Trial number: NOR-109

Protocol Title: A Phase 1, Randomized, Double-blind, Multi-center, Placebo-controlled Trial to Evaluate the Safety and Immunogenicity of the Intramuscular Norovirus GI.1/GII.4 Bivalent VLP Vaccine in Healthy Japanese Infants 5 Months of Age at First Trial Vaccine Administration

NCT:06007781

A Phase 1, Randomized, Double-blind, Multi-center, Placebo-controlled Trial to Evaluate the Safety and Immunogenicity of the Intramuscular Norovirus GI.1/GII.4 Bivalent VLP Vaccine in Healthy Japanese Infants 5 Months of Age at First Trial Vaccine Administration

(Safety and Immunogenicity of HIL-214 in Healthy Japanese Infants)

Sponsor:	HilleVax 75 State St., Suite 100 - #9995 Boston, MA 02109, USA
Trial Identifier:	NOR-109
IND Number:	Not Applicable **EudraCT Number:** Not Applicable
Investigational Vaccine:	• Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine
Control:	• Placebo
Protocol Date:	15 May 2023
Version:	Version 3.0

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

1.2 Approval

REPRESENTATIVES OF HILLEVAX

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, but not limited to 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].
- ICH, E6 (R2) GCP: Consolidated Guideline [2].
- All applicable laws and regulations, including, but not limited to 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
12 October 2022	1.0	Not applicable	Japan
13 April 2023	2.0	Not applicable	Japan
15 May 2023	3.0	Non-substantial	Japan

1.3.2 Summary of Changes

Summary of changes for protocol amendment 2 dated 15 May 2023 to protocol version 2.0 dated 13 April 2023

Rationale for the amendment:

- Replacement of Quanticate by PPD for safety.

Section	Description of Change	Rationale for Change
10.4.1	All findings must be reported on the AE eCRF ~~and on the~~ form~~*~~, if necessary (see Section 10.4.4).	Procedures adjusted in-line with the provider procedures.
	~~*SAE reporting will be done with an SAE form emailed or faxed to Quanticate (safety@quanticate.com).~~	Procedures adjusted in-line with the provider procedures.
10.4.4	~~A sponsor SAE form must be completed, in English, and signed by the investigator~~ ***All SAEs will be recorded in the eCRF database*** immediately or within 24 hours of first onset or notification of the event.	Procedures adjusted in-line with the provider procedures.
	~~The SAE form should be transmitted within 24 hours to safety@quanticate.com.~~	Procedures adjusted in-line with the provider procedures.
	If the eCRF system is unavailable, a paper sponsor ***or designee*** SAE form/paper CRF should be completed and ***sent to pvcsrjapansafetyreporting.sm@ppd.com within 24 hours. T~~t~~***he event must be entered into the eCRF once access is restored.	Procedures adjusted in-line with the provider procedures.
10.5.2	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~~ ***enter the information into the eCRF*** immediately.	Procedures adjusted in-line with the provider procedures.

Summary of changes for protocol amendment 1 dated 13 April 2023 to protocol version 1.0 dated 12 October 2022

Rationale for the amendment:

- To adapt the protocol according to advice from the PMDA prior to submission to any ethics committee.

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2.0 TRIAL SUMMARY

Name of Sponsor: HilleVax, Inc.		**Product Name:** HIL-214
Trial Title: A Phase 1, Randomized, Double-blind, Multi-center, Placebo-controlled Trial to Evaluate the Safety and Immunogenicity of the Intramuscular Norovirus GI.1/GII.4 Bivalent VLP Vaccine in Healthy Japanese Infants 5 Months of Age at First Trial Vaccine Administration		
IND No.: Not applicable		**EudraCT No.:** Not applicable
Trial Identifier: NOR-109	**Phase:** 1	**Blinding Schema:** Double-blind
Indication: Prevention of norovirus-associated acute gastroenteritis.		

Background and Rationale:

Noroviruses have emerged as the single most significant cause of gastroenteritis in both middle-high income countries and low resource settings worldwide. Those most at risk of severe illness include the very young, the elderly, and immunocompromised individuals. Noroviruses are highly infectious, highly resistant to environmental conditions, and have multiple routes of transmission including person-to-person, food-borne, and contaminated surfaces. Noroviruses can cause acute, mild to severe illness characterized by vomiting, diarrhea, fever, dehydration, and abdominal pain, representing a significant burden to public health. The clinical presentation in adults and older children is similar. While mortality due to acute gastroenteritis (AGE) caused by norovirus in the pediatric population is rare in industrialized countries, it is more common in developing countries. Although potentially a cause for hospitalization in very young children, there are fewer cases during the first 6 months of life, possibly due to the protection offered by maternal antibodies from transplacental transfer and in breast milk. In addition, norovirus infections have significant socioeconomic impact on hospitals, schools, day care centers, and other closed settings. 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 AGE in many countries around the world. Currently, there is no available vaccine to counter the disease burden associated with norovirus.

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, GII.4 causes the vast majority of norovirus cases in children worldwide.

The investigational vaccine, HIL-214 (previously called TAK-214), is being developed for the prevention of norovirus-associated AGE. HIL-214 contains GI.1 virus-like particles (VLPs) and norovirus GII.4 consensus (GII.4c) VLPs 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 of HIL-214 (50/150 µg GI.I/GII.4) to be used in this phase 1 trial in Japanese infants is based on the results of trial NOR-202, a phase 2 dose-finding, safety and immunogenicity trial in 839 children aged 6 weeks to <9 years. The results of trial NOR-202 show that HIL-214 is immunogenic and had an acceptable 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, 7026 healthy volunteers have been dosed in Takeda Vaccines Inc.-sponsored HIL-214 trials and up to 4531 have received different compositions of HIL-214, including 839 children aged 6 weeks to <9 years.

The clinical trials for HIL-214 have so far been performed in Europe, the United States and several countries in Latin America. The incidence rate of norovirus-attributable disease in Japan is at least as high as in other developed countries with the highest rates occurring in children below the age of 5 years and hospitalization most common in very young and very old populations. The inclusion of infants (5 months [±14 days] of age

at the time of first trial vaccine administration) serves to compare the data obtained for infants of non-Japanese descent with Japanese infants, in alignment with the global clinical program, and to support the inclusion of Japanese infants into phase 3. Enrollment and vaccination of the infants will be performed either before or after the required routine childhood vaccines per the national immunization schedule.

This phase 1 trial in Japan aims to assess the safety and immunogenicity of two doses of HIL-214 administered 4 to 8 weeks apart, in 21 healthy infants aged 5 months at the time of the first trial vaccine dose administration. A placebo arm is included to allow an unbiased assessment of safety and immunogenicity.

The 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.

Objectives for the Trial:

Objectives, endpoints and summary measures are presented in Section 2.1.

Trial Design:

This is a phase 1, randomized, double-blind multi-center, placebo-controlled trial in Japan to evaluate the safety and immunogenicity of HIL-214 in healthy infants 5 months of age (-14/+14 days) at first trial vaccine administration. In this protocol, because the trial is blinded, trial vaccine refers to both the investigational vaccine (HIL-214) and placebo.

Subjects (infants – 5 months ±14 days) will be allocated (2:1) into 1 of 2 trial arms by interactive response technology (IRT):

- **Arm 1 (N = 14):** One dose of HIL-214 at Visit 1 (Day 1) and one dose of HIL-214 at Visit 2 (Day 29 to Day 57).
- **Arm 2 (N = 7):** One dose of placebo at Visit 1 (Day 1) and one dose of placebo at Visit 2 (Day 29 to Day 57).

The second dose of trial vaccine can be administered from 28 to 56 days after the first dose. Trial vaccine doses will be given at least 14 days before or after all non-live vaccines and oral live vaccines, and at least 28 days before or after parenteral live vaccines.

Trial procedures:

- All subjects will be followed for solicited local and systemic adverse events (AEs) up to 7 days after each dose of trial vaccine and unsolicited AEs up to 28 days after each dose of trial vaccine.
- AEs leading to trial vaccine withdrawal will be collected up to the time of second dose administration (between Day 29 and Day 57).
- All subjects will be followed throughout the trial (from Day 1) for serious adverse events (SAEs), medically-attended AEs (MAAEs), and AEs leading to trial withdrawal.
- All subjects will have four blood draws: pre-dose 1 (Visit 1), pre-dose 2 (Visit 2), 28 days post-dose 2 (Visit 3), and 6 months post-dose 2 (Visit 4), to measure all anti-norovirus total immunoglobulin (pan-Ig) and histoblood group antigen (HBGA) blocking antibodies and conduct exploratory serological immunogenicity testing.
- All subjects will have four safety phone/home contacts (2 and 7 days after each dose).
- All subjects will be followed-up for 6 months after the last dose (Visit 4) for safety.

The trial design diagram is shown in Section 2.2. The schedule of procedures is shown in Section 2.3.

Subject Population:

Healthy Subjects: Yes

Age Range: 5 months (-14/+14 days).

Planned Number of Subjects: 21.

Planned Number of Trial Arms: 2.

- HIL-214: N=14 subjects.

- Placebo: N=7 subjects.

Estimated total: 21 randomized.

Inclusion Criteria:

Subject eligibility is determined according to the following criteria:

- Male or female subject aged 5 months (-14/+14 days).
- 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 legally acceptable representative (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.
- The subject's LAR is willing and able to comply with trial procedures and is available for the duration of follow-up.

Exclusion Criteria:

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

- Clinically significant abnormality in growth by length/height, weight, or head circumference (according to national 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.
- Chronic use of oral corticosteroids (equivalent to 20 mg/day prednisolone for ≥12 weeks / ≥2 mg/kg body weight /day for ≥2 weeks) within 60 days prior to Visit 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
- Use of parenteral corticosteroids (equivalent to 20 mg/day prednisolone for ≥12 weeks / ≥2 mg/kg body weight /day for ≥2 weeks. Use of inhaled, intranasal or topical corticosteroid is allowed) within 60 days prior to Visit 1.
- Receipt of immunostimulants within 60 days prior to Visit 1.
- Receipt of parenteral, epidural or intra-articular immunoglobulin (Ig) preparations, blood products, and/or plasma derivatives within 90 days prior to Visit 1 or planned during the full duration of the trial.
- Receipt of immunosuppressive therapy prior to Visit 1.
- Known hypersensitivity or allergy to any of the trial vaccine components (including excipients).
- Any clinically significant active infection (as assessed by the investigator) or temperature ≥38.0°C (>100.4°F), regardless of method used, within 3 days prior to intended trial vaccine administration.
- Gastroenteritis within 7 days before planned dosing (can warrant delay of trial vaccine administration).
- 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.
- Abnormalities of splenic or thymic function.
- Known or suspected impairment/alteration of immune function.
- Known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
- Receipt or scheduled receipt of any other approved or authorized vaccines within 14 days (for all non-live vaccines or oral live vaccines) or 28 days (for parenteral live vaccines) before or after trial vaccine administration.
- Participation in any clinical trial with another investigational product 30 days prior to first trial visit or intention to participate in another clinical trial at any time during the conduct of this trial.
- Seropositive for, or in evaluation for, possible human immunodeficiency virus infection.

- Hepatitis B or C infection.
- Any heritable immunodeficiency or autoimmune disease.
- Subject's LAR or subject's first-degree relatives involved in the trial conduct.

Trial Vaccine:

Investigational vaccine: HIL-214 for injection is provided by HilleVax Inc. 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 $Al(OH)_3$.

Placebo: 0.9% NaCl (saline) for injection is provided by HilleVax Inc. in a container allowing delivery of a 0.5 mL dose. The placebo does not contain any preservatives.

Route of administration: intramuscular (IM) injection (anterolateral thigh).

Duration of the Trial and Duration of Subject Participation:

Expected duration of trial participation for each subject is up to approximately 8 months.

Criteria for Evaluation and Analyses:

Objectives, endpoints and summary measures are presented in Section 2.1.

Statistical Considerations:

Analysis sets

Safety Set (SAF): The SAF will consist of all subjects who received at least one dose of HIL-214 or placebo. The SAF will be used as the primary population for analyses of safety data. The analyses using the SAF will be performed according to the trial vaccine actually administered at Visit 1.

Full-Analysis Set (FAS): The FAS will include all subjects who are randomized and received at least one dose of HIL-214 or placebo. The analyses using the FAS will be performed according to the trial vaccine that the subject was randomized to receive.

Per-Protocol Set (PPS): The PPS will include all subjects in the FAS who have no major protocol deviations. A major protocol deviation is defined as any change or departure from the trial design or procedures of a trial protocol, which affects evaluation of immunogenicity objectives. The categories of major protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial vaccine, (3) receiving prohibited therapies, and (4) other major protocol deviations. Prior to unblinding, all protocol deviations will be reviewed to determine the final list of deviations leading to the exclusions from the PPS.

The PPS will be used as primary population for analyses of immunogenicity data.

Analysis of demographics and baseline characteristics

Age, sex, and baseline characteristics will be summarized descriptively, by trial arm and overall, for all randomized subjects, for the SAF and for the PPS. Summaries for the FAS may be provided if necessary.
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.

Immunogenicity analyses

Immunogenicity data will be summarized by trial arm, for each immunogenicity assay, at all relevant time points.
Antibody titers will be summarized using geometric mean and its 95% confidence interval (CI), geometric standard deviation, and minimum and maximum values.
Count and percentage of subjects who demonstrated seroresponse will be calculated. Seroresponse is defined as at least 4-fold increase in antibody titer value from baseline. Baseline is defined as last measurement taken before dose 1. For the percentage (seroresponse rate) 95% CIs will be computed using exact Clopper-Pearson method.
The immunogenicity analyses will be done using the PPS. Supportive analyses using the FAS may also be provided.

Safety analyses

All safety data analyses will be performed using the SAF. Summaries will be provided for each trial arm and overall.

Solicited AEs

Solicited AEs will be assessed during 30 minutes after administration of each dose of trial vaccine and then daily for 7 days (including the day of administration). For each solicited AE, the number and percentage of subjects will be computed, for each day from Day 1 to Day 7 after each trial vaccine dose administration (including the day of trial vaccine administration) and overall.

Solicited AEs will be summarized by intensity and, for systemic events, by relationship to the trial vaccine. For subjects with more than 1 episode of the same event within an interval, the maximum intensity and strongest relationship 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 will be summarized separately.

Unsolicited AEs

Any unsolicited AEs, SAEs, MAAEs, and AEs leading to trial 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 subject with an AE. Subjects with more than one occurrence for the term will be counted only once for this term.

For any unsolicited AEs, collected up to 28 days after administration of each dose of trial vaccine (including the day of administration), summaries will also be provided by event intensity (mild, moderate, severe) and relationship (not related, related) to trial vaccine or trial procedures. For subjects with more than one AE within a SOC or PT, then the AE with the maximum intensity or strongest relationship within each SOC and each PT will be included in the summaries by intensity or relationship, respectively.

Any unsolicited AEs will be summarized in the following 3 time intervals: 1) overall up to 28 days after trial vaccine administration, 2) with onset between 1 and 7 days after each dose (including the day of trial vaccine administration), and 3) with onset between 8 and 29 days after each dose (including the day of trial vaccine administration).

AEs leading to trial vaccine withdrawal

AEs leading to trial vaccine withdrawal will be collected up to the planned time of the second dose administration.

AEs leading to trial withdrawal

AEs leading to withdrawal from the trial will be collected throughout the trial and summarized up to 28 days after the second dose, and for the overall trial period.

SAEs and MAAEs

SAEs and MAAEs will be collected throughout the trial. SAEs and MAAEs will be coded using MedDRA and summarized by SOC and PT for each trial arm up to 28 days after the second dose (Visit 3) and for the overall trial period.

Sample Size Justification:

The objective of this trial is to evaluate the safety and immunogenicity of two IM injections of HIL-214 in infants aged 5 months (±14 days) at first trial vaccine administration. This trial is designed to be descriptive, and therefore the sample size was not determined based on formal statistical power calculations.

Data Analysis:

The primary analysis will be performed after the primary safety and immunogenicity data up to 28 days after the second dose (Visit 3) become available.

This analysis requires the unblinding of data and will be performed by the unblinded team, not involved in the trial conduct. The final unblinded analysis will address all trial objectives.
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-109 Version 3.0 (15 May 2023)

2.1 Objectives, Endpoints and Summary Measures

Primary Objective	Endpoints	Summary Measures
• To assess the safety of HIL-214 compared to placebo.	• Occurrence and intensity of solicited local reactions up to 7 days after each dose of trial vaccine. • Occurrence, intensity, and relationship of solicited systemic AEs up to 7 days after each dose of trial vaccine. • Occurrence, intensity, and relationship of unsolicited AEs up to 28 days after each dose of trial vaccine. • Occurrence, intensity, and relationship of AEs leading to withdrawal of trial vaccine up to 56 days post-dose 1.	Number of, and proportion of subjects with: • Solicited local reactions* up to 7 days post-dose 1 and dose 2. • Solicited systemic AEs** up to 7 days post-dose 1 and dose 2. • Unsolicited AEs up to 28 days post-dose 1 and dose 2. • AEs leading to withdrawal of trial vaccine up to 56 days post-dose 1. In the SAF.
Secondary Objectives		
Safety		
• To further assess the safety of HIL-214 compared to placebo.	• Occurrence, intensity, and relationship of AEs leading to withdrawal from the trial, SAEs and MAAEs throughout the entire trial period	• AEs leading to withdrawal from the trial, SAEs and MAAEs throughout the entire trial period. In the SAF.
Immunogenicity		
• To assess the immunogenicity of HIL-214.	At baseline, pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2: • HBGA blocking antibody titers. • Pan-Ig antibody titers.	• SRR*** for GI.1 titers pre-dose 2 and 28 days post-dose 2 • SRR*** for GII.4 titers pre-dose 2 and 28 days post-dose 2. • GI.1 GMTs at baseline, pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2. • GII.4 GMTs at baseline, pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2. • GI.1 GMFR from baseline to pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2. • GII.4 GMFR from baseline to pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2. In the PPS. Selected analyses may be provided using the FAS.

Abbreviations and notes on the next page.

2.1 Objectives, Endpoints and Summary Measures (continued)

Exploratory Objectives	Endpoints	Summary Measures
[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; FAS, full-analysis set; GI.1/GII.4, genotype 1, genotype 4; GMFR, geometric mean fold rise; GMT, geometric mean titer; HBGA, histoblood group antigen; MAAE, medically-attended adverse event; pan-Ig, total immunoglobulin; PPS, Per-Protocol set; SAE, serious adverse event; SAF, Safety-Analysis set; SRR, seroresponse rate.

Notes:

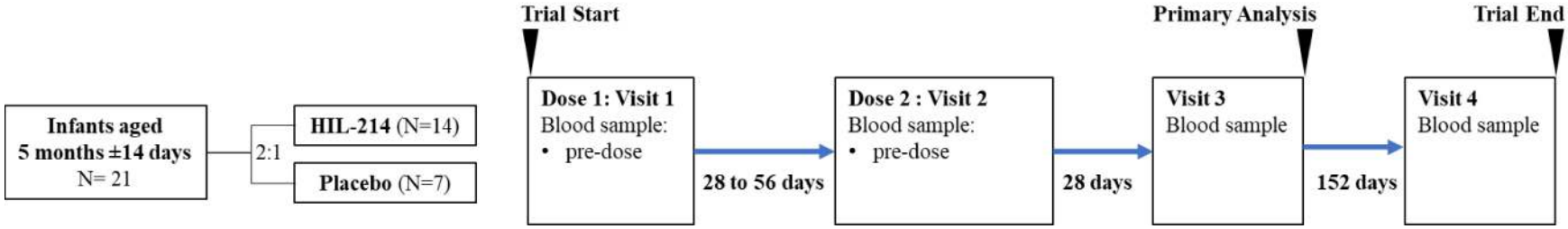
The first dose is administered on Day 1 and second dose of trial vaccine can be administered from 28 to 56 days after the first dose.

* Injection site pain, erythema, induration, and swelling.

** Irritability/fussiness, drowsiness, loss of appetite, fever, vomiting (number per day/intensity), and diarrhea (number per day/consistency).

*** Seroresponse is defined as at least 4-fold increase in antibody titer value from baseline. Baseline is defined as last measurement taken before dose 1.

2.2 Trial Design Diagram



Note: Safety phone contacts will be performed 2 and 7 days after each trial vaccine dose administration.

2.3 Schedule of Trial Procedures – Infants aged 5 Months ±14 Days

	Visit 1 Day 1	Post-dose 1			Post-dose 2			
		Phone Contact Day 3	Phone Contact Day 8	Visit 2 Day 29	Phone Contact Day 3	Phone Contact Day 8	Visit 3 Day 29	Visit 4 Day ET
Timing (+allowed window)	V1	V1+2 (+2)	V1+7 (+2)	V1+28 (+28)	V2+2 (+2)	V2+7 (+2)	V2+28 (±3)	V2+180 (±10)
Procedure								
Signed informed consent[a]	X							
Assessment of eligibility criteria[b]	X			X				
Assessment of criteria for delay of vaccine administration[c]	X			X				
Demographics[d]	X							
Medical history	X							
Medication/Vaccination history	X			X				
Documentation of trial entrance/Randomization	X							
Physical examination[e]	X			X			X	X
Vital signs[f]	X			X				X
Blood draw[g]	X			X			X	X
Trial vaccine administration[h]	X			X				
Diary card training[i]	X			X				
Solicited AEs[j]	X	X	X	X	X	X		
Unsolicited AEs[k]	X	X	X	X	X	X	X	
Concomitant medications and vaccines[k]	X	X	X	X	X	X	X	
Diary card review				X			X	
SAEs[l]	Throughout the trial							
MAAEs	Throughout the trial							
AEs leading to trial vaccine withdrawal	X	X	X	X				
AEs leading to withdrawal from trial	Throughout the trial							

Abbreviations: AE, adverse event; MAAEs, medically attended adverse events; SAE, serious adverse event.

Footnotes are on the following page.

Footnotes:

(a) If the subject randomization visit is rescheduled more than 15 days after screening, a new signed informed consent form (ICF) should be obtained and eligibility criteria re-assessed.

(b) Eligibility by review of all exclusion criteria or contraindications will be documented before trial vaccine dose administration at Visit 1 and Visit 2.

(c) Review of criteria for delay of trial vaccine administration will be documented before each trial vaccine dose administration.

(d) At each of the visits or phone contacts, the investigator should ask and record whether the child is breastfeeding or not.

(e) Complete physical examination prior to trial vaccine administration will be performed for all subjects on Visit 1. Complete physical examination includes but is not limited to 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), weight, height/length, and head circumference. A targeted physical examination will be performed at all subsequent clinic visits.

(f) Vital signs include (but are not limited to heart rate and temperature) prior to each trial vaccine dose administration and at the end of the trial.

(g) The maximum volume of blood taken at any single visit is approximately 3 mL, and the approximate total volume of blood taken during the trial is maximum 12 mL for all subjects. Samples will be taken for all subjects prior to trial vaccine administration.

(h) The first dose of trial vaccine is administered at Visit 1 (subject aged 5 months -14/+14 days) and the second dose at Visit 2 (29 to 56 days after the first dose).

(i) Careful training of the subject's legally-acceptable representative (LAR) on how to measure solicited local reactions, solicited systemic symptoms and body temperature, and how often to complete the diary card.

(j) Solicited local reactions and solicited systemic AEs for 7 days after each trial vaccine dose administration will be recorded on the diary card by the subject's LAR.

(k) Unsolicited AEs and concomitant medications and (other) vaccination up to 28 days after each trial vaccine dose will be recorded on the diary card by the subject's LAR.

(l) SAEs must be reported to the sponsor as soon as possible but within 24 hours of the investigator becoming aware of the event.

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 Investigator/Principal Investigator/Coordinating Investigator

Selection criteria for the investigator(s)/principal investigator(s) and/or coordinating investigator will include significant knowledge of the trial protocol, the trial vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. HilleVax will select one or more signatory/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 event of special interest
AGE	acute gastroenteritis
$Al(OH)_3$	aluminum hydroxide
CFR	Code of Federal Regulations
CSR	clinical study report
CTM	clinical trial material
DMC	data monitoring committee
eCRF	electronic case report form
FAS	Full-analysis set
FDA	US Food and Drug Administration
GCP	good clinical practice
GI/GII	genogroup I/genogroup 2
GI.1/GII.4	genotype I.1/genotype II.4
GII.4c	GII.4 consensus
HBGA	histoblood group antigen
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
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
PPS	per-protocol set
PT	Preferred Term
QTL	quality tolerance limit
SAE	serious adverse event
SAF	Safety set
SAP	statistical analysis plan
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
VLP	virus-like particle
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Noroviruses have emerged as the single most significant cause of gastroenteritis in both middle-high income countries and low resource settings worldwide [3-6]. Those most at risk of severe illness include the very young, the elderly, and immunocompromised individuals [7-11]. Noroviruses are highly infectious, highly resistant to environmental conditions, and have multiple routes of transmission including person-to-person, food-borne, and contaminated surfaces. Noroviruses can cause acute, mild to severe illness characterized by vomiting, diarrhea, fever, dehydration, and abdominal pain, representing a significant burden to public health [7]. The clinical presentation in adults and older children is similar. While mortality due to acute gastroenteritis (AGE) caused by norovirus in the pediatric population is rare in industrialized countries, it is more common in developing countries [12,13]. Although potentially a cause for hospitalization in very young children, there are fewer cases during the first 6 months of life, possibly due to the protection offered by maternal antibodies from transplacental transfer and in breast milk [14]. In addition, norovirus infections have significant socioeconomic impact on hospitals, schools, day care centers, and other closed settings [15]. 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 AGE in many countries around the world [16]. Currently, there is no available vaccine to counter the disease burden associated with norovirus.

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 [17-19]. Some norovirus strains drift from year to year, and although both GI and GII and numerous genotypes are reported, GII.4 causes the vast majority of norovirus cases in children worldwide [20-25].

The investigational vaccine, HIL-214 (previously called TAK-214), is being developed for the prevention of norovirus-associated AGE. HIL-214 contains GI.1 virus-like particles (VLPs) and norovirus GII.4 consensus (GII.4c) VLPs 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 [$Al(OH)_3$].

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 IB [26].

4.2 Rationale for the Proposed Trial

The rationale for trial NOR-109 is to evaluate the safety and immunogenicity of HIL-214 in Japanese pediatric subjects and establish whether the data obtained is consistent with that

previously obtained for non-Japanese pediatric subjects, and to support the inclusion of Japanese infants in a phase 3 trial.

The composition of HIL-214 (50/150 µg GI.I/GII.4) to be used in this phase 1 trial in Japanese infants is based on the results of trial NOR-202, a phase 2 dose-finding, safety and immunogenicity trial in 839 children aged 6 weeks to <9 years. The results of trial NOR-202 show that HIL-214 is immunogenic and had an acceptable 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, 7026 healthy volunteers have been dosed in Takeda Vaccines Inc.-sponsored HIL-214 trials and up to 4531 have received different compositions of HIL-214, including 839 children aged 6 weeks to <9 years.

The clinical trials for HIL-214 have so far been performed in Europe, the United States and several countries in Latin America [26]. The incidence rate of norovirus-attributable disease in Japan is at least as high as in other developed countries with the highest rates occurring in children below the age of 5 years and hospitalization most common in very young and very old populations. The inclusion of infants (5 months [±14 days] of age at the time of first trial vaccine administration) serves to compare the data obtained for infants of non-Japanese descent with Japanese infants, in alignment with the global clinical program, and to support the inclusion of Japanese infants into phase 3. Enrollment and vaccination of the infants will be performed either before or after the required routine childhood vaccines per the national immunization schedule.

This phase 1 trial in Japan aims to assess the safety and immunogenicity of two doses of HIL-214 administered 4 to 8 weeks apart, in 21 healthy infants aged 5 months at the time of the first trial vaccine dose administration. A placebo arm is included to allow an unbiased assessment of safety and immunogenicity.

The 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 SUMMARY MEASURES

Primary Objective	Endpoints	Summary Measures
• To assess the safety of HIL-214 compared to placebo.	• Occurrence and intensity of solicited local reactions up to 7 days after each dose of trial vaccine. • Occurrence, intensity, and relationship of solicited systemic AEs up to 7 days after each dose of trial vaccine. • Occurrence, intensity, and relationship of unsolicited AEs up to 28 days after each dose of trial vaccine. • Occurrence, intensity, and relationship of AEs leading to withdrawal of trial vaccine up to 56 days post-dose 1.	Number of, and proportion of subjects with: • Solicited local reactions* up to 7 days post-dose 1 and dose 2. • Solicited systemic AEs** up to 7 days post-dose 1 and dose 2. • Unsolicited AEs up to 28 days post-dose 1 and dose 2. • AEs leading to withdrawal of trial vaccine up to 56 days post-dose 1. In the SAF.
Secondary Objectives		
Safety		
• To further assess the safety of HIL-214 compared to placebo.	• Occurrence, intensity, and relationship of AEs leading to withdrawal from the trial, SAEs and MAAEs throughout the entire trial period	• AEs leading to withdrawal from the trial, SAEs and MAAEs throughout the entire trial period. In the SAF.
Immunogenicity		
• To assess the immunogenicity of HIL-214.	At baseline, pre-dose 2, and 28 days post-dose 2 and 6 months post-dose 2: • HBGA blocking antibody titers. • Pan-Ig antibody titers.	• SRR*** for GI.1 titers pre-dose 2 and 28 days post-dose 2 • SRR*** for GII.4 titers pre-dose 2 and 28 days post-dose 2. • GI.1 GMTs at baseline, pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2. • GII.4 GMTs at baseline, pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2. • GI.1 GMFR from baseline to pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2. • GII.4 GMFR from baseline to pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2. In the PPS. Selected analyses may be provided using the FAS.

Abbreviations and notes on the next page.

5.0 Objectives, Endpoints and Summary Measures (continued)

Exploratory Objectives	Endpoints	Summary Measures
• [redacted]	• [redacted]	[redacted]

Abbreviations: AE, adverse event; FAS, full-analysis set; GI.1/GII.4, genotype 1, genotype 4; GMFR, geometric mean fold rise; GMT, geometric mean titer; HBGA, histoblood group antigen; pan-Ig, total immunoglobulin; MAAE, medically-attended AE; PPS, Per-Protocol set; SAE, serious AE; SAF, Safety-Analysis set; SRR, seroresponse rate.

Notes:

The first dose is administered on Day 1 and second dose of trial vaccine can be administered from 28 to 56 days after the first dose.

* Injection site pain, erythema, induration, and swelling.

** Irritability/fussiness, drowsiness, loss of appetite, fever, vomiting (number per day/intensity), and diarrhea (number per day/consistency).

*** Seroresponse is defined as at least 4-fold increase in antibody titer value from baseline. Baseline is defined as last measurement taken before dose 1.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase 1, randomized, double-blind multi-center, placebo-controlled trial in Japan to evaluate the safety and immunogenicity of HIL-214 in healthy infants 5 months of age (-14/+14 days) at first trial vaccine administration. In this protocol, because the trial is blinded, trial vaccine refers to both the investigational vaccine (HIL-214) and placebo.

Subjects (infants - 5 months ±14 days) will be allocated (2:1) into 1 of 2 trial arms by interactive response technology (IRT):

- **Arm 1 (N = 14):** One dose of HIL-214 at Visit 1 (Day 1) and one dose of HIL-214 at Visit 2 (Day 29 to Day 57).
- **Arm 2 (N = 7):** One dose of placebo at Visit 1 (Day 1) and one dose of placebo at Visit 2 (Day 29 to Day 57).

The second dose of trial vaccine can be administered from 28 to 56 days after the first dose. Trial vaccine doses will be given at least 14 days before or after all non-live vaccines and oral live vaccines, and at least 28 days before or after parenteral live vaccines.

Trial procedures:

- All subjects will be followed for solicited local and systemic AEs up to 7 days after each dose of trial vaccine and unsolicited AEs up to 28 days after each dose of trial vaccine.
- AEs leading to trial vaccine withdrawal will be collected up to the time of second dose administration (between Day 29 and Day 57).
- All subjects will be followed throughout the trial (from Day 1) for serious adverse events (SAEs), medically-attended AEs (MAAEs), and AEs leading to trial withdrawal.
- All subjects will have four blood draws: pre-dose 1 (Visit 1), pre-dose 2 (Visit 2), 28 days post-dose 2 (Visit 3), and 6 months post-dose 2 (Visit 4), to measure all anti-norovirus total immunoglobulin (pan-Ig) and histoblood group antigen (HBGA) blocking antibodies and conduct exploratory serological immunogenicity testing.
- All subjects will have four safety phone/home contacts (2 and 7 days after each dose).
- All subjects will be followed-up for 6 months after the last dose (Visit 4) for safety.

The trial design diagram is shown in Section 2.2. The schedule of procedures is shown in Section 2.3.

6.2 Justification for Trial Design, Dose, and Endpoints

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 28 days to 56 days. HIL-214 and placebo will be administered separately from the routine infant/childhood vaccines.

A single dose of HIL-214 (50/150 µg GI.1/GII4c adjuvanted with 500 µg $Al(OH)_3$) is being tested in a phase 1 adult trial.

Please refer to the IB [26].

6.3 Planned Duration of Subject's Participation in the Trial

Expected duration of trial participation for each subject is up to approximately 8 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 trial 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.
- Significant deviation from GCP that compromises the ability to achieve the primary trial objectives or compromises subject safety.
- The DMC recommends that the trial should be suspended or terminated. (if applicable).
- The sponsor decides to terminate or suspend the trial.

6.4.2 Criteria for Premature Termination or Suspension of the Investigational Site

A trial site may be terminated prematurely or suspended if the site (including the investigator) is found in significant deviation from GCP, the trial 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 the Investigational Site

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. Male or female subject aged 5 months (-14/+14 days).
2. 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.
3. The subject's legally acceptable representative (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.
4. The subject's LAR is willing and able to comply with trial procedures and is 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 length/height, weight, or head circumference (according to national 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. Chronic use of oral corticosteroids (equivalent to 20 mg/day prednisolone for ≥12 weeks / ≥2 mg/kg body weight /day for ≥2 weeks) within 60 days prior to Visit 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
4. Use of parenteral corticosteroids (equivalent to 20 mg/day prednisolone for ≥12 weeks / ≥2 mg/kg body weight /day for ≥2 weeks. Use of inhaled, intranasal or topical corticosteroid is allowed) within 60 days prior to Visit 1.
5. Receipt of immunostimulants within 60 days prior to Visit 1.
6. Receipt of parenteral, epidural or intra-articular immunoglobulin (Ig) preparations, blood products, and/or plasma derivatives within 90 days prior to Visit 1 or planned during the full duration of the trial.
7. Receipt of immunosuppressive therapy prior to Visit 1.

8. Known hypersensitivity or allergy to any of the trial vaccine components (including excipients).
9. Any clinically significant active infection (as assessed by the investigator) or temperature ≥38.0°C (>100.4°F), regardless of method used, within 3 days prior to intended trial vaccine administration.
10. Gastroenteritis within 7 days before planned dosing (can warrant delay of trial vaccine administration).
11. 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.
12. Abnormalities of splenic or thymic function.
13. Known or suspected impairment/alteration of immune function.
14. Known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
15. Receipt or scheduled receipt of any other approved or authorized vaccines within 14 days (for all non-live vaccines or oral live vaccines) or 28 days (for parenteral live vaccines) before or after trial vaccine administration. Also, refer to Section 7.3.
16. Participation in any clinical trial with another investigational product 30 days prior to first trial visit or intention to participate in another clinical trial at any time during the conduct of this trial.
17. Seropositive for, or in evaluation for, possible human immunodeficiency virus infection.
18. Hepatitis B or C infection.
19. Any heritable immunodeficiency or autoimmune disease.
20. 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 Trial Vaccine Administration and/or Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of the 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.

- Subjects with a clinically significant active infection (as assessed by the investigator).
- Subjects with a body temperature ≥38.0°C (>100.4°F), within 3 days of planned trial vaccine administration.
- Receipt or scheduled receipt of any other approved or authorized vaccines within 14 days (for all non-live vaccines or oral live vaccines) or 28 days (for parenteral live vaccines) before or after trial vaccine administration.
- Subjects who have been given antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration. 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. 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 documented 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 withdrawal from participation is 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 subject's LAR and the 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.**

For screen failure subjects, refer to Section 9.1.9.

7.5 Criteria for Premature Discontinuation of Trial Vaccine Administration

There are circumstances under which receipt of a further trial vaccine dose is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions after the first trial vaccine administration. If these reactions occur, the subject must not receive additional trial vaccine but the subject's LAR is encouraged to allow the child to continue participating in the trial for safety follow-up.

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 data according to the 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 data according to the 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 documented attempts to contact the subject's LAR were unsuccessful.
3. **Withdrawal of consent**: The subject's LAR wishes the subject to withdraw from the trial. The primary reason for early termination will be withdrawal of consent if the subject withdraws 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 eCRF.
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**.

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 the investigational vaccine (HIL-214), 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 (CTM).

8.1 Trial Vaccine

Descriptions for the investigational vaccine and the placebo are provided in the following sections. In this protocol, because the trial is blinded, trial vaccine refers to the investigational vaccine (HIL-214) and placebo.

8.1.1 Investigational Vaccine

HIL-214 for injection is provided by HilleVax, Inc. 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]

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 HilleVax, Inc. 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.

8.2 Labeling

A clinical label will be affixed to trial vaccine containers in accordance with local regulatory requirements. Trial vaccine identity (label text will state “HIL-214 or placebo”) will be included on the trial vaccine container label.

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.a.

Table 8.a Trial Vaccine Dose and Regimen for Trial NOR-109

Arm	Number of Subjects	Route of Administration	Regimen	
HIL-214*	14	IM (anterolateral thigh)	Day 1	Days 29-57
Placebo**	7			

Abbreviation: IM, intramuscular.

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

**Placebo (0.9% NaCl [saline]).

8.5 Trial Vaccine Assignment and Dispensing Procedures

Trial vaccine assignment will be determined using a randomization code list generated by an independent statistician. This list will be stored in a secured area, accessible only to authorized unblinded trial personnel.

The investigational vaccine (HIL-214) and placebo are visually distinguishable and therefore, to maintain the blind, the trial vaccine doses (HIL-214 and placebo) will be prepared and administered by the unblinded personnel according to the instructions in the pharmacy manual.

The investigator or designee will be responsible for overseeing the administration of the trial vaccine to subjects enrolled in the trial according to the procedures stipulated in this trial protocol, but will not directly observe the administration of trial vaccine. The trial vaccine will be administered only by unblinded personnel who are qualified to perform that function under applicable laws and regulations for that specific trial.

Expired trial vaccines must not be administered.

8.6 Precautions to Be Observed When Administering the Trial Vaccine

Prior to trial vaccine administration (HIL-214 or placebo), a subject must be determined to be eligible to receive trial vaccine (Sections 7.1 and 7.2), and it must be clinically appropriate in the judgment of the investigator.

Prior to subsequent trial vaccine administration, site staff must determine if the subject is eligible to receive the trial vaccine by evaluating the criteria outlined in Sections 7.3, 7.4 and 7.5.

Standard vaccination practices are to be observed and care should be taken when administering a trial vaccine intramuscularly in the anterolateral thigh area. In addition, World Health Organization (WHO) recommendations to reduce anxiety and pain at the time of vaccination should be followed [27]. Before administration of the 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 after trial vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

8.7 Randomization Code Creation and Storage

Trial vaccine assignment will be generated by an independent statistician using block randomization. The randomization code list will be stored in a secured area, accessible only to authorized unblinded trial personnel.

When the investigator or designee determines that a subject is eligible to receive trial vaccine, the authorized unblinded trial personnel will randomize the subject to either the HIL-214 or placebo arm of the trial by selecting a randomization code from the ordered randomization code list, using a unique subject number assigned to the subject.

Subjects who are randomized but not dosed will be replaced.

8.8 Trial Vaccine Blind Maintenance

This is a randomized, double-blind trial. The subjects, 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 8.7). 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.

8.9 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 an independent authorized unblinded individual who will have access to the randomization code list.

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 electronic case report form (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.

8.10 Accountability and Destruction of Sponsor-Supplied 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 CTM (including ancillary materials, as applicable) received and administered during their entire participation in the trial. Accountability includes, but is not limited to:

- 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 of the trial vaccine.

- 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 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 staff 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 2.3. All procedures must be performed by qualified and trained staff. Details about the trial procedures can be found in the Procedures Manual. All information collected should be recorded in the subject's eCRFs.

9.1.1 Informed Consent Form

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 after informed consent is obtained. If all eligibility criteria are fulfilled (Section 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 and Other Vaccinations

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 but not limited to any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications and vaccines, 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 disappeared or resolved at or prior to signing of the ICF.

Adverse medical occurrences emerging during the time between signing of 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 or received by the subjects in the following timeframes will be collected as *prior* (prior to Day 1 [Visit 1]), or *concomitant* (from Day 1 [Visit 1] to the time specified up to the end of the trial):

- Medications: from 2 months prior to Day 1 (day of first trial vaccine administration), to the time specified up to the end of the trial.
- Vaccines: within 14 days before or after either dose of the trial vaccine, to the time specified up to the end of the trial.
- Blood products: 90 days prior to Day 1 (day of first trial vaccine administration), to the time specified up to the end of the trial.
- Antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration 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 after trial vaccine administration. 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 randomization/entry into the active phase. The randomization schedule will be created by an independent statistician. The randomization specification will be approved by the sponsor's trial statistician, or designee.

If the subject is ineligible for randomization, the investigator should record the primary reason for failure on the subject screening and enrollment log.

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. A physical examination includes but is not limited to the following: 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). Weight, length and head circumference will be measured. A complete physical exam will be performed on Day 1, prior to trial vaccine administration, according to the investigator's standard practice. Additional targeted 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

During the physical examination, a subject should have their vital signs measured. These will include (but are not limited to), heart rate and body temperature. The investigator will follow standard of care for trial population and operational feasibility.

9.1.6 Immunogenicity Assessments

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

- Visit 1 (Day 1; pre-dose 1);
- Visit 2 (Day 28-56; pre-dose 2);
- Visit 3 (28 days post-dose 2);
- Visit 4 (6 months post-dose 2; end-of-trial; unscheduled visit).

All samples must be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken at any single visit is approximately 3 mL, and the approximate total volume of blood for the trial is maximum 12 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 (Section 9.4).

9.1.8 Safety Assessments

Safety assessments by site staff are planned immediately following each dose of trial vaccine at Visit 1 and Visit 2, on Day 3 and Day 8 post-dose 1 and dose 2 (phone contacts with the subject's LAR), when subjects return to clinic for dose 2 (Visit 2), 28 days post-dose 2 (Visit 3), and at 6 months post-dose 2 (Visit 4). These assessments will include collection and recording of unsolicited AEs (serious and non-serious) and MAAEs. In addition, the subject's LAR will collect solicited local (injection site) and systemic AEs daily for the 7 days post-dose 1 and dose 2 via the diary card. 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 whom 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 trial vaccine given to the subject.

9.3 Schedule of Observations and Procedures

The schedule of procedures is shown in Section 2.3. Assessments should be completed at the designated visit(s)/time point(s). In the event that the second dose of trial vaccine is not administered, no blood will be collected at Visit 3 and Visit 4, however these visits should be conducted for safety monitoring at time points relative to the window during which the second dose was to be administered.

9.3.1 Pre-Vaccination Procedures (Visits 1 and 2)

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. Demographics (Section 9.1.2; Visit 1 only).
4. Medical history (Section 9.1.2; Visit 1 only).
5. Medication/vaccination history (Section 9.1.2).
6. Randomization (Section 8.5; Visit 1 only).
7. Concomitant medications and vaccines (Section 9.1.2).
8. Documentation of trial entrance/randomization (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 (~ 3 mL) (Section 9.1.6).

9.3.2 Vaccination Procedures (Visits 1 and 2)

After completing all pre-vaccination procedures (Section 9.3.1), randomizing the subject at Visit 1 (Day 1), and assessing the criteria for the delay of trial vaccine administration, the investigator will administer the trial vaccine according to the procedures described in

Section 8.5. At Visit 2 (Day 29-57 post-dose 1), it will be confirmed that the subject does not meet any criteria for delaying, or premature discontinuation of, additional trial vaccine administration, as described in Section 7.3.

9.3.3 Post-Vaccination Procedures (Visits 1 and 2)

The following post-vaccination procedures will be performed at Visits 1 and 2:

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

The diary card instructions must include the following:

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

Please note:

The diary card will be the only source document allowed for remote collection of solicited local (injection site) reactions and systemic AEs (including body temperature measurements). The following additional rules apply to the documentation of safety information collected by diary card:

- The diary card should be reviewed with the subject's LAR.
- No corrections or additions to the diary card will be allowed after it is reviewed with the investigator/designee.
- Any blank fields on the diary card not otherwise corrected will be missing in the eCRF.
- Any newly described solicited safety information should be added to the diary card by the subject's LAR, and dated. Any new unsolicited safety information would be recorded in the subject's source document as a verbally-reported event and therefore captured as an AE and recorded in the AE eCRF.
- Starting on the day of trial vaccine administration, the subject's LAR will check for specific types of events at the injection site, any specific generalized symptoms (solicited systemic AEs), 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 AEs and body temperature other symptoms and medications will be recorded on the diary card. Assessments should preferably take place in the evening.

- Temperature measurement is to be performed 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 fever, the highest body temperature observed that day should be recorded on the diary card.
- The measurements of solicited local (injection site) reactions are to be performed using the ruler provided by the site.
- The collection on the diary card of body temperature, solicited local (injection site) reactions, and solicited systemic AEs will continue for a total of 7 days after each trial vaccine administration (Visits 1 and 2). The collection on the diary card of unsolicited AEs and concomitant medications and vaccines will continue for 28 days after trial vaccine administration.

After trial vaccine administration, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited local (injection site) reactions, and solicited systemic AEs and body temperature measurement. Information should be recorded in the eCRF. The investigator or delegate will take the opportunity to remind the subject's LAR how to measure solicited local (injection site) reactions and body temperature as part of this observation period. All safety data will be collected in the subject's source documents.

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

The subject's LAR will receive a written reminder of the next planned trial activity. The subject's LAR will be reminded to complete the diary card daily 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 Phone Contacts - Reminder Calls (2 and 7 days post-vaccination)

Post-vaccination reminder phone calls (or text messages) will be performed on 2 and 7 days post each dose. The purpose is to remind the subject's LAR about completion of the diary card. 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 record the information on the diary card 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 3)

A site visit that does not include a trial vaccine administration will occur at 28 days (Visit 3) post-dose 2. Procedures include targeted physical examination, vital signs, diary card review, concomitant medications and vaccinations and blood draw. 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 and vaccinations have been administered.

Blood (~ 3 mL) should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing.

At Visit 3, the site staff should schedule the next site visit or other trial activity 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 (Visit 4)

The final (end of trial) visit will be performed at 6 months (Day 180) post-dose 2. Procedures include targeted physical examination, vital signs, and blood draw (~ 3 mL; should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing). At Visit 4, the healthcare professional will determine if additional MAAEs or SAEs not already made known to the site occurred after Visit 3, and if concomitant medications and vaccines were used. 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 the 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 subject's 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 subject's LAR, be used to assess, improve, or develop tests related to norovirus

or the trial vaccine that will allow more reliable measurement of the response to the trial vaccine. Serum samples could also be used for further exploratory testing. 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 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 a 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 after administration of trial vaccine (including the day of administration), at Visits 1 and 2, and will be recorded on the AE eCRF page as applicable and as listed in Table 10.a.

Any solicited local reactions or systemic AEs observed as continuing on Day 8 after the trial vaccine administration will be recorded as an AE on the AE eCRF for follow-up. For these persistent/prolonged solicited AEs the end date will be captured on the AE eCRF to permit a separate analysis from the unsolicited AEs (see Section 10.4.2).

Table 10.a Solicited Local (Injection Site) Reactions and Systemic AEs

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 ≥38°C (100.4°F) regardless of method used [28].

The intensity of solicited safety parameters will be assessed as described in Table 10.b.

Table 10.b Solicited Safety Parameters

Adverse Event	Intensity 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) Subject's LAR to record greatest surface diameter in mm on the diary card.
(b) Fever is defined as body temperature ≥38°C (100.4°F) regardless of method used [28].

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

An MAAE is defined as an AE 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.
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 AE to the trial vaccine, including solicited systemic AEs (solicited local reactions are considered as related by default) 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.

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.

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 Collection and Reporting Procedures

10.4.1 Collection and Reporting of Adverse Events

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 form, if necessary (see Section 10.4.4). All findings in a subject experiencing an AE must also be documented in that subject's source documents. Any unsolicited AE will be collected by the subject's LAR or designated person for 28 days post-dose via the diary card as a memory aid for reporting to the site at the subsequent clinic visit (Visit 2 or Visit 3). 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, all efforts

should be made to continue the collection of safety data according to the protocol.

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.
- Outcome of event.

10.4.2 Collection and Reporting of Solicited Adverse Events

The occurrence of selected indicators of safety will be collected on the diary card by the subject's LAR for 7 days after administration of each dose of trial vaccine (including the day of administration, corresponding to Day 1 for Dose 1 and Day 29-57 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 AEs to differentiate them from unsolicited AEs. Any solicited local (injection site) or systemic AE observed as continuing on Day 8 after any trial vaccine administration will be recorded as an AE on the AE eCRF for follow-up. For these persistent/prolonged solicited AEs, the end date will be captured on the AE eCRF to permit a separate analysis from the unsolicited AEs.

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

- Solicited local (injection site) reactions or systemic AEs that lead the subject's LAR to withdraw the child from the trial or further dose.
- Solicited local (injection site) reactions or systemic AEs that lead to the subject being withdrawn from the trial or further dose by the investigator.
- Solicited local (injection site) reactions and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.2).

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 need to be reported to the sponsor as soon as possible after the investigator becomes aware of the event.

MAAEs must be recorded as an AE on the AE eCRF page. MAAEs will be summarized separately up to 28 days post-dose 2 (for the planned data analysis), and throughout the trial (i.e. from Day 1 through to the end of the trial).

10.4.4 Collection and Reporting of Serious Adverse Events

Collection of SAEs will commence from the time that the subject is administered the trial vaccine (Visit 1, Day 1). Routine collection of SAEs will continue until the end of the trial (Visit 4, Day 180 post-dose 2).

SAEs should be reported according to the following procedure:

All SAEs will be recorded in the eCRF database 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.

If the eCRF system is unavailable, a paper sponsor or designee SAE form/paper CRF should be completed and sent to pvcsrjapansafetyreporting.sm@ppd.com within 24 hours. The event must be entered into the eCRF once access is restored.

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.

10.5.2 Serious Adverse Events

If information not available at the time of the first report becomes available later, the investigator should enter the information into the eCRF 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 of any personal information for privacy.

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

10.5.3 Safety Reporting to Investigators or Investigational 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 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.

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 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 in the performance 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 (but are not limited to) 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 (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-109 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 Sets

Safety Set (SAF): The SAF will consist of all subjects who received at least one dose of HIL-214 or placebo. The SAF will be used as the primary population for analyses of safety data. The analyses using the SAF will be performed according to the trial vaccine actually administered at Visit 1.

Full-Analysis Set (FAS): The FAS will include all subjects who are randomized and received at least one dose of HIL-214 or placebo. The analyses using the FAS will be performed according to the trial vaccine that the subject was randomized to receive.

Per-Protocol Set (PPS): The PPS will include all subjects in the FAS who have no major protocol deviations. A major protocol deviation is defined as any change or departure from the trial design or procedures of a trial protocol, which affects evaluation of immunogenicity objectives. The categories of major protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial vaccine, (3) receiving prohibited therapies, and (4) other major protocol deviations. Prior to unblinding, all protocol deviations will be reviewed to determine the final list of deviations leading to the exclusions from the PPS.

The PPS will be used as primary population for analyses of immunogenicity data.

13.1.2 Analysis of Demographics and Baseline Characteristics

Age, sex, and baseline characteristics will be summarized descriptively, by trial arm and overall, for all randomized subjects, for the SAF and for the PPS. Summaries for the FAS may be provided if necessary.

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.

13.1.3 Immunogenicity Analyses

Immunogenicity data will be summarized by trial arm, for each immunogenicity assay, at all relevant time points.

Antibody titers will be summarized using geometric mean and its 95% confidence interval (CI), geometric standard deviation, and minimum and maximum values.

Count and percentage of subjects who demonstrated seroresponse will be calculated. Seroresponse is defined as at least 4-fold increase in antibody titer value from baseline. Baseline is defined as last measurement taken before dose 1. For the percentage (seroresponse rate) 95% CIs will be computed using exact Clopper-Pearson method [29].

The immunogenicity analyses will be done using the PPS. Supportive analyses using the FAS may also be provided.

13.1.4 Safety Analyses

All safety data analyses will be performed using the SAF. Summaries will be provided for each trial arm and overall.

Solicited AEs

Solicited AEs will be assessed during 30 minutes after administration of each dose of trial vaccine and then daily for 7 days (including the day of administration). For each solicited AE, the number and percentage of subjects will be computed, for each day from Day 1 to Day 7 after each trial vaccine dose administration (including the day of trial vaccine administration) and overall.

Solicited AEs will be summarized by intensity and, for systemic events, by relationship to the trial vaccine. For subjects with more than 1 episode of the same event within an interval, the maximum intensity and strongest relationship 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 will be summarized separately.

Unsolicited AEs

Any unsolicited AEs, SAEs, MAAEs, and AEs leading to trial 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 subject with an AE. Subjects with more than one occurrence for the term will be counted only once for this term.

For any unsolicited AEs, collected up to 28 days after administration of each dose of trial vaccine (including the day of administration), summaries will also be provided by event intensity (mild, moderate, severe) and relationship (not related, related) to trial vaccine or trial procedures. For subjects with more than one AE within a SOC or PT, then the AE with the maximum intensity or strongest relationship within each SOC and each PT will be included in the summaries by intensity or relationship, respectively.

Any unsolicited AEs will be summarized in the following 3 time intervals: 1) overall up to 28 days after trial vaccine administration, 2) with onset between 1 and 7 days after each dose

(including the day of trial vaccine administration), and 3) with onset between 8 and 29 days after each dose (including the day of trial vaccine administration).

AEs leading to trial vaccine withdrawal

AEs leading to trial vaccine withdrawal will be collected up to the planned time of the second dose administration.

AEs leading to trial withdrawal

AEs leading to withdrawal from the trial will be collected throughout the trial and summarized up to 28 days after the second dose, and for the overall trial period.

SAEs and MAAEs

SAEs and MAAEs will be collected throughout the trial. SAEs and MAAEs will be coded using MedDRA and summarized by SOC and PT for each trial arm up to 28 days after the second dose (Visit 3) and for the overall trial period.

13.1.5 Other Analyses

Other analyses may be performed for samples obtained at different timepoints. These analyses will be described in the SAP.

13.2 Data Analysis

The primary analysis will be performed after the primary safety and immunogenicity data up to 28 days after the last dose (Visit 3) are available.

This analysis requires the unblinding of data and will be performed by the unblinded team, not involved in the trial conduct.

The final unblinded analysis will address all trial objectives.

13.3 Determination of Sample Size

The objective of this trial is to evaluate the safety and immunogenicity of two IM injections of HIL-214 in infants aged 5 months (±14 days) at first trial vaccine administration. 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 (but not limited) to the investigator site file, trial vaccine records, subject medical records, ICF documentation, documentation of authorization to use personal health information (if separate from the ICFs) by the subject's LAR, 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 (e.g., US Food and Drug Administration [FDA]). 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 abstention from voting must also be obtained.

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 notification/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 the 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 the subject's LAR 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 [2] and 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 both 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.

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 accordingly, 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 eCRF. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject's LAR.

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 eCRF, and the subject's LAR 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, but not limited to, 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's 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 [LSLV]).

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.

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

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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 subject's LAR 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 eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years after 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 CTM, and return all unused sponsor-supplied CTM 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 CSR, 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 (e.g., the United Kingdom, United States, and Japan), 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 trial vaccine.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within the sponsor, 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.