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

Safety and Immunogenicity of HIL-214 with Routine Pediatric Vaccines

Sponsor:	HilleVax, Inc. 75 State Street, Suite 100 - #9995 Boston, MA 02109, USA
Trial Identifier:	NOR-206
IND Number:	014421 **EudraCT Number:** Not Applicable
Trial Vaccines:	• Norovirus GI.1/GII.4c Bivalent Virus-like Particle Vaccine • Placebo
Protocol Date:	9 July 2023
Version:	Version 2.0

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

The list of contacts will be provided to the/each site.

1.2 Approval

REPRESENTATIVES OF HILLEVAX, Inc.

This trial will be conducted with the highest respect for the individual subjects in accordance with the requirements of this clinical trial protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki [1].
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline [2].
- All applicable laws and regulations, including those related to data privacy and clinical trial disclosure.

SIGNATURES

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure (IB), and any other product information provided by the sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and protect the rights, safety, privacy, and well-being of trial subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki [1].
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), E6 (R2) Good Clinical Practice: Consolidated Guideline [2].
- All applicable laws and regulations, including those related to data privacy and clinical trial disclosure.
- Regulatory requirements for reporting serious adverse events defined in Section 10.4.4 of this protocol.
- Terms outlined in the clinical trial site agreement.
- Appendix A – Responsibilities of the investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix B of this protocol.

_____ _____

Signature of the investigator Date

_____

Investigator name (print or type)

_____

Investigator's title

_____

Location of Facility (City, State)

_____

Location of Facility (Country)

1.3 Summary of Changes

1.3.1 Version History

Date	Version	Change Type	Region
25 January 2023	1.0	Not applicable	Global
9 July 2023	2.0	Non-substantial	Global

1.3.2 Summary of Changes

Summary of changes for protocol amendment 1 dated 9 July 2023 to protocol version 1.0 dated 25 January 2023

Rationale for the amendment:

- Increase of the Visit 1 (age 2 months) window from +14 days to +28 days to facilitate enrollment.

Section	Description of Change	Rationale for Change
2.0	Various changes	Consistent with the body of the protocol.
2.1	Adjustments to the trial design diagram	Increased window at Visit 1 from +14 days to +28 days.
2.2	Adjustment to the schedule of trial procedures	Increased window at Visit 1 from +14 days to +28 days.
4.2	The rationale for administration of HIL-214 to infants 4 months (+~~14~~7 days) of age at the time of initial trial vaccine administration is based on epidemiological data which shows that the risk of norovirus AGE increases in infants aged ~6 months old [14]; the rationale for inclusion of infants 2 months (+~~14~~***28*** days) of age at enrolment is that infants also receive the required routine childhood vaccines in the participating countries at this age as per national guidelines.	Clarification.
	'This phase 2 trial aims … (+~~14~~***28*** days) … the planned phase 3 HIL-214 efficacy trial.'	Clarification.
5.1.3	'…unsolicited AEs (for 28 days [including day of administration] after each dose of trial vaccine ***and routine vaccine***), serious adverse events (SAEs) and AEs leading to trial withdrawal (from first dose of trial vaccine to 12 months of age), medically-attended adverse events (MAAEs;…'	Clarification.
5.2.3	• Occurrence (yes/no) of any unsolicited AE during the first 28 days (including day of administration) after each dose of trial vaccine ***and routine vaccine***, overall, by severity and by relatedness.	Clarification.
6.1	~~Up to~~ ***Approximately*** 400 subjects (infants aged 2 months [+~~14~~***28*** days]) will be enrolled and randomized (1:1) to two arms by interactive response technology (IRT) (Table 6.1):	Clarification.
	• All subjects will be followed for solicited local and systemic reactions up to 7 days (including day of administration) after each dose of trial vaccine and unsolicited AEs up to 28 days	Clarification.

	(including day of administration) after each dose of trial vaccine ***and routine vaccine***.	
6.2	'This trial, NOR-206 will evaluate …. Solicited ~~and unsolicited~~ events will only be collected for the trial vaccines.'	Clarification.
7.1	1. The subject is aged 2 months (+~~14~~***28*** days).	Clarification.
7.3	~~After enrollment, s~~***S***ubjects may encounter clinical circumstances that warrant a delay in the administration of a trial vaccine. These situations are listed below. In the event that a subject meets a criterion for delay of trial vaccine administration, the subject may receive the trial vaccine once the window for delay has passed as long as the subject is otherwise eligible for trial participation.	Clarification.
8.4	Table 8.1: Dose and Regimen	Clarification for the route of administration of RV1.
8.7	This is a randomized, double-blind trial as from Visit 2 (trial vaccine administration). The subjects***'s LAR***, data collectors (e.g., investigator)	Clarification.
9.1.5	~~During the physical examination, a subject should have their v~~***V***ital signs measured~~. These~~ will include heart rate and body temperature.	Clarification.
9.1.6	All samples must be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken at Visit 2 is ~~approximately~~ 4 mL and at Visit 4 is ~~approximately~~ 6 mL, and the total ~~approximate~~ volume of blood for the trial is maximum 10 mL.	Clarification.
9.3.3	The following post-vaccination procedures will be performed at Visit~~s 1,~~ 2 ~~and 3~~:	Clarification.
	• Any data that are identified as implausible or incorrect and confirmed by the subject's LAR to be an error, should be corrected by ~~the subject's LAR~~***investigator/designee*** ~~on the eDiary~~ within the allowed ***review*** time. • Starting on the day of trial vaccine administration, the subject's LAR will check for specific types of events at the injection site on the RIGHT thigh, any specific generalized symptoms (solicited systemic reactions), body temperature (rectal or axillary), any other symptoms or change in the subject's health status, and any medications given to the subject (excluding vitamins and minerals). These solicited reactions and body temperature~~, and other symptoms and medications~~ will be recorded in the eDiary. ***Other symptoms and medications will be recorded in the memory aid section of the eDiary. Measurements*** ~~Assessments~~ should preferably take place in the evening. • Temperature measurement is to be performed ***daily*** using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject's LAR should check their temperature. If the subject has a fever, the highest body temperature observed that day should be recorded on the eDiary.	

	• The ***subject's LAR should use*** ~~measurements of solicited local reactions are to be performed using~~ the ruler provided by the site ***to measure the solicited local reactions***. • The collection on the eDiary of body temperature, solicited local and systemic reactions will continue for a total of 7 days (including day of administration) after each trial vaccine administration (Visits 2 and 3). The ~~collection~~ ***recording*** ~~on the eDiary~~ of ***other symptoms*** ~~unsolicited AEs~~ and concomitant medications ***in the memory aid section of the eDiary*** will continue for 28 days (including day of administration) after trial vaccine administration. The site staff should schedule the next trial activity reminder call***/message*** or visit. The ***site staff will provide*** ~~subject's LAR will receive~~ a written reminder of the next planned trial activity ***to the subject's LAR***. ***The site staff will remind the*** subject's LAR ~~will be reminded~~ to complete the eDiary daily ~~(~~up to Day 7 ***after each trial vaccine administration),*** ~~then~~ ***and to record other symptoms and concomitant medications in the memory aid section of the eDiary as needed (***up to Day 28 ***after each trial vaccine administration),*** ~~and~~ to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject's LAR.	
9.3.4	Post-vaccination phone calls will be performed 7 days post each dose of trial vaccine (Call 1 at 7 days after Visit 2, and Call 2 at 7 days after Visit 3). The purpose is to ~~remind~~ ***review the completed eDiary with*** the subject's LAR ~~about completion of the eDiary~~. If the subject's LAR wishes to describe safety information, this information should only be collected by a trained healthcare professional at the site, and the safety data described must be recorded in source documents. The subject's LAR should be reminded to ***continue*** record***ing*** the information ***about other symptoms and concomitant medications*** in the ***memory aid section of the*** eDiary and to contact the site via the telephone number provided in the ICF to discuss medical questions.	Clarification.
9.3.5	A site visit that does not include a trial vaccine administration will occur when the subject is approximately 7 months old (Visit 4) ~~and 12 months old (Visit 5)~~. Procedures include targeted physical examination, vital signs, eDiary ***memory aid*** review and blood …that leads to a hospitalization or an emergency room visit.'	Clarification.
10.1.5	5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT in the offspring of a subject ***(not applicable)***.	Clarification.
10.2	Relationship (causality) to the trial vaccine will also be assessed by the investigator. The relationship of each unsolicited AE to the trial vaccine ***and routine vaccine*** will be assessed using the following categories:	Clarification.

10.4.1	SAE reporting will be done with an SAE form ~~emailed~~ ***sent to*** [redacted]	Procedures adjusted in-line with the provider procedures.
10.4.4	[redacted]	Procedures adjusted in-line with the provider procedures.
13.1.3	Any unsolicited AEs, SAEs, MAAEs, and AEs leading to trial vaccine***, routine vaccine*** or trial withdrawal, will be coded using MedDRA, and summarized by system organ class (SOC) and preferred term (PT) using number and percentage of subjects with an AE. Subjects with more than one occurrence for the term will be counted only once for this term. Unsolicited AEs will be collected up to 28 days after administration of each dose of trial vaccine ***and routine vaccine*** (including the day of administration); summaries will also be provided by event severity (mild, moderate, severe) and relationship (not related, related) to trial vaccine***, routine vaccine*** or trial procedures. For subjects with more than one AE within an SOC or a PT, the AE with the maximum severity or strongest relationship within each SOC and each PT will be included in the summaries by severity or relationship, respectively.	Clarification.
13.2	~~Trial objectives will be evaluated in two steps:~~ ~~• Primary analysis: A snapshot of the database will be taken after Visit 4 to evaluate the primary immunogenicity objective and analyze the safety data collected up to this visit. Depending on data availability, the secondary immunogenicity objective may also be evaluated at this time point.~~ ~~• Final analysis: After the end of the trial (Visit 5), final database lock will be performed and safety data collected up to the end of trial will be summarized.~~ ***Interim*** Analysis ***No interim analysis is planned for this trial.***	Adjustment to reflect there will be no interim analysis.
All	Minor editorial changes.	For consistency

[redacted]

TABLE OF CONTENTS

List of In-Text Tables

List of Appendices

2.0 TRIAL SUMMARY

Name of Sponsors: HilleVax, Inc. 75 State Street, Suite 100 - #9995 Boston, MA 02109, USA		**Product Name:** HIL-214
Trial 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		
IND No.: 014421		**EudraCT No.:** Not applicable
Trial Identifier: NOR-206	**Phase:** 2	**Blinding Schema:** Double-blind
Indication: Prevention of norovirus-associated acute gastroenteritis		

Background and Rationale:

Noroviruses are single-stranded, positive-sense RNA viruses that contain a non-segmented RNA genome and comprise a genetically diverse family consisting of at least 10 genogroups, 5 of which (GI, GII, GIV, GVIII and GIX) cause human disease. Some norovirus strains drift from year to year, and although both GI and GII and numerous genotypes are reported, genotype II.4 (GII.4) causes the vast majority of norovirus cases in children worldwide, including Latin America, where this trial will be primarily performed. Epidemiologic studies have shown that gastroenteritis in infants is associated with several viruses, including norovirus, sapovirus and rotavirus. These viruses together or individually can be associated with illness ranging from asymptomatic to serious. Asymptomatic infection can create a reservoir, allowing further spread of the virus, whereas serious illness can lead to death, particularly in the very young, very old or immunocompromised. As the burden of rotavirus in children decreases due to successful rotavirus vaccination programs in infants, norovirus infections are increasingly recognized as the primary cause of acute gastroenteritis (AGE) in many countries around the world. Currently, there is no available vaccine to counter the disease burden associated with norovirus. Vaccinating at an early age would reduce the severe illness in young children and also reduce the asymptomatic cases which act as a vehicle for transmission within the population. As infants already receive multiple vaccines during the first months of life, an additional vaccination must fit into the immunization scheme in a convenient way for compliance. It must also have an acceptable safety profile, and be immunogenic without interfering with the immune response to routine childhood vaccines.

The investigational vaccine, HIL-214 (previously called TAK-214), contains GI.1 virus-like particles (VLPs) and norovirus GII.4 consensus VLPs (GII.4c) which represents a consensus sequence of 3 GII.4 strains, as antigens. Norovirus VLPs are non-infectious because they do not contain viral RNA but are immunogenic because they preserve particulate antigen conformation and structure that mimic the functional interactions of the virus with cellular receptors. The investigational vaccine used in this trial is adjuvanted with aluminum as aluminum hydroxide [$Al(OH)_3$]. The composition and 2-dose regimen of HIL-214 (50/150 µg GI.I/GII.4c) to be used in this phase 2 trial is based on the results of trial NOR-202, a phase 2 dose-finding, safety and immunogenicity trial which enrolled 840 children aged 6 weeks to <9 years. The results of trial NOR-202 show that HIL-214 is immunogenic and had a generally good safety profile in children aged 6 weeks to <9 years for all GI.1/GII.4c VLP compositions adjuvanted with 500 µg of aluminum as $Al(OH)_3$ as (1) a one or two-dose regimen in infants aged 6 to 12 months, and (2) as a two or three-dose regimen in infants aged 6 weeks to <6 months for the same composition. So far, up to 4531 healthy participants have received different compositions of HIL-214, including 3692 adults >18 years old and 839 children aged 6 weeks to less than 9 years.

The rationale for administration of HIL-214 to infants 4 months (+7 days) of age at the time of initial trial vaccine administration is based on epidemiological data which shows that the risk of norovirus AGE increases in infants aged ~6 months old; the rationale for inclusion of infants 2 months (+28 days) of age at enrolment is that infants also receive the required routine childhood vaccines in the participating countries at this age as per national guidelines.

This phase 2 trial aims to evaluate the immune response to routine pediatric vaccines (diphtheria [DT] and tetanus toxoid [TT] and acellular pertussis [aP] adsorbed, hepatitis B [HepB], inactivated polio vaccine

[IPV], and *Haemophilus influenzae* type b [Hib] or DTaP-Hib-IPV-HepB, rotavirus [RV1], and pneumococcal conjugate [PCV13] vaccines) when co-administered with HIL-214 at 4 and 6 months of age, compared to that of the routine pediatric vaccines co-administered with placebo. Infants will be enrolled at the age of 2 months (+28 days) and will receive their routine childhood vaccines as part of the trial at 2, 4 and 6 months of age. HIL-214 will be administered as a 2-dose regimen, the first one when the child is 4 months of age and the second one when the child is 6 months of age, concomitantly with routine pediatric vaccines. The second trial arm will receive the routine childhood vaccines, co-administered with placebo at the age of 4 and 6 months. A placebo arm is included to allow an unbiased evaluation of the immunogenicity and safety of HIL-214 when administered with routine pediatric vaccines. A target number of at least 100 subjects will be recruited in the US to obtain co-administration data for this population. This trial is designed to support the concomitant administration of routine pediatric vaccines during the planned phase 3 HIL-214 efficacy trial.

This phase 2 trial will be conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines, and applicable regulatory requirements.

Primary Objectives:

Primary immunogenicity objective:

- 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.

Secondary Objective:

Secondary immunogenicity objective:

- 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.

Safety objective:

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.

Primary Endpoints and Estimands:

Primary immunogenicity estimand:

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 immunoglobulin G (IgG) concentration ≥0.1 IU/mL.
- Binary variable indicating anti-TT IgG concentration ≥0.1 IU/mL.
- Anti-pertussis (filamentous hemagglutinin [FHA], pertactin [PRN] and pertussis toxin [PTX]) IgG concentrations.
- Binary variable indicating anti-poliovirus neutralizing antibody titers ≥1:8, for poliovirus types 1, 2 and 3.
- Binary variable indicating anti-*Haemophilus influenzae* type b unconjugated capsular polysaccharide (PRP) IgG concentration ≥0.15 µg/mL.
- Binary variable indicating anti-hepatitis b surface antigen (HBsAg) IgG 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 IgG 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.

Intercurrent event strategies:

In the primary immunogenicity estimands, lack of compliance with vaccine administration schedule (both for routine vaccines and trial vaccine) will be handled using a hypothetical strategy, i.e., as if all subjects could adhere to the schedule. 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).

Secondary Endpoints and Estimands:

Secondary immunogenicity estimand:

Population:

Same as for the primary immunogenicity estimand.

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.

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

Safety Estimand:

Population:

Same as for the primary immunogenicity estimand.

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 and routine 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.

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.

Trial Design:

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.

Approximately 400 subjects (infants aged 2 months [+28 days]) will be enrolled and randomized (1:1) to two arms by interactive response technology (IRT) (**Table S1**):

- **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.

Table S1: Timing of Routine Vaccine and HIL-214 Administration

	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	

Trial procedures:

- Randomization will occur prior to trial vaccine administration (Visit 2).
- All subjects will be followed for solicited local and systemic reactions up to 7 days (including day of administration) after each dose of trial vaccine and unsolicited adverse events (AEs) up to 28 days (including day of administration) after each dose of trial vaccine and routine vaccine.
- All subjects will be followed for AEs leading to trial vaccine withdrawal (from Visit 2 to Visit 3).
- All subjects will be followed for medically-attended AEs (MAAEs), and serious adverse events (SAEs) and AEs leading to trial withdrawal throughout the trial.
- Solicited local and systemic reactions will be recorded by the subject's legally-authorized representative (LAR) in an electronic diary (eDiary).
- 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-pertussis IgG (FHA, PRN, and PTX), PRP IgG, HbsAg IgG, anti-polio 1, 2 and 3 neutralizing antibodies [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. • All subjects will have up to 5 visits. • The subject's LAR will have two safety phone contacts (7 days after each dose of trial vaccine; Call 1 will be 7 days after Visit 2 and Call 2 will be 7 days after Visit 3). • All subjects will be followed-up for 6 months after the last dose of trial vaccine (Visit 3) for safety. The trial design diagram is shown in Section 2.1. The schedule of procedures is shown in Section 2.2.
Subject Population: *Healthy Subjects*: Yes. *Age Range*: 2 months (+28 days). *Planned Number of Subjects*: 400. *Planned Number of Trial Arms:* 2 (HIL-214+Routine Vaccines [N=200] and Placebo+Routine Vaccines [N=200]).
Inclusion Criteria: • The subject is aged 2 months (+28 days). • Male or female. • Infants who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator. • The subject's LAR signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements. • Infants whose LARs can and are willing to comply with trial procedures and are available for the duration of follow-up.
Exclusion Criteria: • Clinically significant abnormality in growth by height, weight, or head circumference (according to local guidelines). • Gastrointestinal abnormalities or any chronic gastrointestinal disease, including any uncorrected congenital malformation of the gastrointestinal tract according to medical history and/or physical examination. • Known hypersensitivity or allergy to any of the investigational vaccine components (including excipients). • Severe reaction to routine childhood vaccine(s) administered at Visit 1. • Any clinically significant active infection (as assessed by the investigator) or temperature ≥38.0°C (>100.4°F), within 3 days of intended trial vaccination. • Any serious chronic or progressive disease according to the judgment of the investigator (e.g., cardiac, renal or hepatic disease). • Individuals with history of, e.g., convulsions/febrile convulsions, or any illness, that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial. • Known or suspected impairment/alteration of immune function. • Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time. • Subjects who received or are scheduled to receive any licensed or authorized vaccines not planned in this trial within 14 days (for inactivated vaccines) or within 28 days (for live vaccines) before or after

any dose of trial vaccine. Note: Flu and/or COVID vaccine can be administered per local guidelines at any time during the trial.
- Subjects participating in any clinical trial with another investigational product 30 days prior to first trial visit or due to participate in another clinical trial at any time during the conduct of this trial.
- Subjects known to be positive for or in evaluation for possible human immunodeficiency virus infection.
- Subject's LAR or subject's first-degree relatives involved in the trial conduct.

Investigational Vaccine, Placebo and Co-administered Vaccines:

Investigational vaccine: HIL-214 for injection is provided by the sponsor in single dose 1 mL pre-filled syringes as a 0.65 mL volume (to deliver a 0.5 mL dose). The investigational vaccine contains 50 µg GI.1/150 µg GII.4c VLPs and 500 µg of aluminum as $Al(OH)_3$.

Placebo: 0.9% sodium chloride (NaCl, saline) for injection is provided by the sponsor, or designated vendor in a container allowing delivery of a 0.5 mL dose. The placebo does not contain any preservatives.

Co-administered vaccines: DTaP-Hib-IPV-HepB, PCV13 and RV1 will be administered according to the manufacturer's instructions for dosing regimen and route of administration. Parenterally-administered (co-administered) vaccines will be administered in the LEFT thigh. Multiple injections in the same thigh must be adequately spaced (at least 2.5 cm apart).

Route of administration for HIL-214 and Placebo: Intramuscular (IM) injection (anterolateral RIGHT thigh).

Planned Duration of Subject Participation:

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

Statistical Considerations:

Analysis of demographics and baseline characteristics:

Age, sex, and other demographic and baseline characteristics will be summarized descriptively, by trial arm and overall. Continuous variables will be summarized using mean, standard deviation, median, minimum and maximum values. For categorical variables, count and percentage of subjects in each category will be computed. Summaries will be provided for all sets of subjects used to evaluate immunogenicity and safety objectives, reflecting intercurrent event strategies.

Immunogenicity analyses:

Immunogenicity data will be summarized by trial arm, for each licensed vaccine and corresponding immunogenicity assay, at all relevant time points, using:

- GMTs or GMCs and GMFR (as applicable) with 95% confidence interval (CI), geometric standard deviation (GSD), and minimum and maximum values, and
- Count and percentage of subjects with antibody titers/concentrations over pre-defined threshold, count and percentage of subjects achieving seroresponse to HIL-214, and 95% CIs for the percentages, computed using exact Clopper-Pearson method.

Assessment of primary objectives:

The primary immunogenicity objective will be assessed using 95% CIs for differences in proportion of subjects with antibody concentrations/titers above a pre-specified threshold, computed by the Miettinen and Nurminen method, and 95% CIs for the geometric mean ratios, computed using the analysis of variance (ANOVA) model with natural logarithm of antibody titer/concentration as the response variable and trial arm as factor. Analyses will be done by licensed vaccine; for those vaccines used in more than one country, analyses will be repeated by country.

To address non-compliance with the vaccine administration schedule, a hypothetical strategy will be used under the assumption that lack of compliance is not related to the immune response to the routine pediatric vaccines and therefore, that infants who were not compliant with the vaccination schedule do not differ from the infants who did comply with regard to their immune response measurements. Hence, the primary immunogenicity analysis will be based on infants who were compliant with the vaccine administration schedule (i.e. received all doses of routine vaccines and trial vaccine within the allowed windows). According to the treatment policy strategy, blood sample results obtained after use of concomitant medications or other vaccines will be included in the analysis. Handling of missing data resulting from

missing blood draws, non-evaluable samples (not enough volume), and blood draws outside the window will be described in the SAP.

Safety analyses:

All safety summaries will be provided for each trial arm and overall.

Solicited reactions:

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). For each solicited reaction, the number and percentage of subjects who experienced an event will be computed, for each day from Day 1 to Day 7 post-dose (including the day of dose) and overall.

Solicited reactions will be summarized by severity. For subjects with more than 1 episode of the same event within an interval, the maximum severity will be used for tabulations.

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 number of days subjects experienced each event will also be provided.

Data from the 30 minutes assessment of solicited reactions immediately post-vaccination will be summarized separately.

Unsolicited AEs:

Any unsolicited AEs, SAEs, MAAEs, and AEs leading to trial vaccine, routine vaccine or trial withdrawal, will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized by system organ class (SOC) and preferred term (PT) using number and percentage of subjects with an AE. Subjects with more than one occurrence for the term will be counted only once for this term. Unsolicited AEs will be collected up to 28 days after administration of each dose of trial vaccine and routine vaccine (including the day of administration); summaries will also be provided by event severity (mild, moderate, severe) and relationship (not related, related) to trial vaccine, routine vaccine or trial procedures. For subjects with more than one AE within an SOC or a PT, the AE with the maximum severity or strongest relationship within each SOC and each PT will be included in the summaries by severity or relationship, respectively.

Any unsolicited AEs will be summarized in the following 3 time intervals: 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), and 3) with onset between 8 and 28 days after dose (including the day of administration).

AEs leading to trial vaccine withdrawal, collected up to the planned time of the second dose administration, and SAEs, MAAEs and AEs leading to withdrawal from the trial, collected throughout the trial, will be summarized up to 28 days after the second dose, and for the overall trial period.

Sample Size Justification:

This trial is designed to be descriptive, and therefore the sample size was not determined based on formal statistical power calculations.

Interim Analysis:

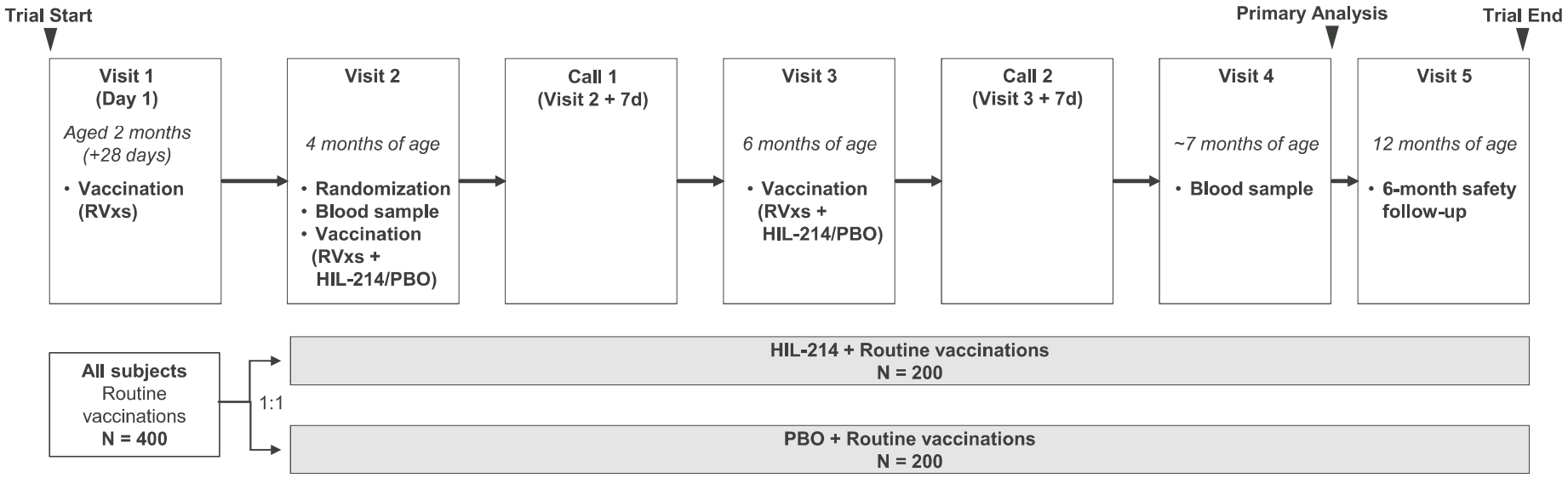
No interim analysis is planned for this trial.

Data Monitoring Committee:

An independent data monitoring committee (DMC) has been established for the HIL-214 clinical development program. The role and responsibilities of the DMC are presented in the DMC charter.

NOR-206 Version 2.0 (9 July 2023)

2.1 Trial Design Diagram



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

2.2 Schedule of Trial Procedures

	Visit 1	Visit 2	Call 1	Visit 3	Call 2	Visit 4	Visit 5
Participant age	2m	4m		6m		7m	12m[a]
Timing	0	0	V2+7d	V2+2m	V3+7d	V3+28d	V4+5m
Window (days)	+28	+7	+2	±7	+2	+7	+14
Procedure							
Signed informed consent[b]	X						
Assessment of eligibility criteria[c]	X	X		X			
Assessment of criteria for delay of vaccination[d]	X	X		X			
Demography	X						
Medical history[e]	X						
Medication/Vaccination history	X	X		X		X	
Randomization		X					
Documentation of trial entrance	X						
Physical examination[f]	X	X		X		X	X
Vital signs[g]	X	X		X		X	
Blood draw[h]		X				X	
Trial vaccine administration[i]		X		X			
Routine vaccine administration[j]	X	X		X			
eDiary training[k]		X					
Solicited reactions[l]		X	X	X	X		
Solicited eDiary review			X		X		
Unsolicited AEs[m]		X	X	X	X	X	
Concomitant medications and other vaccines	X	X	X	X	X	X	X
AEs leading to trial vaccine withdrawal		From Visit 2 to Visit 3					
MAAEs	Throughout the trial						
SAEs[n]	Throughout the trial						
AEs leading to withdrawal from trial	Throughout the trial						

Abbreviations: AEs, adverse events; d, day; ICF, informed consent form; LAR, legally-authorized representative; m, month; MAAEs, medically-attended adverse events; SAEs, serious adverse events. Footnotes are on the following page.

Footnotes:

(a) Corresponds to 6 months post-dose 2 of trial vaccine. 1 month corresponds to 30.4375 days.
(b) The subject randomization visit is scheduled 2 months after screening.
(c) Eligibility by review of all exclusion criteria or contraindications will be documented before routine or trial vaccine administration at Visits 1, 2 and 3.
(d) Review of criteria for delay of trial or routine vaccine administration will be documented before routine or trial vaccine administration at Visits 1, 2 and 3.
(e) At each of the visits or phone contacts, the investigator should ask and record whether the child is being breastfed or not.
(f) Complete physical examination will be performed for all subjects at trial entry (age 2 months), prior to routine childhood vaccine administration, and again at Visit 2 (age 4 months), prior to trial vaccine administration, according to the investigator's standard practice. Complete physical examination includes a check of general appearance, auscultation of heart and lungs, palpation of the abdomen, and inspection of extremities (including skin over the intended injection site), and measuring of weight, height/length, and head circumference. A symptom-directed physical examination may be performed if deemed necessary.
(g) Vital signs (heart rate and temperature) prior to vaccination at Visit 1, Visit 2 and Visit 3 and at when the child reaches 7 months of age (Visit 4).
(h) The maximum volume of blood taken at Visit 2 is 4 mL and at Visit 4 is 6 mL, and the total volume of blood taken during the trial is maximum 10 mL for all subjects. Samples will be taken for all subjects prior to trial or routine vaccine administration.
(i) The first dose of trial vaccine is administered at Visit 2 (subject aged 4 months) and the second dose at Visit 3 (subject aged 6 months). Trial vaccine is to be administered in the RIGHT thigh.
(j) Routine vaccines are to be administered in the LEFT thigh.
(k) Careful training of the subject's LAR on how to measure solicited local and systemic reactions and body temperature, and how often to complete the eDiary.
(l) Solicited local and systemic reactions for 7 days (including day of administration) after each trial vaccine dose administration will be recorded on the eDiary by the subject's LAR.
(m) Unsolicited AEs and concomitant medications and (other) vaccination will be collected for up to 28 days (including day of administration) after each trial vaccine and routine vaccine dose.
(n) SAEs must be reported to the sponsor as soon as possible but within 24 hours of the investigator becoming aware of the event.

Table 2.1 Intervals Between Visits

	Interval	Window (days)
Visit 2 to Call 1	7 days	+2
Visit 2 to Visit 3	2 months	±7
Visit 3 to Call 2	7 days	+2
Visit 3 to Visit 4	28 days	+7
Visit 4 to Visit 5	5 months	+14

Note: The first dose of trial vaccine is administered at Visit 2 (subject aged 4 months) and the second dose at Visit 3 (subject aged 6 months).

3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-Related Responsibilities

The sponsor will perform all trial-related activities with the exception of those identified in the trial-related responsibilities form. The vendors identified in the template for specific trial-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigators and Coordinating Investigator

Selection criteria for the principal investigators and coordinating investigators will include significant knowledge of the trial protocol, the investigational vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. The sponsor will select one or more signatories from the investigators who participate in the trial. The signatory investigator(s) will be required to review and sign the clinical protocol. The signatory investigator(s) will also be required to review and sign the clinical study report (CSR) and by doing so agree(s) that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	adverse event
AESI	adverse events of special interest
AGE	acute gastroenteritis
$Al(OH)_3$	aluminum hydroxide
ANOVA	analysis of variance
CFR	Code of Federal Regulations
CI	confidence interval
CSR	clinical study report
CTM	clinical trial material
DMC	data monitoring committee
DT	diphtheria toxoid
DTaP-Hib-IPV-HepB	diphtheria, tetanus, acellular pertussis adsorbed, *Haemophilus influenzae* type b, poliovirus and hepatitis B vaccine
eCRF	electronic case report form
eDiary	electronic diary
FHA	filamentous hemagglutinin
GCP	good clinical practice
GI.1/GII.4	genotype GII.4
GII.4c	GII.4 consensus
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
GSD	geometric standard deviation
HBGA	histo-blood group antigen
HBsAg	hepatitis B surface antigen
Hib	*Haemophilus influenzae* type b
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig	immunoglobulin
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
LAR	legally acceptable representative
MAAE	Medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
PCV13	pneumococcal conjugate vaccine
PRN	pertactin

PRP	unconjugated capsular polysaccharide
PT	Preferred Term
PTX	pertussis toxin
QTL	quality tolerance limit
RV1	rotavirus vaccine
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
TT	tetanus toxoid
VLP	virus-like particles
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Noroviruses are single-stranded, positive-sense RNA viruses that contain a non-segmented RNA genome and comprise a genetically diverse family consisting of at least 10 genogroups, 5 of which (GI, GII, GIV, GVIII and GIX) cause human disease [3-5]. Some norovirus strains drift from year to year, and although both GI and GII and numerous genotypes are reported, genotype II.4 (GII.4) causes the vast majority of norovirus cases in children worldwide, including Latin America, where this trial will be primarily performed [6-9]. Epidemiologic studies have shown that gastroenteritis in infants is associated with several viruses, including norovirus, sapovirus and rotavirus [10]. These viruses together or individually can be associated with illness ranging from asymptomatic to serious. Asymptomatic infection can create a reservoir, allowing further spread of the virus, whereas serious illness can lead to death, particularly in the very young, very old or immunocompromised. As the burden of rotavirus in children decreases due to successful rotavirus vaccination programs in infants, norovirus infections are increasingly recognized as the primary cause of acute gastroenteritis (AGE) in many countries around the world [11-12]. Currently, there is no available vaccine to counter the disease burden associated with norovirus. Vaccinating at an early age would reduce the severe illness in young children and also reduce the asymptomatic cases which act as a vehicle for transmission within the population. As infants already receive multiple vaccines during the first months of life, an additional vaccination must fit into the immunization scheme in a convenient way for compliance. It must also have an acceptable safety profile, and be immunogenic without interfering with the immune response to routine childhood vaccines.

The investigational vaccine, HIL-214 (previously called TAK-214), contains GI.1 virus-like particles (VLPs) and norovirus GII.4 consensus VLPs (GII.4c) which represents a consensus sequence of 3 GII.4 strains, as antigens. Norovirus VLPs are non-infectious because they do not contain viral RNA but are immunogenic because they preserve particulate antigen conformation and structure that mimic the functional interactions of the virus with cellular receptors. The investigational vaccine used in this trial is adjuvanted with aluminum as aluminum hydroxide [$Al(OH)_3$].

The composition and 2-dose regimen of HIL-214 (50/150 µg GI.I/GII.4c) to be used in this phase 2 trial is based on the results of trial NOR-202, a phase 2 dose-finding, safety and immunogenicity trial which enrolled 840 children aged 6 weeks to <9 years [13]. The results of trial NOR-202 show that HIL-214 is immunogenic and had a generally good safety profile in children aged 6 weeks to <9 years for all GI.1/GII.4c VLP compositions adjuvanted with 500 µg of aluminum as $Al(OH)_3$ as (1) a one or two-dose regimen in infants aged 6 to 12 months, and (2) as a two or three-dose regimen in infants aged 6 weeks to <6 months for the same composition. So far, up to 4531 healthy participants have received different compositions of HIL-214, including 3692 adults >18 years old and 839 children aged 6 weeks to less than 9 years.

More detailed information about the known and expected benefits and risks, and the reasonably expected adverse events (AEs) of the investigational vaccine can be found in the current investigator's brochure (IB).

4.2 Rationale for the Proposed Trial

The rationale for administration of HIL-214 to infants 4 months (+7 days) of age at the time of initial trial vaccine administration is based on epidemiological data which shows that the risk of norovirus AGE increases in infants aged ~6 months old [14]; the rationale for inclusion of infants 2 months (+28 days) of age at enrolment is that infants also receive the required routine childhood vaccines in the participating countries at this age as per national guidelines.

This phase 2 trial aims to evaluate the immune response to routine pediatric vaccines (diphtheria [DT] and tetanus toxoid [TT] and acellular pertussis [aP] adsorbed, hepatitis B [HepB], inactivated polio vaccine [IPV], and *Haemophilus influenzae* type b [Hib] or DTaP-Hib-IPV-HepB, rotavirus [RV1], and pneumococcal conjugate [PCV13] vaccines) when co-administered with HIL-214 at 4 and 6 months of age, compared to that of the routine pediatric vaccines co-administered with placebo. Infants will be enrolled at the age of 2 months (+28 days) and will receive their routine childhood vaccines as part of the trial at 2, 4 and 6 months of age. HIL-214 will be administered as a 2-dose regimen, the first one when the child is 4 months of age and the second one when the child is 6 months of age, concomitantly with routine pediatric vaccines. The second trial arm will receive the routine childhood vaccines, co-administered with placebo at the age of 4 and 6 months. A placebo arm is included to allow an unbiased evaluation of the immunogenicity and safety of HIL-214 when administered with routine pediatric vaccines. A target number of at least 100 subjects will be recruited in the US to obtain co-administration data for this population. This trial is designed to support the concomitant administration of routine pediatric vaccines during the planned phase 3 HIL-214 efficacy trial.

This phase 2 trial will be conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) Guidelines, and applicable regulatory requirements [2].

5.0 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS

The trial objectives, endpoints and estimands are listed in Section 5.1 and Section 5.2.

This section presents trial objectives and estimands, which identify the target of estimation to answer the clinical question of interest for each objective.

An estimand describes a clinically meaningful effect of vaccination on the population level and contains the following attributes:

- Description of the population (individuals targeted by the clinical question).
- Vaccination regimen.
- Variable (endpoint: the value that has to be obtained for each trial participant in order to address the clinical question of interest).
- Population level summary of this variable.
- Strategies to handle intercurrent events (events occurring after vaccination which affect either the interpretation or the existence of the measurements associated with the clinical question of interest).

5.1 Objectives

Trial NOR-206 has primary (Section 5.1.1) and secondary immunogenicity objectives (Section 5.1.2), and a safety objective (Section 5.1.3).

5.1.1 Primary Immunogenicity Objective

The primary objective 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.

This objective will be assessed using measurements of immune response to the concomitant vaccines (anti-DT immunoglobulin G [IgG], anti-TT IgG, anti-pertussis IgG (filamentous hemagglutinin [FHA], pertactin [PRN], and toxoid [PTX]), anti-*Haemophilus influenzae* type b (unconjugated capsular polysaccharide [PRP]) IgG, anti-hepatitis B surface antigen [HBsAg] IgG, anti-polio 1, 2 and 3 neutralizing antibodies [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) at Visit 4 (28 days post-dose 2).

5.1.2 Secondary Immunogenicity Objective

The secondary immunogenicity objective 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.

This objective will be assessed using measurements of anti-norovirus (GI.1 and GII.4c) HBGA blocking antibodies at Visit 2 (subjects aged 4 months) and Visit 4 (28 days post-dose 2).

5.1.3 Safety Objective

The safety objective 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.

This objective will be assessed using data collected for the solicited reactions (AEs; for 7 days [including day of administration] after each dose of trial vaccine), unsolicited AEs (for 28 days [including day of administration] after each dose of trial vaccine and routine vaccine), serious adverse events (SAEs) and AEs leading to trial withdrawal (from first dose of trial vaccine to 12 months of age), medically-attended adverse events (MAAEs; from first dose of trial vaccine to 28 days post-dose 2) and AEs leading to vaccine withdrawal (from first dose of trial vaccine to planned administration of the second dose at 6 months of age).

5.2 Endpoints and Estimands

Trial NOR-206 has primary (Section 5.1.1) and secondary (Section 5.1.2) endpoints and estimands.

5.2.1 Primary Endpoints and Estimands

Primary immunogenicity estimand:

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 IgG 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 IgG 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.

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 hypothetical strategy, i.e., as if all subjects adhere to the schedule. 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).

5.2.2 Secondary Endpoints and Estimands

Secondary estimand (immunogenicity):

Population:

Same as for the primary immunogenicity estimand.

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.

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 estimand.

5.2.3 Safety Endpoints and Estimand

Population:

Same as for the primary immunogenicity estimand.

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 and routine 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.

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.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

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.

Approximately 400 subjects (infants aged 2 months [+28 days]) will be enrolled and randomized (1:1) to two arms by interactive response technology (IRT) (Table 6.1):

- **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.

Table 6.1 Timing of Routine Vaccine and HIL-214 Administration

	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	

Trial procedures:

- Randomization will occur prior to trial vaccine administration (Visit 2).
- All subjects will be followed for solicited local and systemic reactions up to 7 days (including day of administration) after each dose of trial vaccine and unsolicited AEs up to 28 days (including day of administration) after each dose of trial vaccine and routine vaccine.
- All subjects will be followed for AEs leading to trial vaccine withdrawal (from Visit 2 to Visit 3).
- All subjects will be followed for MAAEs, and SAEs and AEs leading to trial withdrawal throughout the trial.
- Solicited local and systemic reactions will be recorded by the subject's legally-authorized representative (LAR) in an electronic diary (eDiary).
- 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 IgG, 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.

- All subjects will have up to 5 visits.
- The subject's LAR will have two safety phone contacts (7 days after each dose of trial vaccine; Call 1 will be 7 days after Visit 2 and Call 2 will be 7 days after Visit 3).
- All subjects will be followed-up for 6 months after the last dose of trial vaccine (Visit 3) for safety.

The trial design diagram is shown in Section 2.1. The schedule of procedures is shown in Section 2.2.

6.2 Justification for Trial Design, Dose, and Endpoints

This trial, NOR-206 will evaluate the safety and immunogenicity of 2 doses of HIL-214 administered concomitantly with routine childhood vaccines. Infants enrolled in the trial will start the routine childhood vaccine regimen at two months of age. Subjects will receive HIL-214 or placebo at 4 and 6 months of age, concurrently with the childhood vaccines required at those times. Safety data will be collected throughout the trial (including SAEs, MAAEs, AEs leading to trial or trial vaccine withdrawal) for all vaccines administered (trial vaccines and routine childhood vaccines). Solicited events will only be collected for the trial vaccines.

HIL-214 will be administered intramuscularly as previously done in the NOR-202 pediatric trial, and in the concurrent NOR-212 trial. Based on NOR-202, the dosage for subjects aged ~5 months will be 50/150 µg GI.1/GII4c adjuvanted with 500 µg $Al(OH)_3$, administered as two doses, at an interval of 2 months (at 4 and 6 months of age).

For further information, please refer to the current IB.

6.3 Planned Duration of Subject Participation

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

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

The trial will be completed as planned unless one or more of the following criteria that require temporary suspension or early termination of the trial are satisfied.

- New information or other evaluation regarding the safety or efficacy of the investigational vaccine that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the trial.
- The data monitoring committee (DMC) recommends that the trial should be suspended or terminated.
- Significant deviation from GCP that compromises the ability to achieve the primary trial objectives or compromises subject safety.
- The sponsor decides to terminate or suspend the trial.

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A trial site may be terminated prematurely or suspended if the site (including the investigator) is found in significant deviation from GCP, this protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

6.4.3 Procedures for Premature Termination or Suspension of the Trial or the Participation of Investigational Sites

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is aged 2 months (+28 days).
2. Male or female.
3. Infants who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
4. The subject's LAR signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
5. Infants whose LARs can and are willing to comply with trial procedures and are available for the duration of follow-up.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the trial:

1. Clinically significant abnormality in growth by height, weight, or head circumference (according to local guidelines).
2. Gastrointestinal abnormalities or any chronic gastrointestinal disease, including any uncorrected congenital malformation of the gastrointestinal tract according to medical history and/or physical examination.
3. Known hypersensitivity or allergy to any of the investigational vaccine components (including excipients).
4. Severe reaction to routine childhood vaccine(s) administered at Visit 1.
5. Any clinically significant active infection (as assessed by the investigator) or temperature ≥38.0°C (>100.4°F), within 3 days of intended trial vaccination.
6. Any serious chronic or progressive disease according to the judgment of the investigator (e.g., cardiac, renal or hepatic disease).
7. Individuals with history of, e.g., convulsions/febrile convulsions, or any illness, that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
8. Known or suspected impairment/alteration of immune function.

9. Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
10. Subjects who received or are scheduled to receive any licensed or authorized vaccines not planned in this trial within 14 days (for inactivated vaccines) or within 28 days (for live vaccines) before or after any dose of trial vaccine. Note: Flu and/or COVID vaccine can be administered per local guidelines at any time during the trial.
11. Subjects participating in any clinical trial with another investigational product 30 days prior to first trial visit or due to participate in another clinical trial at any time during the conduct of this trial.
12. Subjects known to be positive for or in evaluation for possible human immunodeficiency virus infection.
13. Subject's LAR or subject's first-degree relatives involved in the trial conduct.

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (e.g., body temperature elevation or recent use of excluded medication(s) or vaccine(s)). Under these circumstances, eligibility for trial enrollment may be considered if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible (Section 7.3).

7.3 Criteria for Delay of Routine Childhood Vaccine Administration, Trial Vaccine Administration and Blood Sampling

Subjects may encounter clinical circumstances that warrant a delay in the administration of a trial vaccine. These situations are listed below. In the event that a subject meets a criterion for delay of trial vaccine administration, the subject may receive the trial vaccine once the window for delay has passed as long as the subject is otherwise eligible for trial participation.

1. Subjects with a clinically significant active infection (as assessed by the investigator) or body temperature >38.0°C (>100.4°F), within 3 days of planned trial vaccine administration.
2. Subjects who have received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months (prior to any dose).
3. Subjects who received any licensed or authorized vaccines not planned in this trial within 14 days before or after any dose of trial vaccine.
4. Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. Trial vaccine administration should be delayed to allow for a full 24 hours to have passed between having used antipyretics and/or analgesic medications and trial vaccine administration.

7.4 Criteria for Early Termination of a Subject's Trial Participation

Under some circumstances, a subject's trial participation may be terminated early. This means that no further trial procedures (including data collection) will be performed on that subject beyond the specific date of early termination of trial participation. The primary reason for early termination of the subject's trial participation should be documented using the following categories:

1. **Adverse Event**: The subject has experienced an AE (irrespective of being related/unrelated to the trial vaccine or trial-related procedures) that requires early termination because continued participation imposes an unacceptable risk to the subject's health and/or the subject's LAR is unwilling to allow the child to continue participation because of the AE. If the subject's LAR is unwilling to allow the child to continue because of the AE, the primary reason for early termination of trial participation in this case will be withdrawal due to AE and not withdrawal of consent, see below.
2. **Lost to follow-up**: The subject did not return to the clinic and at least three attempts to contact the subject's LAR were unsuccessful.
3. **Withdrawal of consent**: The subject's LAR wishes to withdraw from the trial. The primary reason for early termination will be withdrawal of consent if the subject's LAR withdraws the child from participation due to a non-medical reason (i.e., reason other than AE). While the subject's LAR has no obligation to provide a reason for withdrawing consent, attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be documented.
4. **Premature trial termination** by the sponsor, a regulatory agency, the IRB, or any other authority.

   If the clinical trial is prematurely terminated by the sponsor, the investigator is to promptly inform the trial subject's LAR and local IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be trial termination.
5. Subject's **death** during trial participation.
6. **Other** reason for early termination that is not captured by the above prespecified categories.

For screen failure subjects, refer to Section 9.1.9.

7.5 Criteria for Premature Discontinuation of Trial Vaccine Administration

There are also circumstances under which receipt of further trial vaccine is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the initial vaccination. If these reactions occur, the subject must not receive additional trial vaccine but is encouraged to allow the subject to continue in trial participation for safety follow-up and in order to collect data for immunogenicity assessment.

Early termination of a subject's trial participation will by default prevent the subject from receiving further doses of trial vaccine, as the subject will no longer be participating in the trial. In addition to criteria for early termination of a subject's participation (see Section 7.4), other situations may apply in which subjects may continue participating in the trial (e.g., contributing safety and immunogenicity data according to protocol) but trial vaccine administration is discontinued. Even if the subject is deemed ineligible to receive further doses of trial vaccine, all efforts should be made to continue the collection of safety and immunogenicity data according to protocol.

In addition, the primary reason for premature discontinuation of trial vaccine administration should be recorded in the electronic case report form (eCRF, end of trial vaccine administration page) using the following categories:

1. **Adverse Event**: The subject has experienced an AE (irrespective of being related/unrelated to the trial vaccine or trial-related procedures) for which subsequent trial vaccine administration(s) pose an unacceptable risk to the subject's health, but the subject will continue trial participation for safety, or a subset of other trial procedures.
2. **Lost to follow-up**: The subject did not return to the clinic and at least three attempts to contact the subject's LAR were unsuccessful.
3. **Withdrawal of consent**: The subject's LAR wishes to withdraw the child from the trial. The primary reason for early termination will be withdrawal of consent if the subject's LAR withdraws the child from participation due to a non-medical reason (i.e., reason other than an AE). The reason for withdrawal, if provided, should be recorded in the CRF.
4. **Premature trial termination** by sponsor, a regulatory agency, the IRB, or any other authority.

   If the clinical trial is prematurely terminated by the sponsor, the investigator is to promptly inform the trial subject's LAR and local IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be trial termination.
5. Subject´s **death** prior to the next trial vaccine administration.
6. **Protocol deviation**: A protocol deviation is any change, divergence, or departure from the trial design or procedures of a trial protocol. The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights (see Section 7.4).
7. **Other** reason for early termination that is not captured by the above prespecified categories.

For criteria which also lead to early termination of a subject's trial participation, please refer to Section 7.4.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all investigational vaccine, co-administered vaccines, placebo, and materials provided directly by the sponsor, and/or sourced by other means, that are required by the trial protocol, including important sections describing the management of clinical trial materials.

8.1 Investigational Vaccine, Placebo and Co-administered Vaccines

The term 'trial vaccine' is used to refer to HIL-214 or placebo, unless specified.

8.1.1 Investigational Vaccine

HIL-214 for injection is provided by the sponsor in single dose 1 mL pre-filled syringes as a 0.65 mL volume (to deliver a 0.5 mL dose). HIL-214 contains 50 µg GI.1/150 µg GII.4c VLPs and 500 µg of aluminum as $Al(OH)_3$. [redacted] HIL-214 does not contain a preservative.

The syringe contents may appear biphasic with a clear upper layer and a white precipitate. After mixing by shaking, a uniformly turbid suspension should be observed.

Each HIL-214 pre-filled syringe will be supplied in a tamper-evident, single dose carton.

8.1.2 Placebo

Placebo, 0.9% NaCl (saline) for injection, is provided by the sponsor or designated vendor in a container allowing delivery of a 0.5 mL dose. The placebo does not contain any preservatives.

The contents of the placebo container will appear clear and therefore, distinguishable from the vaccine.

Each placebo container will be supplied in a tamper-evident, single dose carton.

8.1.3 Co-administered Vaccines

DTaP-Hib-IPV-HepB, PCV13 and RV1 will be administered according to the manufacturer's instructions for dosing regimen and route of administration.

8.2 Labeling

A clinical label will be affixed to trial vaccine containers in accordance with local regulatory requirements. Routine (commercial) vaccine containers will include a clinical over-label specific to the trial, in accordance with local regulatory requirements.

8.3 Inventory and Storage

Vaccines will be shipped in refrigerated, temperature-controlled containers with a temperature monitor. The trial vaccine must be stored, kept away from light, and maintained at a controlled temperature of 2°C to 8°C (36°F to 46°F), as specified on the label. The trial vaccine must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. The trial vaccine must not be frozen. Each kit is intended for single use only.

Receipt and dispensing of trial vaccine must be recorded by authorized personnel at the trial site. All sponsor-supplied investigational vaccine and placebo must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the vaccine storage area must be maintained. Temperature excursions must be reported to the sponsor as soon as possible and use of these vaccines requires sponsor approval. Temperature excursion information can be found in the pharmacy manual.

8.4 Dose and Regimen

The investigational vaccine 50 µg GI.1/ 150 µg GII.4c VLPs and 500 µg of aluminum as $Al(OH)_3$ or placebo will be administered as shown in Table 8.1.

Table 8.1: Dose and Regimen

Arm	N	Trial Vaccine	Route	Location	Age at Trial dose administration		
					2 months	4 months	6 months
1	**200**	**HIL-214***	**IM**	anterolateral RIGHT thigh		x	x
2	**200**	**Placebo****				x	x
1 and 2	**400**	**DTaP-Hib-IPV-HepB**		anterolateral LEFT thigh	x	x	x
		PCV13			x	x	x
		RV1	**PO**	Oral/mouth	x	x	

Abbreviations: IM, intramuscular; PO, *per os* (by mouth).

*50 µg GI.1/ 150 µg GII.4c VLPs and 500 µg of aluminum as $Al(OH)_3$.

**Placebo (0.9% sodium chloride [saline]).

8.5 Trial Vaccine Assignment and Dispensing Procedures

The vaccine identification number of the kit to be administered will be assigned by the IRT.

The vaccine and placebo are visually distinguishable and therefore, to maintain the blind, the trial vaccine doses will be prepared and administered by the unblinded designee according to the instructions in the pharmacy manual.

The investigator or designee will be responsible for overseeing the administration of vaccine to subjects enrolled in the trial according to the procedures stipulated in this trial protocol. All

vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable laws and regulations for that specific trial.

Expired vaccines must not be administered.

If sponsor-supplied kit is lost or damaged, the site can request a replacement from the IRT (refer to IRT manual supplied separately). At the subsequent dose-administration visit, the investigator or designee will again contact the IRT to request an additional kit for a subject.

8.5.1 Precautions to be Observed when Administering the Trial Vaccine

Prior to trial vaccine administration, site staff must determine if the subject is eligible to receive trial vaccine (Sections 7.1, 7.2 and 7.3), and it must be clinically appropriate in the judgment of the investigator to administer the trial vaccine.

Standard vaccination practices are to be observed and care should be taken when administering a vaccine intramuscularly in the anterolateral thigh area (RIGHT side for the trial vaccine and LEFT side for the routine pediatric vaccines). Multiple injections in the same thigh must be adequately spaced (at least 2.5 cm apart). In addition, World Health Organization (WHO) recommendations to reduce anxiety and pain at the time of vaccination should be followed [15]. Before administration of a trial vaccine, the injection site must be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. Refer to the pharmacy manual for details on preparation and administration of trial vaccine.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccination. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

8.6 Randomization Code Creation and Storage

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.

8.7 Trial Vaccine Blind Maintenance

This is a randomized, double-blind trial as from Visit 2 (trial vaccine administration). The subjects's LAR, data collectors (e.g., investigator) and data evaluators are blinded to the material

administered. In this protocol, because the trial is blinded, trial vaccine refers to both the investigational vaccine (HIL-214) and placebo.

Trial vaccine administration must be done by designated unblinded site staff, in which the trial vaccine is selected using the subject's number (see Section 8.6). 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.

8.8 Unblinding Procedure

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.

The sponsor's pharmacovigilance department must be notified as soon as possible if the trial blind is broken by the investigator and the completed SAE form, if applicable, must be sent within 24 hours. The date, time, and reason the trial blind is broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

If any subject is unblinded, the subject must be withdrawn from the trial and their data no longer evaluated. Subjects should continue to be monitored for safety follow-up.

8.9 Accountability and Destruction of Sponsor-supplied Trial Vaccine, and Other Clinical Trial Materials

The investigator or designee must ensure that the sponsor-supplied investigational vaccine and placebo are used in accordance with the approved protocol and are administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied trial vaccine, the investigator must maintain records of all sponsor-supplied trial vaccine delivery to the site, site inventory, administration and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied trial vaccine, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the trial vaccine is received within the labeled storage conditions (i.e., no cold chain break has occurred during transit), and is in good condition. If quantity and conditions are acceptable, investigator or designee will acknowledge receipt of the shipment by recording in IRT.

If there are any discrepancies between the packing list versus the actual product received, the sponsor or designee must be contacted to resolve the issue. The packing list should be filed in the pharmacy investigator site file.

The investigator must maintain 100% accountability for all sponsor-supplied investigational vaccine and placebo doses, and other clinical trial materials (CTM; including ancillary materials,

as applicable) received and administered during their entire participation in the trial. Accountability includes:

- Verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the vaccine lot (or investigational vaccine/placebo ID or job number) used to prepare each dose.
- Verifying that all kits used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must record the current inventory of all sponsor-supplied trial vaccine on a sponsor-approved accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied trial vaccine, date, and amount. The log (IRT) should include all required information as a separate entry for each subject to whom sponsor-supplied trial vaccine is administered.

The investigator will be notified of any expiry date or retest date extension of trial vaccine during the trial conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired CTM for return to the sponsor or designee for destruction.

All CTM will be provided by the trial site, sponsor or designee, depending upon availability. The list of CTM and source information can be found in the pharmacy manual. Prior to site closure or at appropriate intervals throughout the trial, before any CTM are returned to the sponsor or designee for destruction, a representative from the sponsor will perform CTM accountability and reconciliation. The investigator will retain a copy of the documentation regarding CTM accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 TRIAL PLAN

9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The schedule of procedures is shown in Section 2.1. All procedures must be performed by qualified and trained staff. All information collected should be recorded in the appropriate source documentation and in the subject's eCRFs.

9.1.1 Informed Consent

The requirements of the ICF are described in Section 15.2.

Informed consent must be obtained before any protocol-directed procedures are performed.

A unique subject number will be assigned to each subject by the IRT after informed consent is obtained. If all eligibility criteria are fulfilled (Sections 7.1 and 7.2), this subject number will be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.9).

9.1.2 Demographics, Medical History and Prior Medications

Demographic information to be obtained will include age/date of birth (if applicable), sex, race (and ethnicity) as described by the subject's LAR.

Medical history will also be collected, including any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses and/or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation if it represents an exacerbation of an underlying disease/preexisting problem. Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have resolved at or prior to signing the ICF. The subject's LAR will also be asked whether the child is breastfeeding.

Adverse medical occurrences emerging during the time between signing the ICF and the first administration of the trial vaccine will be recorded in the medical history eCRF page. If such an adverse medical occurrence is assessed as related to a screening procedure this should be recorded as an AE related to trial procedure in the eCRF.

Details of all medications, vaccines and blood products administered to the subjects in the following timeframes will be collected as *prior* (prior to Visit 1 [age 2 months]), or *concomitant* (from Visit 1[age 2 months] to Visit 5 [age 12 months]).

Antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration (at Visit 2) and the reason for their use (prophylaxis versus treatment) must be documented. Administration of the trial vaccine should be delayed if the subject has received antipyretics within 24 hours prior to trial vaccine administration.

Medications taken for prophylaxis are those intended to prevent the onset of AEs following vaccination. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

These data must be recorded in the source documents.

9.1.3 Documentation of Trial Entry/Randomization

Only subjects for whom there is a signed ICF, and who meet all of the inclusion criteria (Section 7.1) and none of the exclusion criteria (Section 7.2), will be eligible for entry into the trial (Visit 1) and randomization/entry into the active phase (Visit 2). The randomization schedule will be created and controlled by the IRT provider. The randomization specification will be approved by the sponsor's trial statistician, or designee.

If the subject is ineligible for randomization or terminated before Visit 2, the investigator should record the primary reason for failure on the subject screening and enrollment log. These subjects will be replaced.

9.1.4 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and as listed within the site responsibility delegation log. For this trial, a physical examination includes the assessment of general appearance, assessment of extremities (including skin over the intended injection site), heart rate and temperature. Weight, length and head circumference will be recorded. A complete physical exam will be performed at trial entry (age 2 months) prior to routine childhood vaccine administration, and again at Visit 2 (age 4 months), prior to trial vaccine administration, according to the investigator's standard practice. Additional physical examinations may be performed if indicated by review of the subject's medical history. The findings should be documented in the subject's source document.

A symptom-directed physical examination may be performed if deemed necessary.

9.1.5 Vital Signs

Vital signs measured will include heart rate and body temperature.

9.1.6 Immunogenicity Assessments

Subjects in both trial arms will undergo blood sampling for serological immunogenicity testing at two clinic visits:

- Visit 2 (age 4 months; pre-trial vaccine dose 1).

- Visit 4 (age ~7 months; 28 days post-trial vaccine dose 2).

All samples must be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken at Visit 2 is 4 mL and at Visit 4 is 6 mL, and the total volume of blood for the trial is maximum 10 mL.

9.1.7 Processing, Labeling and Storage of Biological Samples

All biological samples (e.g., blood and serum) will be processed, labeled and stored according to the laboratory manual or other appropriate guideline provided to the site.

9.1.8 Safety Assessments

Safety assessments will begin at Visit 1 for MAAEs, SAEs, and AEs leading to withdrawal from the trial.

Safety assessments by site staff are planned immediately following each dose of trial vaccine. In addition, the subject's LAR will collect solicited local and systemic reactions daily for the 7 days (including day of administration) post-dose 1 (when the subject is aged 4 months) and dose 2 (when the subject is aged 6 months) of the trial vaccine via eDiary.

Safety assessments will also be made when the subject returns to the clinic for the second dose of trial vaccine (Visit 3), when the subject is aged 6 months, then at Visit 4 and Visit 5 (whether subject is aged ~7 months and 12 months, respectively). These assessments will include collection and recording of unsolicited AEs (serious and non-serious), withdrawal from trial vaccine (Visit 2 and Visit 3), withdrawal from trial, SAEs and MAAEs.

Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.5.

9.1.9 Documentation of Subjects Who Are Not Randomized

Investigators must account for all subjects for who there is a signed ICF. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF.

The primary reason for non-randomization is recorded in the eCRF using the following categories:

- Screen failure (did not meet one or more inclusion criteria or did meet one or more exclusion criteria).
- Withdrawal by the subject’s LAR.
- Withdrawal by the investigator.
- Trial terminated by the sponsor.

Subject numbers assigned to subjects who fail screening should not be re-used.

9.2 Monitoring Subject Compliance

The investigator will record all injections of routine childhood vaccines and trial vaccines given to the subject.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Section 2.2. Assessments should be completed at the designated visit(s)/time point(s).

The subject's approximate age at each visit is:

- **Visit 1**: 2 months.
- **Visit 2**: 4 months.
- **Visit 3**: 6 months.
- **Visit 4**: ~7 months.
- **Visit 5**: 12 months.

9.3.1 Pre-Vaccination Procedures (Visits 1, 2 and 3)

1. Informed consent or ICF (Section 9.1.1; Visit 1 only).
2. Assessment of eligibility criteria (Section 7.1 and Section 7.2).
3. Assessment of criteria for delay of vaccination (Section 7.3).
4. Demographics (Section 9.1.2; Visit 1 only).
5. Medical history (Section 9.1.2; Visit 1 and Visit 2).
6. Medication/vaccination history (Section 9.1.2).
7. Randomization (Section 8.6; Visit 2).
8. Documentation of trial entrance (Section 9.1.3; Visit 1 only).
9. Complete physical examination (Section 9.1.4).
10. Vital signs (Section 9.1.5).
11. Blood sampling (~ 4 mL) (Section 9.1.6; Visit 2).
12. Concomitant medications (Section 9.1.2).

9.3.2 Vaccination Procedures (Visits 1, 2 and 3)

After completing all pre-vaccination procedures (Section 9.3.1), randomizing the subject at Visit 2, and assessing the criteria for the delay of routine childhood vaccine (Visits 1, 2 and 3) and trial vaccine administration (Visits 2 and 3), the investigator will administer the vaccines

according to the procedures described in Section 8.5. At Visit 2, the investigator will confirm that the subject does not meet any criteria for delaying, or premature discontinuation of, additional routine childhood vaccine or trial vaccine administration, as described in Section 7.3.

9.3.3 Post Vaccination Procedures (Visits 1, 2 and 3)

After routine pediatric vaccine administration (Visit 1), the subject will be observed for at least 30 minutes including observation for AEs and body temperature measurement. Information should be recorded in the eCRF.

After trial vaccine administration (Visit 2 and Visit 3), the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited local and systemic reactions and body temperature measurement. Information should be recorded in the eCRF.

The following post-vaccination procedures will be performed at Visit 2:

- The individual(s) who will enter the information into the eDiary will be trained on how to measure solicited local reactions and body temperature, how to complete the electronic diary card (eDiary) and how often to complete the eDiary. Training should be directed at the individual(s) who will perform the measurements of solicited local reactions (specifying that the RIGHT thigh must be evaluated) and those who will enter the information into the eDiary. This individual may or may not be the subject's LAR, but if a person other than the subject's LAR enters information into the eDiary, this person's identity must be documented in the source documents and this person must receive training on the eDiary. Training of the subject's LAR or these individuals on how to measure an injection site reaction, and how to take body temperature, and how to record the information in the eDiary, should be performed while the subject is under observation after trial vaccine administration.

eDiary instructions must include the following:

- The individual(s) who will enter the information into the eDiary must understand that timely completion of the eDiary on a daily basis is a critical component of trial participation.

Please note:

The eDiary will be the only source document allowed for remote collection of solicited local and systemic reactions and body temperature measurements. The following additional rules apply to the documentation of safety information collected by eDiary:

- The eDiary should be reviewed with the subject's LAR.
- No corrections or additions to the eDiary will be allowed after it is reviewed with the investigator/designee.
- Any data that are identified as implausible or incorrect and confirmed by the subject's LAR to be an error, should be corrected by the investigator/designee within the allowed review time.

- Starting on the day of trial vaccine administration, the subject's LAR will check for specific types of events at the injection site on the RIGHT thigh, any specific generalized symptoms (solicited systemic reactions), body temperature (rectal or axillary), any other symptoms or change in the subject's health status, and any medications given to the subject (excluding vitamins and minerals). These solicited reactions and body temperature will be recorded in the eDiary. Other symptoms and medications will be recorded in the memory aid section of the eDiary. Measurements should preferably take place in the evening.
- Temperature measurement is to be performed daily using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject's LAR should check their temperature. If the subject has a fever, the highest body temperature observed that day should be recorded on the eDiary.
- The subject's LAR should use the ruler provided by the site to measure the solicited local reactions.
- The collection on the eDiary of body temperature, solicited local and systemic reactions will continue for a total of 7 days (including day of administration) after each trial vaccine administration (Visits 2 and 3). The recording of other symptoms and concomitant medications in the memory aid section of the eDiary will continue for 28 days (including day of administration) after trial vaccine administration.

The site staff should schedule the next trial activity reminder call/message or visit.

The site staff will provide a written reminder of the next planned trial activity to the subject's LAR. The site staff will remind the subject's LAR to complete the eDiary daily (up to Day 7 after each trial vaccine administration), and record other symptoms and concomitant medications in the memory aid section of the eDiary as needed (up to Day 28 after each trial vaccine administration), to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject's LAR.

9.3.4 Phone Contacts (Call 1 and Call 2)

Post-vaccination phone calls will be performed 7 days post each dose of trial vaccine (Call 1 at 7 days after Visit 2, and Call 2 at 7 days after Visit 3). The purpose is to review the completed eDiary with the subject's LAR. If the subject's LAR wishes to describe safety information, this information should only be collected by a trained healthcare professional at the site, and the safety data described must be recorded in source documents. The subject's LAR should be reminded to continue recording the information about other symptoms and concomitant medications in the memory aid section of the eDiary and to contact the site via the telephone number provided in the ICF to discuss medical questions.

9.3.5 Site Visits After Vaccination (Visit 4)

A site visit that does not include a trial vaccine administration will occur when the subject is approximately 7 months old (Visit 4). Procedures include targeted physical examination, vital signs, eDiary memory aid review and blood draw (Visit 4 only). The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject's LAR and will determine if any additional diagnoses and/or AEs are present and/or if concomitant medications have been used. Blood (~ 6 mL) should be taken at Visit 4 from the subject using an aseptic venipuncture technique for serological immunogenicity testing. At Visit 4, the site should schedule the next site visit with the subject's LAR. The subject's LAR will receive a written reminder of the next planned trial activity. The subject's LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

9.3.6 Final (End of Trial) Visit

The final (end of trial) visit will be performed at Visit 5 when the subject has reached the age of 12 months. The subject will undergo a physical examination at this visit and the applicable safety assessments (Section 9.1.8). If a subject terminates earlier, the final (end of trial) visit procedures should be performed at their last trial visit, if possible. The investigator must complete the end of trial eCRF page for all subjects who received trial vaccine.

9.3.7 Post-Trial Care

No post-trial care will be provided.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.6. After blood draw and serum processing, the serum samples will be preserved and retained at a central laboratory that was contracted by the sponsor for this purpose for up to but not longer than 20 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

Serum samples will be used for the analyses defined in this protocol, but can also, with permission from the subject's LAR, be used to assess, improve or develop tests related to norovirus or HIL-214 that will allow more reliable measurement of the response to HIL-214.

If the subject's LAR does not consent to future testing of samples on the ICF, the subject can still participate in the trial.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 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 trial vaccine administration. An AE is also defined as any untoward medical occurrence in a clinical investigation subject from the time they enter the trial.

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of an trial vaccine whether or not it is considered related to the trial vaccine.

AEs will be graded by the investigator in the following manner:

Mild	Grade 1	• Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities. Relieved with or without symptomatic treatment.
Moderate	Grade 2	• Sufficient discomfort is present to cause interference with normal activity. Only partially relieved with symptomatic treatment.
Severe	Grade 3	• Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities. Not relieved with symptomatic treatment.

10.1.2 Solicited Adverse Events

The occurrence of selected indicators of safety will be measured/collected for 7 days (including day of administration) following administration of each trial vaccine dose (including the day of administration) and will be recorded on the local and systemic AE CRF page as applicable and as listed in Table 10.1.

Any solicited local (in the RIGHT thigh) or systemic reactions observed as continuing beyond 7 days (including day of administration) following each trial vaccine dose will be recorded as an AE on the AE CRF for follow-up. For these persistent/prolonged solicited reactions the end date will be captured on the AE CRF to permit a separate analysis from the unsolicited AEs (see Section 10.4.2).

Table 10.1 Solicited Local (Injection Site) and Systemic Reactions

Solicited local (injection site) reactions:	Pain
	Erythema
	Induration
	Swelling
Systemic adverse events:	Drowsiness
	Irritability/fussiness
	Loss of appetite
	Fever*
	Vomiting
	Diarrhea

Body temperature will be collected and recorded. *Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method used [16].

The severity of solicited safety parameters will be assessed as described in Table 10.2.

Table 10.2 Solicited Safety Parameters

Adverse Event	Severity Grade	Intensity
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Erythema at injection site[(a)]	0	≤10 mm
	1	Mild: >10 – ≤20 mm
	2	Moderate: >20 – ≤40 mm
	3	Severe: >40 mm
Induration at injection site[(a)]	0	≤10 mm
	1	Mild: >10 – ≤20 mm
	2	Moderate: >20 – ≤40 mm
	3	Severe: >40 mm
Swelling at injection site[(a)]	0	≤10 mm
	1	Mild: >10 – ≤20 mm
	2	Moderate: >20 – ≤40 mm
	3	Severe: >40 mm
Drowsiness	0	Behavior as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Irritability/fussiness	0	Behavior as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all
Vomiting	0	None
	1	Mild: No interference with activity or 1 – 2 episodes/24h
	2	Moderate: Some interference with activity or >2 episodes/24h
	3	Severe: Prevents activity, requires outpatient IV hydration
Diarrhea	0	None
	1	Mild: 2 – 3 loose stools/24h
	2	Moderate: 4 – 5 loose stools/24h
	3	Severe: ≥6 watery stools/24h or requires outpatient IV hydration
Fever[(b)]	Record body temperature in °C/°F	

Abbreviations: h, hour; IV, intravenous.

(a) The greatest surface diameter will be recorded in mm on the diary.
(b) Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method used [16].

10.1.3 Adverse Events of Special Interest

Not applicable. No adverse event of special interest (AESI) has been identified for this trial.

10.1.4 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.

10.1.5 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term life threatening refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT in the offspring of a subject (not applicable).
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 to 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

10.2 Causality of Adverse Events

Relationship (causality) to the trial vaccine will also be assessed by the investigator. The relationship of each unsolicited AE to the trial vaccine and routine vaccine will be assessed using the following categories:

Related:	There is suspicion that there is a relationship between the trial vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the trial vaccine contributed to the AE.
Not Related:	There is no suspicion that there is a relationship between the trial vaccine and the AE; there are other more likely causes and administration of the trial vaccine is not suspected to have contributed to the AE.

Solicited local and systemic reactions are deemed related to trial vaccine by default.

10.2.1 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as related to trial procedure if the investigator considers that there is a reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as not related.

AEs deemed related to routine pediatric vaccines administered as part of the trial will be recorded as related to trial procedure.

10.2.2 Outcome of Adverse Events

The outcome of AEs can be described as follows:

Resolved:	The subject has fully recovered from the event or the condition has returned to the level observed at baseline.
Resolving:	The event is improving but the subject is still not fully recovered.
Not resolved:	The event is ongoing at the time of reporting and the subject has still not recovered.
Resolved with sequelae:	As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g., became blind, deaf or paralysed).
Fatal:	The subject died due to the event. If the subject died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (e.g., not resolved or resolving).
Unknown:	If outcome is not known or not reported.

10.3 Additional Points to Consider for Adverse Events

An untoward occurrence generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. Intermittent events for pre-existing conditions or underlying disease should not be considered as AEs.
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require trial vaccine discontinuation or a change in concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses *vs.* signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as AEs.

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after administration of the trial vaccine, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., worsening of…).
- If the subject experiences a worsening or complication of an AE, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., worsening of…).

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of the ICF are not considered as AEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Trial procedures:

- Adverse occurrences related to trial procedures after signing of the ICF are considered as AEs and should be reported as AEs.

Other:

- If possible, include anatomical location to the AE verbatim.
- Death is the outcome of an AE, not the AE term.
- Cause of death is the AE term.

10.4 Procedures

10.4.1 Collection and Reporting Procedures

All AEs, whether considered related to the use of the trial vaccine or not, must be monitored by the investigator until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full autopsy report should be supplied, if possible. All findings must be reported on the AE eCRF and on the SAE form*, if necessary (see Section 10.4.4). All findings in subjects experiencing AEs must also be documented in that subject's source documents. Any unsolicited

AE will be recorded by the subject's LAR for 28 days after Dose 1 (including day of administration; administered when the subject is aged 4 months) and for 28 days after Dose 2 (including day of administration; administered when the subject is aged 6 months) via the eDiary as a memory aid for reporting to the site at the subsequent clinic visit. AEs leading to trial vaccine discontinuation will be collected up to the second trial vaccine dose administration and AEs leading to withdrawal from the trial will be collected throughout the trial. Even if the subject is deemed ineligible to receive further doses of trial vaccine and/or routine vaccine(s), all efforts should be made to continue the collection of safety data according to the protocol. Attempts should also be made to collect remaining blood samples, if the subject's LAR agrees.

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date, duration.
- Serious (Y/N).
- Intensity.
- Investigator's opinion of the causality (relationship) between the event and administration of trial vaccine (related or not related).
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.
- Action taken with the trial vaccine and/or routine vaccine(s).
- Outcome of event.

**SAE reporting will be done with an SAE form sent to* [redacted] *Back up encrypted email* [redacted]

10.4.2 Collection and Reporting of Solicited Reactions

The occurrence of selected indicators of safety will be collected on the eDiary by the subject's LAR for 7 days (including day of administration) after administration of each dose of trial vaccine (including the day of administration, corresponding to Visit 2 (when the subject is 4 months of age) for Dose 1 and Visit 3 (when the subject is 6 months of age) for Dose 2 and will be recorded on the local and systemic AEs eCRF, as applicable. These will be summarized in the final CSR under the category solicited reactions to differentiate them from unsolicited AEs. Any solicited local or systemic reaction observed as continuing beyond 7 days after any trial vaccine administration will be recorded as an AE on the AE eCRF for follow-up.

Any solicited reaction that meets any of the following criteria must be entered as an AE on the AE eCRF page.

- Solicited local or systemic reactions that lead the subject to withdraw from the trial or further dose.
- Solicited local or systemic reactions that lead to the subject being withdrawn from the trial or further dose by the investigator.

Solicited local and systemic reactions that otherwise meet the definition of an SAE (see Section 10.1.5).

10.4.3 Collection and Reporting of Adverse Events of Special Interest/ Medically-Attended Adverse Events

AESIs will not be collected.

MAAEs will be collected by close monitoring throughout the trial. MAAEs must be recorded as an AE on the AE eCRF page.

10.4.4 Collection and Reporting of Serious Adverse Events

Collection of SAEs will commence from the time that the ICF is signed (at Visit 1, when the subjects are 2 months of age). Routine collection of SAEs will continue until the end of the trial (when the subjects reach 12 months of age).

SAEs should be reported according to the following procedure:

A sponsor SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason the event is categorized as serious.
- Causality assessment.
- Protocol number.
- Subject identification number.
- Investigator's name.

The SAE form should be transmitted within 24 hours to [redacted]
Back up encrypted email: [redacted]

10.5 Follow-up Procedures

10.5.1 Adverse Events

All AEs will be monitored until resolution or a stable status is reached or until a formal diagnosis can be made or until the end of the trial, whichever occurs first.

[redacted]

10.5.2 Serious Adverse Events

If information not available at the time of the first report becomes available later, the investigator should complete a follow-up SAE form or provide other written documentation immediately. Copies of any relevant data from the hospital notes (e.g., laboratory tests, discharge summary, postmortem results) should be sent to the sponsor after redaction for privacy.

All SAEs should be followed up until resolution, permanent outcome of the event, or is otherwise explained. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.5.3 Safety Reporting to Investigators, Institutional Review Boards, and Regulatory Authorities

The sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSARs) and any other SAEs to regulatory authorities, investigators and IRB, as applicable, in accordance with national guidelines and regulations. Relative to the first awareness of the event by/or further provision to the sponsor or designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of the trial vaccine, or that would be sufficient to consider changes in the trial vaccine administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to its IRB in accordance with national guidelines and regulations.

10.5.4 Post-Trial Events

Any SAE that occurs outside of the protocol-specified observation period or after the end of the trial but is considered to be caused by the trial vaccine must be reported to the sponsor. These SAEs will be processed by the sponsor or designee. Instructions for how to submit these SAEs will be provided in a handout in the investigator site file.

11.0 TRIAL-SPECIFIC REQUIREMENTS

An independent DMC has been established for the HIL-214 clinical development program. The role and responsibilities of the DMC are presented in the DMC charter.

The DMC is composed of a minimum of 3 individuals who are entirely independent of the sponsor. Committee members include clinicians with pediatric infectious disease and/or vaccine expertise, and at least one individual with training in biostatistics who is knowledgeable about statistical methods for clinical trials.

12.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the data management plan. AEs, medical history, and concurrent medical conditions will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the current World Health Organization (WHO) Drug Dictionary.

12.1 Electronic CRFs

Completed eCRFs are required for each subject for whom there is a signed ICF.

The sponsor or designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected during the conduct of this trial to the sponsor and regulatory authorities. eCRFs must be completed in English. Data entered onto the eCRFs must be checked against the source documents.

After completion of the entry process, computer logic checks will be run to identify erroneous items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designee) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The sponsor or designee will be permitted to review the subject's medical and hospital records pertinent to the trial to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator must agree to keep the records stipulated in Appendix A and those documents that include the trial-specific documents, and the log that identifies all the medical records of the participating subjects. The investigator must also agree to keep temporary media, such as thermal sensitive paper (which should be copied and certified), source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICF), electronic copies of eCRFs, including the audit trail, and detailed records of vaccine disposition, to enable evaluations or audits from regulatory authorities, the sponsor or designee. Furthermore, ICH E6 Section 4.9.5 [2] requires the investigator to retain essential

documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified vaccine indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical trial site agreement between the investigator and sponsor.

Refer to the clinical trial site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

The statistical considerations for NOR-206 are described in the following sections.

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of the trial arms. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

13.1.1 Analysis of Demographics and Baseline Characteristics

Age, sex, and other demographic and baseline characteristics will be summarized descriptively, by trial arm and overall. Continuous variables will be summarized using mean, standard deviation, median, minimum and maximum values. For categorical variables, count and percentage of subjects in each category will be computed. Summaries will be provided for all sets of subjects used to evaluate immunogenicity and safety objectives, reflecting intercurrent event strategies.

13.1.2 Immunogenicity Analysis

Immunogenicity data will be summarized by trial arm, for each licensed vaccine and corresponding immunogenicity assay, at all relevant time points, using:

- GMTs or GMCs and GMFR (as applicable) with 95% confidence interval (CI), geometric standard deviation (GSD), and minimum and maximum values, and
- Count and percentage of subjects with antibody titers/concentrations over pre-defined threshold, count and percentage of subjects achieving seroresponse to HIL-214, and 95% CIs for the percentages, computed using exact Clopper-Pearson method [17].

Assessment of primary objective:

The primary immunogenicity objective will be assessed using 95% CIs for differences in proportion of subjects with antibody concentrations/titers above a pre-specified threshold, computed by the Miettinen and Nurminen method [18], and 95% CIs for the geometric mean ratios, computed using the analysis of variance (ANOVA) model with natural logarithm of antibody titer/concentration as the response variable and trial arm as factor. Analyses will be done by licensed vaccine; for those vaccines used in more than one country, analyses will be repeated by country.

To address non-compliance with the vaccine administration schedule, a hypothetical strategy will be used under the assumption that lack of compliance is not related to the immune response to the routine pediatric vaccines and therefore, that infants who were not compliant with the vaccination schedule do not differ from the infants who did comply with regard to their immune response measurements. Hence, the primary immunogenicity analysis will be based on infants who were compliant with the vaccine administration schedule (i.e. received all doses of routine

vaccines and trial vaccine within the allowed windows). According to the treatment policy strategy, blood sample results obtained after use of concomitant medications or other vaccines will be included in the analysis. Handling of missing data resulting from missing blood draws, non-evaluable samples (not enough volume), and blood draws outside the window will be described in the SAP.

13.1.3 Safety Analysis

All safety summaries will be provided for each trial arm and overall.

Solicited reactions:

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). For each solicited reaction, the number and percentage of subjects who experienced an event will be computed, for each day from Day 1 to Day 7 post-dose (including the day of dose) and overall.

Solicited reactions will be summarized by severity. For subjects with more than 1 episode of the same event within an interval, the maximum severity will be used for tabulations.

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 number of days subjects experienced each event will also be provided.

Data from the 30 minutes assessment of solicited reactions immediately post-vaccination will be summarized separately.

Unsolicited AEs:

Any unsolicited AEs, SAEs, MAAEs, and AEs leading to trial vaccine, routine vaccine or trial withdrawal, will be coded using MedDRA, and summarized by system organ class (SOC) and preferred term (PT) using number and percentage of subjects with an AE. Subjects with more than one occurrence for the term will be counted only once for this term. Unsolicited AEs will be collected up to 28 days after administration of each dose of trial vaccine and routine vaccine (including the day of administration); summaries will also be provided by event severity (mild, moderate, severe) and relationship (not related, related) to trial vaccine, routine vaccine or trial procedures. For subjects with more than one AE within an SOC or a PT, the AE with the maximum severity or strongest relationship within each SOC and each PT will be included in the summaries by severity or relationship, respectively.

Any unsolicited AEs will be summarized in the following 3 time intervals: 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), and 3) with onset between 8 and 28 days after dose (including the day of administration).

AEs leading to trial vaccine withdrawal, collected up to the planned time of the second dose administration, and SAEs, MAAEs and AEs leading to withdrawal from the trial, collected throughout the trial, will be summarized up to 28 days after the second dose, and for the overall trial period.

13.2 Interim Analysis

No interim analysis is planned for this trial.

13.3 Sample Size Justification

This trial is designed to be descriptive, and therefore the sample size was not determined based on formal statistical power calculations.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial-Site Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or designee (clinical research organization) and by the IRB.

All aspects of the trial and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including the investigator site file, trial vaccine records, subject medical records, ICF documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the medical monitor (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the sponsor or designee. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments. If the trial site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section 14.1.

14.4 Trial Risk Management

The ICH E6 addendum (R2) guidance [2] encourages a risk-based approach to the management of clinical trials and includes requirements for risk control and risk reporting. Before initiation of the trial, the sponsor or designee will establish quality tolerance limits (QTL) taking into consideration the medical and statistical characteristics of the variables and the statistical design of the trial. This process will be performed according to the sponsor’s internal procedures.

At the end of the trial, the quality management approach implemented will be described in the CSR. If applicable, the CSR will summarize important deviations from the predefined QTL and the remedial actions taken.

15.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the trial subjects according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki [1], and the ICH Harmonized Tripartite Guideline for GCP E6 (R2) [2]. Each investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the Responsibilities of the Investigator that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 Institutional Review Board Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject ICF must be obtained and submitted to the sponsor or designee before commencement of the trial (i.e., before shipment of the trial vaccine or trial specific screening activity). The IRB approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives approval no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by the subject's LAR, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or designee.

Incentives should not be used to exert undue influence on subjects for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki [1] and the ICH Guidelines for GCP [2and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for the purpose of conducting the trial. The ICF and the subject information sheet further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the subject and the fact that the subject's LAR is free to withdraw their child at any time without giving a reason and without prejudice to the subject's further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet must be approved by the IRB and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet must be written in a language fully comprehensible to the prospective subject's LAR. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject's LAR. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the subject is not capable of rendering adequate written informed consent, then the subject's LAR may provide such consent for the subject in accordance with applicable laws and regulations.

The subject's LAR must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to allow the child to participate in the trial. If the subject's LAR determines their child will participate in the trial, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject's LAR at the time of consent and prior to the subject entering into the trial. The subject's LAR should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to the subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet will be stored in the investigator's site file. The investigator must document the date the subject's LAR signs the ICF in the subject's medical record and CRF. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by the subject's LAR in the same manner as the original ICF. The date the revised consent was obtained should be recorded in the subject's medical record and CRF, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designee affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this trial, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee, representatives from any regulatory authority, the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including laboratory test result reports, electrocardiogram (ECG) reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject's LAR as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Clinical Trial Registration, Publication and Disclosure Policy

15.4.1 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the sponsor will, as a minimum register all clinical trials conducted in subjects that it sponsors anywhere in the world, on publicly accessible websites such as ClinicalTrials.gov, according to local requirements, before trial initiation. The sponsor contact information, along with the investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.2 Clinical Trial Results Disclosure

The sponsor clinical trial disclosure policy aims to comply with the clinical trial data disclosure requirements of all relevant regions. The sponsor will post the results of this clinical trial regardless of outcome, on publicly accessible websites such as ClinicalTrials.gov, as required by applicable laws and/or regulations.

Completion of trial corresponds to the date on which the final subject was examined or received an intervention for the purpose of final collection of data (usually corresponds to last subject last visit).

In the US, submission of results information is required not later than 1 year after the completion date (referred to as the primary completion date) of the clinical trial, which is defined as the date of final data collection for the primary outcome measure. If the deadline for results disclosure cannot be met, an application for extension with scientific justification must be provided.

In line with EC Regulation N° 1901/2006 [19], the sponsor will submit a summary of the results of a pediatric trial within six months of completion and irrespective of whether it is part of a paediatric investigation plan) (completed or not yet completed) or not, or whether it is intended for submission later on as part of a variation, extension or new stand-alone marketing authorization application or not.

15.4.3 Publication of Trial Results

The results of this trial are expected to be published in a peer-reviewed scientific journal. Publication of trial results will follow the sponsor's publication policies, applicable international standards and guidelines for good publication practice, applicable laws, and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical trial insurance against the risk of injury to clinical trial subjects. Refer to the clinical trial site agreement regarding the sponsor's policy on subject compensation

and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

1. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/en/30publications/10policies/b3.
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH harmonized guideline. Integrated Addendum to ICH E6 (R2): Guideline for Good Clinical Practice E6.
3. Tan M and Jiang X. Association of histo-blood group antigens with susceptibility to norovirus infection may be strain-specific rather than genogroup dependent. J Infect Dis. 2008;198(6):940-1; author reply 942-3.
4. https://www.cdc.gov/norovirus/downloads/global-burden-report.pdf. (accessed 19 September 2022).
5. Chhabra P, de Graaf M, Parra GI, Chan MC, Green K, Martella V, Wang Q, White PA, Katayama K, Vennema H, Koopmans MPG, Vinjé J. Updated classification of norovirus genogroups and genotypes. J Gen Virol. 2019;100(10):1393-1406.
6. Ferreira MS, Victoria M, Carvalho-Costa FA, Vieira CB, Xavier MP, Fioretti JM et al. Surveillance of norovirus infections in the state of Rio De Janeiro, Brazil 2005-2008. J Med Virol. 2010;82(8):1442-8.
7. Estévez A, Arvelo W, Hall AJ, López MR, López B, Reyes L et al. Prevalence and genetic diversity of norovirus among patients with acute diarrhea in Guatemala. J Med Virol. 2013;85(7):1293-8.
8. Cannon JL, Bonifacio J, Bucardo F, Buesa J, Bruggink L, Chan MC et al. Global Trends in Norovirus Genotype Distribution among Children with Acute Gastroenteritis. Emerg Infect Dis. 2021;27(5):1438-1445.
9. Safadi MA, Riera-Montes M, Bravo L, Tangsathapornpong, Lagos R, Thisyakorn et al. The burden of norovirus disease in children: a multi-country study in Chile, Brazil, Thailand and the Philippines. Int J Infect Dis. 2021;109:77-84.
10. Pitkänen O, Markkula J, Hemming-Harlo M. Sapovirus, Norovirus and Rotavirus Detections in Stool Samples of Hospitalized Finnish Children With and Without Acute Gastroenteritis. Pediatr Infect Dis J. 2022;41(5):e203-e207.
11. Becker-Dreps S, Bucardo F, Vilchez S, Zambrana LE, Liu L, Weber DJ et al. Etiology of childhood diarrhea after rotavirus vaccine introduction: a prospective, population-based study in Nicaragua. Pediatr Infect Dis J. 2014;33(11):1156-63.
12. Siebenga JJ, Vennema H, Zheng DP, Vinjé J, Lee BE, Pang XL et al. Norovirus illness is a global problem: emergence and spread of norovirus GII.4 variants, 2001-2007. J Infect Dis. 2009;200(5):802-12.

13. Vesikari T, Saez-Llorens X, Blazevic V, Lopez P, Lopez E, Masuda T et al. Immunogenicity of a bivalent virus-like particle norovirus vaccine in children from 1 to 8 years of age: A phase 2 randomized, double-blind study. Vaccine. 2022;40(26):3588-3596.
14. Jiang X, Huang P, Zhong W, Tan M, Farkas T, Morrow AL et al. Human milk contains elements that block binding of noroviruses to human histo-blood group antigens in saliva, J Infect Dis. 2004;190(10):1850-9.https://www.cdc.gov/norovirus/downloads/global-burden-report.pdf. (accessed 19 September 2022).
15. WHO 2015. Reducing pain at the time of vaccination: WHO position paper. Vaccine. 2015, 90, 505-516.
16. Kohl KS, Marcy M, Blum M, Jones MC, Dagan R, Hansen J. et al. Fever after immunization: current concepts and improved future scientific understanding. Clin Infect Dis 2004;39:389-94.
17. Clopper C, Pearson ES (1934). “The use of confidence or fiducial limits illustrated in the case of the binomial”. Biometrika. 26 (4): 404–413.
18. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985; 4(2):213-226.
19. EC Regulation N° 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for pediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

APPENDIX A RESPONSIBILITIES OF THE INVESTIGATOR

Clinical research trials sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with this protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. Ensure that trial related procedures, including trial specific (non-routine/non-standard panel) screening assessments, are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB that conforms to 21 Code of Federal Regulations (CFR) Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from the LAR of each subject who participates in the trial, and document the date of consent in the subject's medical chart. The valid ICF is the most current version approved by the IRB. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from the subject's LAR.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including CRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied vaccines, and return all unused sponsor-supplied vaccines to the sponsor.

12. Report AEs to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
13. Review and provide a signature as approval of the content of the clinical study report, if needed.

APPENDIX B INVESTIGATOR CONSENT TO USE OF PERSONAL INFORMATION

The sponsor will collect and retain personal information of the investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world, including the following:

- The sponsor, its affiliates, and licensing partners.
- Business partners assisting the sponsor, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs.

The investigator's personal information may be retained, processed, and transferred by the sponsor and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other vaccines used in other clinical trials that may contain the same chemical compound present in the investigational vaccine.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within the sponsor's organization, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country. The investigator acknowledges and consents to the use of his or her personal information by the sponsor and other parties for the purposes described above.

[redacted]

DocuSign

Certificate Of Completion

[redacted]

Record Tracking

[redacted]

Signer Events	Signature	Timestamp
[redacted]		

[redacted]

[redacted]

Signer Events	Signature	Timestamp

[redacted]

In Person Signer Events	Signature	Timestamp
Editor Delivery Events	Status	Timestamp
Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp

[redacted]

Witness Events	Signature	Timestamp
Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps

[redacted]

Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

[redacted]

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Hillevax (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

[redacted]

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Hillevax:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to:[redacted]

To advise Hillevax of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at [redacted] and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Hillevax

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to j[redacted]and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Hillevax

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

[redacted]

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to [redacted] and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Hillevax as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Hillevax during the course of your relationship with Hillevax.