of administration) after each dose of trial vaccine, overall and by severity.
- Occurrence (yes/no) of any unsolicited AE during the first 28 days (including day of administration) after each dose of trial vaccine, overall, by severity and by relatedness.
- Occurrence (yes/no) of SAEs, MAAEs, AEs leading to vaccine or trial withdrawal, during the corresponding collection periods, overall, by severity and by relatedness.

Population level summaries:

Percentages of subjects reporting specific events, overall, by severity and by relatedness, for each trial arm.

The analysis methods for the safety endpoints used in the safety estimands are outlined in **Section 10.1.2**.

Intercurrent events strategies:

Lack of compliance with the routine and trial vaccine administration schedule, and use of concomitant medications and other vaccines will be handled according to the treatment policy strategy, i.e., collected AE data will be used regardless of whether or not these events occurred.

Rationale:

The safety estimands aim to evaluate the safety outcomes in pediatric subjects that receive all at least one dose of childhood vaccines or HIL-214.

5 Study Methods

5.1 General Study Design and Plan

This is a phase 2, multi-country, randomized, double-blind, placebo-controlled trial to evaluate the immune response to routine pediatric vaccinations when co-administered with HIL-214 or placebo in healthy infants. This trial will also evaluate the safety profile of a 2-dose regimen of HIL-214 co-administered with routine pediatric vaccines.

As shown in **Figure 1,** the study comprises of 5 scheduled visits along with 2 telephone calls.

Subjects are randomized prior to trial vaccine administration at Visit 2 to either HIL-214 or Placebo. Throughout this document trial vaccine will refer to the investigational vaccine administration of HIL-214 or placebo.

Routine vaccine and HIL-214 administration is outlined in **Table 1**.

Table 1: Timing of Routine Vaccine and HIL-214 Administration

Vaccine	Age		
	2 months	4 months	6 months
HIL-214 or Placebo		x	x
DTaP-Hib-IPV-HepB	x	x	x
PCV13	x	x	x
RV1	x	x	

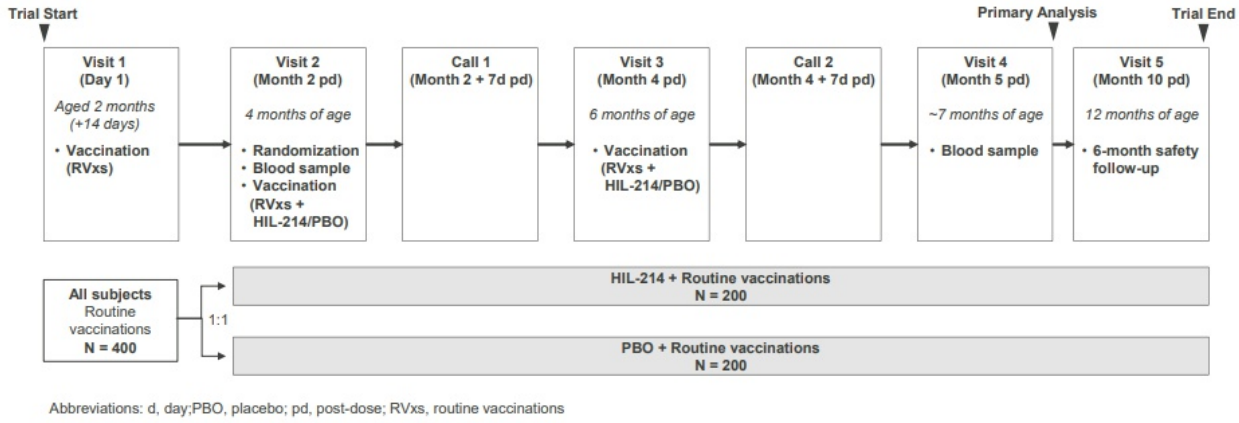
All subjects will have blood drawn at 2 clinic visits:

- Visit 2 (subjects aged 4 months) to measure anti-norovirus (GI.1 and GII.4c) HBGA blocking antibodies
- Visit 4 (28 days post-dose 2) to measure anti-norovirus (GI.1 and GII.4c) HBGA blocking antibodies, and to measure antibodies to the concomitant vaccines (anti-DT IgG, anti-TT IgG,

anti-FHA, PRN and PT, anti-PRP IgG, anti-HBsAg Ig, anti-polio 1, 2 and 3 NAbs, anti-pneumococcal capsular polysaccharide IgG [serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F], and anti-RV1 IgA). The maximum amount of blood drawn at Visit 2 is 4 mL and at Visit 4 is 6 mL.

The overall planned duration of subject participation is up to 10 months.

Figure 1: Trial Design Diagram



Abbreviations: d, day;PBO, placebo; pd, post-dose; RVxs, routine vaccinations

5.2 Randomisation and Blinding

Up to 400 subjects (infants aged 2 months [+14 days]) will be enrolled and randomized (1:1) to two arms by interactive response technology (IRT):

- Arm 1 (N=200): HIL-214 (1 dose at 4 months of age and 1 dose at 6 months of age) and routine childhood vaccines according to schedule.
- Arm 2 (N=200): Placebo (1 dose at 4 months of age and 1 dose at 6 months of age) and routine childhood vaccines according to schedule.

The investigator or investigator's designee will access the IRT on Visit 1 to obtain the subject number.

The investigator or investigator's designee will utilize the IRT to randomize all subjects into either the HIL-214 or placebo arms at Visit 2. During this contact, the investigator or designee will provide the necessary subject identifying information. Randomization will be stratified by country.

Randomization information will be stored in a secured area, accessible only by authorized personnel.

The subjects, data collectors (e.g., investigator) and data evaluators are blinded to the material administered.

Trial vaccine administration must be done by designated unblinded site staff, in which the trial vaccine is selected using the subject's number. The designated unblinded site staff must not be involved with data collection of any sort including safety evaluation of the subject after administration of the trial vaccine.

The trial blind shall not be broken by the investigator unless information concerning HIL-214 is necessary for the medical treatment of a subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the trial blind is broken to discuss the need for unblinding. For unblinding a subject, the trial vaccine assignment will be obtained by the investigator, by accessing the IRT.

If any subject is unblinded, the subject must be withdrawn from the trial and their data no longer evaluated.

5.3 Derived variables

5.3.1 General

5.3.1.1 Baseline

Unless otherwise stated, baseline is defined as the last non-missing pre-trial vaccine assessment prior to the first trial vaccine.

5.3.1.2 Relative Day

The relative day from first routine vaccine of an assessment will be calculated as:

- For measurement performed on or after the date of first dose of routine vaccine:
  Date of assessment – date of first routine vaccine + 1

- For measurements performed before the date of first dose of routine vaccine:
  Date of assessment – date of first routine vaccine

The relative day from first dose of trial vaccine of an assessment will be calculated as:

- For measurement performed on or after the date of first dose of trial vaccine:
  Date of assessment – date of first trial vaccine + 1

- For measurements performed before the date of first dose of trial vaccine:
  Date of assessment – date of first trial vaccine

5.3.1.3 Demographic and Background Data

Age at screening will be calculated in days. Age at screening will be calculated as follows:

Age at Screening (days) = Screening date (Visit 1) – Date of Birth + 1.

Weight may be recorded in kilograms or pounds. Weight in pounds will be converted to weight in kilograms as follows:

Weight (kg) = Weight (lb) * 0.4536.

Weight will be presented to 1 dp in the listings.

Length may be recorded in centimetres or inches. Length in inches will be converted to length in centimetres as follows:

Length (cm) = Length (inches) * 2.54.

Length will be presented to 1 dp in the listings.

Head Circumference may be recorded in centimetres or inches. Head circumference in inches will be converted to head circumference in centimetres as follows:

Head circumference (cm) = Head circumference (inches) * 2.54.

Head circumference will be presented to 1 dp in the listings.

Temperature may be recorded in Degrees Celsius or Fahrenheit. Temperature in Fahrenheit will be converted to temperature in Degrees Celsius as follows:

Temperature (°C) = (Temperature (°F) – 32) * 0.5556.

Temperature will be presented to 1 dp in the listings.

5.3.1.4 Time Between First and Second Trial Vaccine Dose

The time between the first and second trial vaccine dose (days) will be calculated as follow:

Date of second trial vaccine dose – Date of first trial vaccine dose + 1.

5.3.2 Efficacy

5.3.2.1 Fold Increase

The fold increase is calculated by taking the ratio of a subject's Visit 2 and Visit 4 assessments. If v_2 is a subject's Visit 2 record and v_4 is a subject's Visit 4 record then the fold increase is:

$$fi = \frac{v_4}{v_2}.$$

5.3.2.2 Seroresponse Rate

Seroresponse is defined as a fold increase from baseline (Visit 2) greater than or equal to 4.

Seroresponse rate (SRR) is defined as the percentage of subjects with a seroresponse.

5.3.2.3 Immunogenicity Assessments

When summarizing immunogenicity assessments the following rules will apply:

- If a record is below the lower limit of detection (LLOD) then 1/2 the LLOD value will be used in the summary
- If a record is below the lower limit of quantification (LLOQ) then the midpoint of the LLOQ value and the LLOD value will be used in the summary

- If a record is above the upper limit of quantification (ULOQ) then the ULOQ will be used in the summary

The following table gives the LLOD's, LLOQ's and ULOQ's for each of the parameters to be assessed on the study.

Table 2: Limits of Detection and Ranges of Quantification for Immunogenicity Assays

Parameter	LLOD	LLOQ	ULOQ
Diphtheria (DT)	0.000010 IU/mL	0.000037 IU/mL	0.005 IU/mL
Tetanus (TT)	0.000038 IU/mL	0.00005 IU/mL	0.041 IU/mL
Polio Type 1	2.50 $\log^2$	N/A	N/A
Polio Type 2	2.50 $\log^2$	N/A	N/A
Polio Type 3	2.50 $\log^2$	N/A	N/A
Hepatitis B (HBsAg)	NA	10 mIU/mL	14043.4 mIU/mL
Pertussis Filamentous Hemagglutinin (FHA)	0.0009 IU/mL	0.0029 IU/mL	1.97 IU/mL
Pertussis Pertactin (PRN)	0.0007 IU/mL	0.003 IU/mL	0.7 IU/mL
Pertussis Toxoid (PT)	0.0004 IU/mL	0.0009 IU/mL	0.29 IU/mL
Haemophilus influenzae type B (PRP)	NA	0.15 µg/mL	28.55 µg/mL
Pneumococcal serotype 1	0.01 µg/mL	0.05 µg/mL	65.63 µg/mL
Pneumococcal serotype 3	0.01 µg/mL	0.05 µg/mL	21.82 µg/mL
Pneumococcal serotype 4	0.01 µg/mL	0.04 µg/mL	22.21 µg/mL
Pneumococcal serotype 5	0.01 µg/mL	0.06 µg/mL	66.32 µg/mL
Pneumococcal serotype 6A	0.01 µg/mL	0.04 µg/mL	67.98 µg/mL
Pneumococcal serotype 6B	0.01 µg/mL	0.07 µg/mL	61.05 µg/mL
Pneumococcal serotype 7F	0.01 µg/mL	0.08 µg/mL	94.95 µg/mL
Pneumococcal serotype 9V	0.01 µg/mL	0.08 µg/mL	52.87 µg/mL
Pneumococcal serotype 14	0.01 µg/mL	0.07 µg/mL	352.99 µg/mL
Pneumococcal serotype 18C	0.01 µg/mL	0.04 µg/mL	33.8 µg/mL
Pneumococcal serotype 19A	0.01 µg/mL	0.05 µg/mL	86.91 µg/mL
Pneumococcal serotype 19F	0.01 µg/mL	0.06 µg/mL	471.56 µg/mL
Pneumococcal serotype 23F	0.01 µg/mL	0.07 µg/mL	92.83 µg/mL
Rotavirus	5.76 U/mL	7.5 U/mL	N/A
Norovirus HBGA CN (GI.1)	19 AU/mL	19 AU/mL	78848 AU/mL
Norovirus HBGA NW (GII.4)	33 AU/mL	33 AU/mL	149504 AU/mL

5.4 Statistical Analysis Methods

5.4.1 Difference in Percentages

The difference in percentage, given by the difference between the proportion of subjects in the vaccine group, p_2, with the event and placebo group, p_1, with the event is calculated using the following formula:

$$\text{Difference in percentage } = (p_2 - p_1) * 100 = \left(\frac{E_2}{n_2} - \frac{E_1}{n_1}\right) * 100 \quad (1)$$

where E_1 and E_2 are the number of events in the placebo and vaccine groups respectively, and n_1 and n_2 are the number of subjects in the placebo and vaccine groups respectively with a valid assessment.

The 95% confidence intervals for the differences in percentages will be computed using the Miettinen and Nurminen (MN) [2] method. The following formula is used for the MN CI:

$$\text{MN CI} = \left((\hat{p}_2 - \hat{p}_1) \pm Z_{1-\frac{\alpha}{2}} \sqrt{\lambda \left(\frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2} + \frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1} \right)} \right) * 100 \quad (2)$$

where $\tilde{p}_1$ and $\tilde{p}_2$ are the maximum likelihood estimators for p_1 and p_2 under the null hypothesis that $p_1 - p_2 = 0$ and $\lambda = \frac{n_1+n_2}{n_1+n_2-1}$ and α is the selected level of significance. All confidence intervals for the difference in percentages outlined in this SAP will be two-sided 95% confidence intervals, i.e. with α = 0.05.

5.4.2 Geometric Mean

The geometric mean (GM) of a set of numbers $x_1, x_2, \ldots, x_N$ is calculated by taking the exponential of the mean of the logged values, as per the following formula

$$GM_x = \exp\left\{ \frac{\sum_{i=1}^{N} ln(x_i)}{N} \right\}.$$

The geometric standard deviation (GSD) for the same set of numbers is given by

$$GSD_x = exp\left\{ \sqrt{\frac{\sum_{i=1}^{n} \left(ln\left(\frac{x_i}{GM_x} \right) \right)^2}{n}} \right\}.$$

The 95% confidence interval (CI) is calculated as per the following formula:

$$95\%\ CI = \exp\left\{ ln(GM) \pm Z_{1-\frac{\alpha}{2}} \frac{ln(GSD)}{\sqrt{n}} \right\}$$

where α is the selected level of confidence. All confidence intervals outlined in this SAP will be two sided 95% confidence intervals, i.e. with α = 0.05.

5.4.3 Geometric Mean Ratio

The geometric mean ratio (GMR) is the ratio of two different geometric means (**Section** Error! Reference source not found.). The GMR and corresponding 95% CI will be calculated using an analysis of variance model (ANOVA). The difference between the natural logarithm of the values and 95% CI will be calculated, with the exponential of these values being the GMR and corresponding 95% CI.

5.4.4 Geometric Mean Fold Rise

The geometric mean fold rise (GMFR) is given by taking the mean of the natural logarithm of the fold increases (**Section 5.3.2.1**). Therefore for the fold increases $fi_1, \ldots, fi_n$, the GMFR is

$$GMFR = \exp \sum_{j=1}^{n} \left(\log\{fi_j\} / n \right).$$

Which is equivalent to

$$GMFR = \frac{GM_4}{GM_2}$$

where GM_2 is the geometric mean at Visit 2 and GM_4 is the geometric mean at Visit 4.

The 95% confidence interval for GMFR will be calculated using the same method as the 95% CI for GM (outlined in **Section 5.4.2**) but using the log of the fold rises rather than the log of concentrations.

6 Sample Size

This trial is designed to be descriptive, and therefore the sample size was not determined based on formal statistical power calculations. The planned number of subjects is approximately 400, with 200 receiving HIL-214 and routine childhood vaccines and 200 receiving Placebo and routine childhood vaccines.

7 General Considerations

7.1 Analysis Sets

For the purposes of analysis, the subject analysis sets are defined in **Table 3**.

Table 3: Subject Analysis Sets

Subject Analysis Set	Description
Enrolled analysis set	• All subjects who signed the informed consent
Randomized analysis set	• All subjects in the enrolled analysis set that were randomized
Immunogenicity evaluable analysis set	• All subjects in the randomized analysis set that receive all doses of all study vaccines (routine and trial vaccines) within the required time window*
Immunogenicity full analysis set	• All subjects in the randomized analysis set that receive at least one dose of a trial vaccine within the required time window*
Safety analysis set	• All subjects in the randomized analysis set who are exposed to the trial vaccine. Subjects will be included in the analyses according to the trial vaccine (HIL-214 or Placebo) they actually received

*This window will be defined at the blinded data review meeting (BDRM)

7.2 Data Point Sets

The data point sets (DPS) are defined in **Table 4** and will be used to evaluate the estimands defined in the protocol.

Table 4: Data Point Sets

Data Point Sets	Description
Data point analysis set 1 (DPS1): Used for the primary immunogenicity estimands and for the secondary immunogenicity estimands	• Immunogenicity evaluable analysis set • For subjects who receive a concomitant medication or other vaccine all data will be included
Data point analysis set 2 (DPS2): Used for the supplementary immunogenicity estimands	• Immunogenicity full analysis set • For subjects who receive a vaccine outside of the required time window*, all data will be included • For subjects who receive a concomitant medication or other vaccine all data will be included
Data point analysis set 3 (DPS3): Used for the analysis of Safety data	• Safety Analysis Set • For subjects who receive a vaccine outside of the required time window*, all data will be included • For subjects who received a concomitant medication or other vaccine all data will be included

*This window will be defined at the blinded data review meeting (BDRM)

7.3 Covariates

For the ANOVA models where only an overall analysis is presented, country will be included as a covariate.

7.4 Subgroups

Table 5 shows the routine vaccines used in each country.

Table 5: Routine Vaccines Used in Each Country

Disease(s)	Routine Vaccine	
	Panama	**USA (and Puerto Rico)**
DTaP-Hib-IPV-HepB	Infanrix Hexa	Vaxelis
PCV13	Prevnar 13	Prevnar 13
RV1	Rotarix	Rotarix

Since the routine vaccines used in Panama and the USA to protect against rotavirus and the pneumococcus are the same, presenting an overall summary for the endpoints related to these vaccines is planned. Analysis of the immunogenicity endpoints for rotavirus and pneumococcal vaccines will be presented both overall and by country.

As the hexavalent vaccines used will be different in Panama and the USA there is no plan to provide an overall summary for immunogenicity endpoints related to antigens contained in these vaccines. Therefore, analysis of all immunogenicity endpoints related to the hexavalent vaccines will be presented by country only.

The following subgroups will be presented:

- Country:
  - Panama
  - USA

7.5 Missing Data

7.5.1 Immunogenicity data

The reasons for having missing immunogenicity data are as follows:

- Study withdrawal prior to the blood draw (Visit 4)
- Non-evaluable samples, which may be as a result of a low volume of blood
- Blood draw outside of the permitted time window

For the primary and secondary immunogenicity estimands a principal stratum approach will be taken for the missing data. Therefore, a complete case (CC) analysis will be performed for these estimands based on the assumption that the data are missing completely at random. Immunogenicity results are not

expected to have any relationship with subject withdrawal from the study. Non-evaluable samples are expected to occur as a result of an issue with sample collection, storage, transportation, or analytical error and not due to the trial vaccine received. Blood draws outside of the permitted time window are expected to occur due to a planning or logistical error and won't be impacted by the trial vaccine received.

For the supplementary immunogenicity estimands a treatment policy approach will be applied to the missing data, using the assumption that any missing data would have been similar in subjects who had the same type of, and number of, trial vaccinations.

There are 4 different trial vaccine options that will be considered, they are:

- 1 placebo vaccination (t_1)
- 2 placebo vaccinations (t_2)
- 1 HIL-214 vaccination (t_3)
- 2 HIL-214 vaccinations (t_4)

To account for the missing data in this setting, inverse probability weighting [3] will be used. For this method, weights, relating to the probability of a subject having CC data, will be calculated for each of the 4 different trial vaccine options. A logistic regression model will be used to calculate the probability of having CC data, with one covariate that has 4 levels for the type of vaccine and the number of doses received.

The weights will be calculated in the following way:

$$w_i = \frac{1}{P(CC|\boldsymbol{t_i})}$$

where $\boldsymbol{t_i}$ describes the trial vaccine option the subject receives, as defined above.

For continuous variables the ANOVA models will include all non-missing data for the parameter of interest and then the weights to account for the missing data. For binary data the proportions, which will be calculated on the complete cases data, will be reweighted, and the reweighted proportions will be used in the calculation of the confidence intervals. Therefore, in Equation (1) in Section 5.4.1 will be calculated as the following:

$$\text{Difference in percentage } = (p_2 - p_1) * 100 = \left(\frac{(E_3|t_3 \times w_3) + (E_4|t_4 \times w_4)}{N_2} - \frac{(E_1|t_1 \times w_1) + (E_2|t_2 \times w_2)}{N_1}\right) * 100$$

Where E_i are the number of observed events in each category t_i and N_1 and N_2 are the number of subjects in the analysis set in the placebo and vaccine groups respectively. If all observed cases are positive in both vaccine groups, then the difference will be set to 0.

Equation (2) in Section 5.4.1 will be calculated as the following:

$$\text{MN CI} = \left((\hat{p}_2 - \hat{p}_1) \pm Z_{1-\frac{\alpha}{2}} \sqrt{\lambda \left(\frac{\tilde{p}_2(1-\tilde{p}_2)}{N_2} + \frac{\tilde{p}_1(1-\tilde{p}_1)}{N_1} \right)} \right) * 100$$

Where $\lambda = \frac{N_1+N_2}{N_1+N_2-1}$.

If all observed cases are positive in both vaccine groups confidence intervals will not be calculated.

In the tables the number of events will be rounded to the nearest integer value and Clopper-Pearson CIs will be calculated using the exact weight-adjusted values using the Beta distribution. If all observed cases are positive the number of events will be set to N_1 and N_2 and these values will be used to calculate the confidence intervals.

If insufficient non-missing data are collected in participants with 1 trial vaccination the vaccine groups will be pooled to give the following vaccine options:

- Placebo vaccinations only (t_1)
- At least one HIL-214 vaccination (t_2)

The above formulae will be adjusted accordingly.

7.5.2 Partial Dates/Times

Partial dates and times for AEs, medical conditions and concomitant medications will be imputed for the purpose of assigning study phases and calculating duration. Imputed dates and times should not be shown in the listings.

Partial AE onset and concomitant medication start dates will be imputed as follows:

- If only the month and year are specified, and the month and year of either trial vaccination are not the same as the month and year of the start date, then use the 1st of the month or the date of birth, whichever is latest.
- If only the month and year are specified, then set to the date of the latest vaccine received in the same month and year. If this results in a start date after a known or partial end date, then use the 1st of the month.
- If only the year is specified, and the year of either trial vaccination is not the same as the year of the start date, then use January 1st of the year of the start date or the date of birth, whichever is latest.
- If only the year is specified, then set to the date of the latest trial vaccine received in the same year. If this results in a date that is after the known end date of the AE/medication then use the date of the earliest trial vaccination or January the 1st, whichever is the latest.

If the start date is completely unknown, then use the date of the last trial vaccination. If this results in a date that is after the known end date of the AE/medication then use the date of the earliest trial vaccination. If this results in a start date after a known or partial end date, do not impute the start date.

Imputation of partial AE start times:

- If the actual or imputed start date is the same as the date of a trial vaccination and the start time is completely missing, then use the time of the corresponding trial vaccination.
- If the actual or imputed start date is not the same as any trial vaccine administration, and the start time is completely missing, then use 00:00.
- If the actual or imputed start date is the same as any trial vaccine administration, and the start time is partially missing (hh:XX) then use the following:
    - If the hour is the same as the hour of the any trial vaccine administration time then use the complete time of trial vaccine administration (i.e., both hours and minutes)
    - If the hour is not the same as the hour of the start time than use hh:00.
- If the actual or imputed start date is not the same as the trial vaccine administration, and the start time is partially missing (hh:XX) then use hh:00.

Partial medical conditions start dates will be imputed as follows:

- If only the month and year are specified, then use the 1st day of the month or the date of birth, whichever is latest.
- If only the year is specified, then use January 1st of that year or the date of birth, whichever is latest.
- If the start date is completely unknown, do not impute the start date.

Partial AE resolution, medical condition stop dates and concomitant medication stop dates will be imputed as follows:

- If the event, condition or medication is flagged as ongoing, do not impute the stop date.
- If only the month and year are specified, then use the last day of the month or the date of data-cut, whichever is earliest.
- If only the year is specified, then use December 31st of that year or the date of data-cut, whichever is earliest.
- If the stop date is completely unknown, do not impute the stop date.

Partial AE resolution and concomitant medication stop times will be imputed as follows:

- If the actual or imputed stop date is non-missing, and the stop time is completely missing, then use 23:59 on that date.
- If the actual or imputed stop date is non-missing, and the stop time is partially missing, then hh:59 for missing minutes.
- If the actual or imputed stop date is missing, do not impute the stop time.

7.6 Interim Analyses and Data Monitoring

7.6.1 Planned Analysis Schedule

The trial objectives will be evaluated once, after completion of all planned assessments and database lock, at the end of the trial.

7.6.2 Practical Measures to Minimise Bias

To maintain the blind throughout the study immunogenicity data related to HIL-214 will not be provided to the blinded Veramed statistical analysis team until after DBL. Any programming of associated datasets and TFLs prior to study unblinding will be done using dummy data.

7.7 Multi-centre Studies

This is a multi-country study with randomization stratified by country.

8 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, trial vaccine and subject, and when appropriate by visit number within subject.

All summary tables, unless otherwise stated, will be structured with a column for each trial vaccine in the order (Placebo, HIL-214) and will be annotated with the total population size relevant to that table/trial vaccine, including any missing observations. The vaccine group labels can be found in **Table 6**.

Table 6: Vaccine group labels for reporting

Output ordered by	Label for use in output	Description
Vaccine group	Placebo	2-dose series of placebo at 4 and 6 months of age, with concomitant routine pediatric vaccines at 2, 4 and 6 months of age
	HIL-214	2-dose series of HIL-214 at 4 and 6 months of age, with concomitant routine pediatric vaccines at 2, 4 and 6 months of age
	Total*	All subjects pooled

*Only presented for study population tables

All summary tables specified in this section will be produced using the randomized analysis set (unless otherwise stated) and will have a summary for each country, as outline in **Section 7.4** and overall.

8.1 Subject Disposition

Completion/withdrawal from the study and completion/discontinuation from trial vaccine regimen, together with reasons for withdrawal from the study or discontinuation from trial vaccine regimen will be listed and the following will also be tabulated:

- Number and percentage of subjects who completed the study
- Number and percentage of subjects who discontinued trial vaccine regimen early and the principal reason for discontinuation
- Number and percentage of subjects withdrawn from the trial vaccine regimen before randomization and the principal reason for withdrawal
- Number and percentage of subjects withdrawn from the study after randomization and the principal reason for withdrawal
- Number and percentage of subjects withdrawn from the study between Visit 2 and Visit 3 and the principal reason for withdrawal
- Number and percentage of subjects withdrawn from the study between Visit 3 and Visit 4 and the principal reason for withdrawal
- Number and percentage of subjects withdrawn from the study between Visit 4 and Visit 5 and the principal reason for withdrawal

For subjects who fail to meet the eligibility criteria the reasons for failure, including the inclusion/exclusion criteria that were not met will be summarized and listed. This output will use the enrolled analysis set.

The number and percentage of subjects that are randomized to each trial arm will be summarized by country and listed.

The number and percentage of subjects included in each analysis set and the reasons for exclusion will be summarized and listed.

The number and percentage of subjects who attended each scheduled visit (including the early withdrawal visit) will be summarized and listed.

8.2 Protocol Deviations

The number and percentage of subjects with at least one important protocol deviation will be summarized by deviation category (major/minor). Designation of important/not important and major/minor protocol deviations will be determined after review of the final list of protocol deviations during the blinded data review meeting. Protocol deviations which lead to exclusion from the per protocol analysis set will be considered both important and major. Other protocol deviations, such as those related to GCP, may also be considered important and/or major protocol deviations. The lead statistician will be responsible for the categorisation of protocol deviations and the categorisation will be approved by the sponsor.

All protocol deviations will be listed.

8.3 Demographic and Baseline Variables

Demographic and baseline variables will be summarised descriptively. The variables to be summarized in the demography table will all be evaluated at randomization and are as follows:

- Age (days)
- Age by category
  - <= 18 years old
- Sex
  - Male
  - Female
  - Other/Not Recorded
- Race
  - American Indian or Alaskan Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Mixed Race
  - Other
  - Not Reported
  - Unknown
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
- Country
  - Panama
  - USA
- Prior Vaccinations
  - Yes
  - No
- Breastfeeding status
  - Breastfeeding
  - Not breastfeeding
- Weight (kg)
- Length (cm)
- Head Circumference (cm)

8.4 Concurrent Illnesses and Medical Conditions

Medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®). The dictionary version used will be 25.1.

Concurrent illnesses and medical conditions will be classified as 'current' if the end date is on or after Visit 2, or the condition has been marked as ongoing. Illnesses and medical conditions that start and end before Visit 2 will be classified as past.

Past and current medical history will be listed for the randomized analysis set.

8.5 Prior and Concomitant Medications

Prior medication definition: If a subject takes a medication before Visit 2, this medication will be classified as 'prior medication'. With this definition, any medication recorded that has been taken for at least 1 day and has been stopped before Visit 2 will be considered as prior.

Concomitant medication definition: Prior medication not stopped before Visit 2 will be classified as 'concomitant medication'. Medication will be labelled as 'concomitant medication' when the start date is between Visit 2 and the final study visit (Visit 5) or, in case of early termination, on the date of the subject's last visit. With this definition, any medication that has been taken for at least 1 day between Visit 2 and Visit 5 will be considered as concomitant.

Medications will be coded according to the 2020 version of the World Health Organization Drug Dictionary (WHODD). Medical procedures will not be coded. Prior and concomitant medications will be listed for the randomized analysis set by trial vaccine group. Concomitant medications will be summarised.

Procedure history will be listed separately by the procedure reported term for the randomized analysis set by trial vaccine group. Concomitant medical procedures carried out during the study will be listed for the randomized analysis set.

9 Immunogenicity Analyses

All immunogenicity variables will be listed by subject within study center. Data will be summarised by trial vaccine group and country.

For all continuous immunogenicity variables a standard summary of the number of subjects with an assessment (n), geometric mean (with 95% CI), geometric standard deviation, median, Q1, Q3, minimum and maximum will be presented alongside the number of assessments below the LLOQ and LLOD and above the ULOQ. The number of subjects missing an assessment will also be summarized.

For categorical variables the count and percentage of subjects with antibody titers/concentrations over a pre-defined threshold, count and percentage of subjects achieving seroresponse to HIL-214, and 95% CIs for the percentages, computed using the exact Clopper-Pearson [1] method, will be presented.

9.1 Primary Immunogenicity Analysis

9.1.1 Estimands

The estimands used for the primary objectives, outlined in **Section 4.2.1**, and the methods for analysing the data are described further in this section.

9.1.1.1 Data Point Sets and Intercurrent Events

The DPS (which outline the analysis set used) and intercurrent event strategies used for each of the primary immunogenicity estimands and primary supplementary immunogenicity estimands are outlined in **Table 7**.

Table 7: Data Point Sets and Intercurrent Event Strategies for the Primary and Supplementary Immunogenicity Estimands

Estimand	DPS	Lack of compliance with the vaccine administration schedule (vaccine administration outside of required time window*)	Occurrence of death before Visit 4 (28 days post dose 2)	Use of concomitant medications or other vaccines
Primary immunogenicity estimands	DPS1	Principal Stratum Strategy: Such subjects are excluded from the analysis set	Principal stratum strategy: Data will not be imputed after death, meaning the subject will not be included in the analysis	Treatment Policy strategy: Data will be used as collected
Supplementary immunogenicity estimands for the primary endpoints	DSP2	Treatment Policy Strategy: Data will be used as collected	Principal stratum strategy: Data will not be imputed after death, meaning subjects will not be included in the analysis	Treatment Policy strategy: Data will be used as collected

*This window will be defined at the blinded data review meeting (BDRM)

9.1.1.2 Endpoints

All primary immunogenicity endpoints will be evaluated at Visit 4 and can be found in **Table *8***.

Table 8: Primary Immunogenicity Endpoints

Related Vaccine	Type of Endpoint	Endpoint
Infanrix Hexa/Vaxelis	Binary	Binary (yes/no) variable indicating anti-DT IgG concentration ≥0.1 IU/mL
		Binary (yes/no) variable indicating anti-TT IgG concentration ≥0.1 IU/mL
		Binary variable indicating anti-poliovirus neutralizing antibody titers ≥1:8, for poliovirus types 1, 2 and 3
		Binary variable indicating anti-PRP IgG concentration ≥0.15 µg/mL
		Binary variable indicating anti-HBsAg Ig concentration ≥10 mIU/mL
	Continuous	Anti-pertussis (FHA) concentrations
		Anti-pertactin (PRN) IgG concentrations
		Anti-toxoid (PTX) IgG concentrations
Prevnar 13	Continuous	Anti-pneumococcal IgG concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F
Rotarix	Continuous	Anti-RV1 IgA concentrations

9.1.1.3 Analysis Methods

A primary immunogenicity estimand and a supplementary estimand will be created for all of the endpoints outlined in **Table 8**. Analyses will be completed for the subgroups defined in **Section 7.4**.

For the primary immunogenicity estimands a complete case analysis will be performed, meaning any subjects with missing data for the parameter of interest will be excluded from the analysis.

For the supplementary immunogenicity estimands for the primary endpoints the missing data will be accounted for by reweighting the estimates using the method of inverse probability weighting. See **Section 7.5.1** for more details.

For the binary primary immunogenicity endpoints a standard summary for the categorical outcome will be presented as well as descriptive statistics for the continuous values. Further, the difference in percentage of subjects in the vaccine group with the event and the percentage of subjects in the

placebo group with the event will be evaluated. This will be presented along with a 95% CI calculated using the Miettinen and Nurminen [2] method as shown in **Section 5.4.1**.

For all continuous primary immunogenicity endpoints the geometric mean titer/concentration (GMT/GMC) with 95% CIs and geometric standard deviation (GSD) will be calculated. The GMRs between the vaccine group and the placebo group along with a 95% CI will be calculated using the analysis of variance (ANOVA) model with natural logarithm of antibody titer/concentration as the response variable and trial arm as a factor. Where country is used as a covariate (see **Section 7.3**) the adjusted GMs will also be presented. Further details can be found in **Section 5.4.3**.

For all primary immunogenicity parameters a reverse cumulative distribution curve will be produced, with titer/concentration on the x-axis and the percentage of patients below the titer value on the y-axis. All graphs will contain the two vaccine groups which will be overlaid.

A forest plot, with 95% CI, will be made for each of the three routine vaccines. Forest plots presenting data for the difference in percentages will have a line at 0 to indicate no difference, and forest plots presenting the data using ratios will have a line at 1 to indicate no difference. Since the routine vaccines of Infanrix Hexa/Vaxelis have endpoints that evaluate the data as both a difference in percentage and a ratio, separate plots will be created. All of these plots will be presented by country, with the plots for the Prevnar 13 and Rotarix vaccines also presented overall.

9.2 Secondary Immunogenicity Analyses

9.2.1 Estimands

The estimands used for the primary objectives, outlined in **Section 4.2.2**, and the methods for analysing the data are described further in this section.

9.2.1.1 Data Point Sets and Intercurrent Events

Secondary Immunogenicity Estimands for the Secondary Endpoints:

Secondary immunogenicity estimands will use the same DPS and intercurrent event strategies as the primary immunogenicity estimands outlined in **Table 7**.

Supplementary Immunogenicity Estimands for the Secondary Endpoints:

Supplementary immunogenicity estimands for the secondary endpoints will use the same DPS and intercurrent event strategies as the supplementary immunogenicity estimands for the primary endpoints outlined in **Table 7**.

9.2.1.2 Endpoints

All secondary immunogenicity endpoints will be evaluated at Visit 4 and are all related to the HIL-214 vaccine.

The binary secondary immunogenicity endpoints are as follows:

- Binary variable indicating seroresponse to the HIL-214, where seroresponse is defined as at least a 4-fold increase from baseline in anti-norovirus GI.1 HBGA-blocking titers
- Binary variable indicating seroresponse to the HIL-214, where seroresponse is defined as at least a 4-fold increase from baseline in anti-norovirus GII.4 HBGA-blocking titers

The continuous secondary immunogenicity endpoints are as follows:

- Anti-norovirus GI.1 and GII.4 HBGA-blocking titers.
- Anti-norovirus GI.1 and GII.4 HBGA-blocking titers fold rise from baseline.

9.2.1.3 Analysis Methods

For the secondary immunogenicity endpoints data will only be analysed for the patients receiving HIL-214.

A secondary immunogenicity estimand and a supplementary estimand will be created for all of the endpoints outlined in **Section 9.2.1.2**. Analyses will be completed for the two country subgroups only, defined in **Section 7.4**.

For the secondary immunogenicity estimands a complete case analysis will be performed, meaning any subjects with missing data for the parameter of interest will be excluded from the analysis.

For the supplementary immunogenicity estimands for the secondary endpoints the missing data will be accounted for by reweighting the estimates using the method of inverse probability weighting. See **Section 7.5.1** for more details.

For all binary secondary immunogenicity endpoints a standard categorical summary will be presented. SRR is defined in **Section 5.3.2.2**.

For all continuous secondary immunogenicity endpoints a standard continuous summary of the outcome will be presented alongside the GM and GMFR and their confidence intervals. Where country is used as a covariate (see **Section 7.3**) the adjusted GMs will also be presented.

For all secondary immunogenicity parameters a reverse cumulative distribution curve will be produced, with titer/concentration on the x-axis and the percentage of patients below the titer/concentration value on the y-axis. All graphs will present the two vaccine groups which will be overlaid.

Line graphs and boxplots summarizing the GMT for each trial vaccine group for the serotypes GI.1 and GII.4 will also be produced. These outputs will both have the visits of baseline and Visit 4 on the x-axis and the GMT on the y-axis, presenting data on the log scale.

Bar plots for seroresponse, with 95% CIs, will also be created with the results for placebo and HIL-214 stacked next to each other and separate sets of bars for the serotypes GI.1 and GII.4.

10 Safety Analyses

All safety analysis is defined in this section. Along with the following summaries, all safety endpoints will be listed by vaccine group. Where summaries are presented overall, after first dose and after second dose subjects will be summarised under the trial vaccine they receive for that period. If a subject receives HIL-214 for either dose they will be summarised under HIL-214 in the overall summary.

All safety summaries of continuous variables will present n (non-missing sample size), mean, standard deviation, median, maximum and minimum. All safety endpoint and summaries will use the safety analysis set.

10.1 Safety Estimands

The estimands used for the safety objectives, outlined in **Section 4.2.3**, and the methods for analysing the data are described further in this section.

10.1.1 Data Point Sets and Intercurrent Events

The DPS (which outline the population used) and intercurrent event strategies used for all safety estimands can be found in **Table *9***.

Table 9: Data Point Sets and Intercurrent Event Strategies for the Safety Estimands

Estimand	DPS	Lack of compliance with the vaccine administration schedule (vaccine administration outside of required time window)	Use of concomitant medications or other vaccines
Safety estimands	DPS3	Treatment Policy Strategy: Any safety data taken after vaccine administration outside of the correct time window will be used as collected	Treatment Policy strategy: Data will be used as collected

10.1.2 Analysis Methods

A safety estimand will be created for all of the AE outputs outlined below. Analyses will be completed for the two country subgroups defined in **Section 7.4** and overall.

Summary tables will contain counts of subjects, percentages of subjects in parentheses and the number of events or descriptive statistics, where applicable.

10.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a trial vaccine; it does not necessarily have to have a causal relationship with trail vaccine administration. An AE is also defined as any untoward medical occurrence in a clinical investigation subject from the time they enter the trial.

All adverse event (AE) summaries will be ordered by alphabetical system organ class (SOC), and decreasing frequency of preferred term (PT) within SOC, in the active arm overall column. A subject who

has multiple events in the same SOC and PT will be counted only once in the subject counts but all events will be included.

10.2.1 Severity of Adverse Event

In summaries including severity, the following severity categories will be summarized: 'Mild', 'Moderate', 'Severe'. For the solicited AE of fever the following categories of severity will be summarized: '<38°C', '38-39°C', '39-40°C', '≥40°C'. Subjects who experience the same event multiple times will be included in the most severe category. Missing severities are not expected, however if these occur they will not be imputed but will be included in relevant summary tables under a missing category.

10.2.2 Relationship to Trial and Routine Vaccinations

In summaries including relationship to trial vaccination and routine vaccinations, the following relationships will be summarized: 'Not Related', 'Related'. Subjects who experience the same event multiple times will be included in the most related category. Missing relationships are not expected, however if these occur they will not be imputed but will be included in relevant summary tables under a missing category.

10.2.3 Solicited Adverse Events

The solicited safety parameters for this study are the injection site reactions of pain, erythema, induration and swelling and the systemic adverse events of drowsiness, irritability/fussiness, loss of appetite, fever (defined as body temperature greater than or equal to 38°C), vomiting and diarrhea.

Solicited reactions will be assessed 30 minutes after administration of each dose of trial vaccine, and then daily for 7 days (including the day of administration).

Body temperature measurements will be summarized in categories (including fever, defined as temperature ≥38°C), without adjustment for the route of measurement. Summaries of the day of first onset of each event and the maximum number of continuous days subjects experienced each event will also be provided.

Any solicited local or systemic reactions observed as continuing beyond 7 days following each trial vaccine dose will be recorded as an AE in the CRF.

Solicited AEs collected daily are entered in diaries by the participants Legally Acceptable Representative (LAR). The site investigator or designee will review the eDiary entries with the LAR and any data deemed to be implausible or incorrect may be updated during this review. The TFLs describe below will use the data entered by the LAR.

10.2.3.1 Summaries

The summaries for solicited AEs will be:

- The number and percentage of subjects with solicited local and systemic reactions during the first 30 minutes after each dose of trial vaccine, overall and by severity.

- The number and percentage of subjects with solicited local and systemic reactions during the first 7 days (including day of administration) after each dose of trial vaccine, overall and by severity (Summaries will be for the time periods of 1-7, 1-3 and 4-7 days after trial vaccine)
- Daily summary of the number and percentage of subjects with solicited local and systemic reactions during the first 7 days (including day of administration) after each dose of trial vaccine overall and by severity
- Summary of the day of first onset of each solicited AE
- Summary of the number of days with each solicited AE within 7 days after each trial vaccination

A horizontal stacked bar plot showing the percentage of participants with each solicited AE, any solicited AE, any solicited injection site reactions, and any solicited systemic AEs after dose 1 and dose 2 will be presented. This plot will break down the percentages by maximum severity, with the percentage of mild, moderate and severe events stacked for each solicited AE.

All solicited AEs will also be listed.

10.2.4 Unsolicited Adverse Events

Unsolicited AEs will be collected up to 28 days after administration of each dose of trial vaccine (including the day of administration). Only unsolicited AEs recorded after the first dose of trial vaccine will be summarised. All AEs will be listed with the timing relative to the first dose indicated.

Any unsolicited AE will be summarized in the following 3 time intervals after each trial vaccine dose visit (Visit 2 and Visit 3):

1) Overall up to 28 days after each dose (including the day of administration)
2) With onset between 1 and 7 days after each dose (including the day of administration)
3) With onset between 8 and 28 days after dose (including the day of administration)

10.2.4.1 Summaries

The summaries for unsolicited AEs will be:

- Overall Overview of the occurrence of all AEs.
- The number and percentage of subjects with any unsolicited AE during the first 28 days (including day of administration) after each dose of trial vaccine overall.
- The number and percentage of subjects with any unsolicited AE during the first 28 days (including day of administration) after each dose of trial vaccine by severity.
- The number and percentage of subjects with any unsolicited AE during the first 28 days (including day of administration) after each dose of trial vaccine by relationship to trial vaccine.
- The number and percentage of subjects with any unsolicited AE during the first 28 days (including day of administration) after each dose of trial vaccine by relationship to trial procedure.

Listings will be presented for all unsolicited AEs.

10.2.5 Serious Adverse Events

10.2.5.1 Summaries

The summaries for SAEs will be:

- The number and percentage of subjects with SAEs during the corresponding collection periods overall
- The number and percentage of subjects with SAEs during the corresponding collection periods by severity
- The number and percentage of subjects with SAEs during the corresponding collection periods by relationship to trial vaccine.
- The number and percentage of subjects with SAEs during the corresponding collection periods by relationship to trial procedure.

All SAEs will be listed.

10.2.6 Medically Attended Adverse Events

Medically Attended Adverse Events (MAAEs) are defined as AEs leading to an unscheduled visit to or by a healthcare professional including visits to an emergency department, but not fulfilling seriousness criteria.

10.2.6.1 Summaries

The summaries for MAAEs will be:

- The number and percentage of subjects with MAAEs during the corresponding collection periods overall
- The number and percentage of subjects with MAAEs during the corresponding collection periods by severity
- The number and percentage of subjects with MAAEs during the corresponding collection periods by relationship to trial vaccine.
- The number and percentage of subjects with MAAEs during the corresponding collection periods by relationship to trial procedure.

All MAAEs will be listed.

10.2.7 Adverse Events Leading to Vaccine or Trial Withdrawal

10.2.7.1 Summaries

The summaries for AEs leading to vaccine or trial withdrawal will be:

- The number and percentage of subjects with AEs leading to vaccine or trial withdrawal, during the corresponding collection periods leading to vaccine or trial withdrawal overall.
- The number and percentage of subjects with AEs leading to vaccine or trial withdrawal, during the corresponding collection periods leading to vaccine or trial withdrawal by severity.

- The number and percentage of subjects with AEs leading to vaccine or trial withdrawal, during the corresponding collection periods leading to vaccine or trial withdrawal by relationship to trial vaccination.

All AEs leading to vaccine or trial withdrawal will be summarised and listed.

10.2.8 Deaths

All AEs that lead to death will be listed by vaccine group.

10.3 Extent of Exposure

All study drug administration details (including date and time, location of administration, and reason for no administration if applicable) will be listed.

The total number of doses each subject received of each childhood vaccination and HIL-214 will be summarised by counts and percentages. The time between doses will also be summarized.

The number and percentage of subjects who fulfil any of the criteria for delay of vaccination will be summarised at each visit along with the criteria that was satisfied.

10.4 Clinical Laboratory Evaluations

There will be no laboratory data collected other than the data needed for the immunogenicity analysis.

10.5 Vital Signs

The vital signs of heart rate and temperature will be summarised descriptively by visit.

Both vital signs parameters will also be listed.

10.6 Physical Characteristics

Age in days, weight (kg), length (cm) and head circumference will be summarised at screening (Visit 1) and randomization (Visit 2). Breastfeeding status will be summarised for all Visits and Calls.

10.7 Physical Examination

Physical examination findings for general appearance, heart and lungs, abdomen, extremities and other at Visit 1 and Visit 2 will be summarised for those that are normal, abnormal or not done.

Physical examination findings for all other visits will be listed only along with findings from Visits 1 and 2.

11 Reporting Conventions

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfil certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is 0, there will be no percentage presented at all
- All other percentage displays will use 1 decimal place

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer
- Mean (arithmetic and geometric), and median will use 1 decimal place more than the original data
- SD will use 2 decimal places more than the original data
- Minimum and maximum will be reported using the same number of decimal places as the original value
- If no subjects have data at a given timepoint, for example, then only n=0 will be presented. However, if n<3, present the n, min and maximum only. If n=3, n, mean, median, minimum and maximum will be presented only; the other descriptive statistics will be left blank.

When reporting estimated statistics from inferential tests and models, the following rules will apply in general:

- Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

12 Technical Details

Statistical evaluation will be performed by Veramed Limited and supervised by the Statistics Department of HilleVax unless otherwise indicated.

The datasets will follow analysis dataset model (ADaM) data specifications and will use the standard data tabulation model (SDTM) data sets. Both SDTMs and ADaMs will be programmed by Veramed.

All analyses will be performed using SAS version 9.2 or higher (SAS Institute, Cary, NC, USA).

13 Summary of Changes to the Protocol

The SAP is based on the latest Protocol which is version 2.0 dated 9th July 2023.

Protocol Version	Summary of Change	Justification for Change
V2.0	The HepB assay will measure Ig and not IgG.	Mistake in the protocol
	A principal stratum strategy will be used to handle lack of compliance with vaccine administration schedule	Strategy change recommended by the FDA, no change to the planned handling of data in these cases.

14 SAP Amendment Details

The following changes were made to this document in version 2.0:

SAP Section	Summary of Change	Justification for Change
5.3.2.2	Table of LLOD's, LLOQ's and ULOQ's for immunogenicity parameters added.	To document the relevant ranges.

7.5.1	Added further clarity on the methods for calculating the differences in percentages and MH CIs using IPW.	For clarity.
	Added IPW approach if insufficient non-missing data are collected in participants with 1 trial vaccination.	To enable the calculation of adjusted proportions if the number of participants for any of t_1 to t_n are 0.
9.2.1.3	Updated supplementary immunogenicity estimands text to refer to secondary endpoints instead of primary endpoints.	Correction of typographical error.
10.2.3	Added paragraph clarifying that LAR data will be presented in TFLs for solicited AEs.	Agreed as the most appropriate approach following review of the available data.
All	A principal stratum strategy will be used to handle lack of compliance with vaccine administration schedule	Strategy change recommended by the FDA, no change to the planned handling of data in these cases.

15 References

[1] Clopper C, Pearson ES (1934). “The use of confidence or fiducial limits illustrated in the case of the binomial”. Biometrika. 26 (4): 404–413.

[2] Miettinen O, Nurminen M. “Comparative analysis of two rates”. Stat Med 1985; 4(2):213-226.

[3] Seaman, Shaun R., and Ian R. White. "Review of inverse probability weighting for dealing with missing data." Statistical methods in medical research 22.3 (2013): 278-295.

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