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

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HilleVax

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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

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Statistical Analysis Plan

Version 2.0

Prepared by:

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List of Abbreviations

AE	adverse event
AGE	acute gastroenteritis
ATC	Anatomical Therapeutic Chemical
CI	confidence intervals
CRF	case report form
CSR	clinical study report
DRM	data review meeting
eCRF	electronic case report form
FAS	full analysis set
GI/GII	genogroup I/genogroup 2
GI.1/GII.4	genotype I.1/genotype II.4
GII.4c	GII.4 consensus VLP
GMFR	geometric mean fold rise
GMT	geometric mean titer
HBGA	histoblood group antigen
ICH	International Council on Harmonisation
IM	intramuscular
IRT	interactive response technology
LAR	legally acceptable representative
LLOQ	lower limit of quantification
LOD	limit of detection
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
Pan-Ig	total immunoglobulin
PPS	per protocol set
PT	preferred term
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SRR	seroresponse rate
ULOQ	upper limit of quantification
VLP	virus-like particle
WHO	World Health Organization

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical methods, data derivations, populations of analysis and data summaries employed in determining the safety and immunogenicity of intramuscular Norovirus GI.1/GII.4 bivalent virus-like particles (VLP) vaccine in healthy Japanese infants 5 months of age.

This SAP is based on the International Council for Harmonisation (ICH) E3 and E9 Guidelines and on the study protocol NOR-109 version 3.0 dated the 15 May 2023. The final version of the SAP will be approved, signed, and dated before the start of the statistical analysis.

Noroviruses have emerged as the single most significant cause of gastroenteritis in both middle-high income countries and low resource settings worldwide[1-4]. Those most at risk of severe illness include the very young, the elderly, and immunocompromised individuals[5-9]. 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[5].

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[10]. 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[11-13]. 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[14-19].

The investigational vaccine, HIL-214 (previously called TAK-214), is being developed for the prevention of norovirus-associated AGE. HIL-214 contains GI.1 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 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.

The clinical trials for HIL-214 have so far been performed in Europe, the United States and several countries in Latin America[20]. 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.

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.

2. Objectives

2.1. Primary Objective

- To assess the safety of HIL-214 compared to placebo.

2.2. Secondary Objectives

- To further assess the safety of HIL-214 compared to placebo.
- To assess the immunogenicity of HIL-214.

2.3. Exploratory Objectives

- [redacted]

3. Investigational Plan

3.1. Overall Study Design and Plan

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.

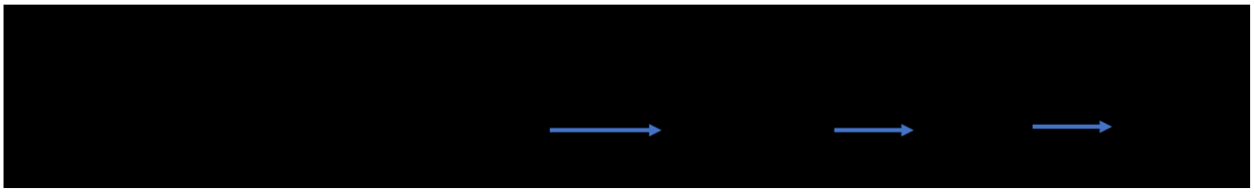
A total of 21 subjects will be allocated to either the HIL-214 or placebo. 14 subjects will be allocated to receive one dose of HIL-214 at Visit 1 (Day 1) and one dose of HIL-214 at Visit 2 (Day 29 to Day 57). 7 subjects will be allocated to receive one dose of placebo at Visit 1 (Day 1) and one dose of placebo at Visit 2 (Day 29 to Day 57).

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.

Serious adverse events (SAEs), medically-attended AEs (MAAEs), and AEs leading to trial withdrawal will all be followed throughout the trial.

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 be followed-up for 6 months after the last dose (Visit 4) for safety.



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

3.2. Study Endpoints

Endpoint	Summary Measures
Primary Endpoints	
• Occurrence and severity of solicited local reactions up to 7 days after each dose of trial vaccine. • Occurrence, severity, and relationship of solicited systemic AEs up to 7 days after each dose of trial vaccine. • Occurrence, severity, and relationship of unsolicited AEs up to 28 days after each dose of trial vaccine. • Occurrence, severity, 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 safety set (SAF).
Secondary Safety Endpoints	
• Occurrence, severity, 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.
Secondary Immunogenicity Endpoints	
At baseline, pre-dose 2, 28 days post-dose 2 and 6 months post-dose 2: • HBGA blocking antibody titers. • Pan-Ig antibody titers	• Seroresponse Rate (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 Geometric Mean Titers (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 Geometric Mean Fold Rise (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 per protocol set (PPS). Selected analyses may be provided using the full analysis set (FAS).
Exploratory Endpoints	
• [redacted]	[redacted]

* Injection site pain, erythema, induration, and swelling.
** Irritability/fussiness, drowsiness, loss of appetite, fever, vomiting (number per day/severity), 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.

3.3. Vaccinations

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). The syringe contents may appear biphasic with a clear upper layer and a white precipitate.

Placebo (0.9% NaCl [saline]) for injection is provided by HilleVax, Inc. in a container allowing delivery of a 0.5 mL dose. The contents of the placebo container will appear clear and therefore, distinguishable from the vaccine.

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 according to the procedures stipulated in this trial protocol, but will not directly observe the administration of trial vaccine.

A single dose of the investigational vaccine or placebo at 0.5 mL should be administered in the anterolateral thigh by authorized personnel.

4. General Statistical Considerations

Continuous data will be analyzed using descriptive statistics (i.e. n, geometric or arithmetic mean, standard deviation, median, minimum, maximum, first quartile (Q1), third quartile (Q3) and 95% confidence intervals [where applicable]). Categorical data will be analyzed using the subject count and percentage in each category. For the summary statistics of all numerical

variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, Q1 and Q3 will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected. Any results that are below the lower limit of quantification (LLOQ) and above the limit of detection (LOD) will be imputed as the middle point between the LOD and the LLOQ. Any results below the LOD will be imputed as half the LOD. Results above the upper limit of quantification (ULOQ) will be imputed as that limit for analysis purposes.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that trial arm within the analysis set of interest, unless otherwise specified.

Unless otherwise specified, baseline will be defined as the last non-missing evaluation taken before dose 1 including both scheduled and unscheduled visits. The study day will be calculated relative to dose 1:

- If assessment date is on or after the date of dose 1 then Study Day = Assessment Date – Dose 1 Date + 1.
- Otherwise, Study Day = Assessment Date – Dose 1 Date

All analyses will be conducted using SAS Version 9.4 or higher.

Unless otherwise specified (i.e., baseline) data will be summarized based on the visit name collected on the case report form (CRF) page and presented by trial arm and overall. Unscheduled visit measurements will be included in the derivation of baseline for safety analyses and included in individual subject data listings as appropriate.

95% confidence intervals (CIs) are provided as 2-sided and by displaying the lower limit and upper limit as follows (XX.X, XX.X).

If a subject receives a different vaccination than the randomized one, this will be considered as a major protocol violation. Subject's immunogenicity data will then be analyzed "as randomized", while safety data will then be analyzed "as treated". If a subject receives one active dose and one placebo dose, this will be analyzed in the HIL-214 group when "after any dose" or "overall" is considered.

For the purpose of inclusion in AE tables, incomplete/missing AE start and stop dates will be imputed as follows:

Partial AE start dates will be imputed as follows:

- If only the month and year are specified, and the month and year of the first trial vaccination is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified, then set to the date of the first trial vaccine received in the same month and year. If this results in a start date after a known or partial end date, then use the 1st of the month.

- If only the year is specified, and the year of the first trial vaccination is not the same as the year of the start date, then use January 1st of the year of the start date.
- If only the year is specified, then set to the date of the first trial vaccine received in the same year. If this results in a date that is after the known end date of the AE then use January the 1st.

If the start date is completely unknown, then use the date of the first trial vaccination.

Partial AE stop dates will be imputed as follows:
- If the event is flagged as ongoing, do not impute the stop date.
- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31st of that year.
- If the stop date is completely unknown, do not impute the stop date.

Unless specified otherwise, no other imputations for missing data will be performed.

4.1. Sample Size

A total of 21 subjects is planned to be enrolled in order to achieve enrolment of 14 subjects in the HIL-214 arm and 7 subjects in the Placebo arm.

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.

4.2. Randomization, Stratification, and Blinding

Trial vaccine assignment will be generated by an independent statistician using block randomization stratified by site. The randomization code list will be stored in a secured area, accessible only to authorized unblinded trial personnel. Eligible subjects will be randomized using interactive response technology (IRT) into one of the two trial arms, HIL-214 and Placebo, in a 2:1 ratio, respectively.

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.

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

The trial blind shall not be broken by the investigator unless information concerning HIL-214 is necessary for the medical treatment of a subject. In the event of a medical emergency, if

possible, the medical monitor should be contacted before the trial blind is broken to discuss the need for unblinding. For unblinding a subject, the trial vaccine assignment will be obtained by an independent authorized unblinded individual who will have access to the randomization code list. 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.

4.3. Analysis Sets

4.3.1. All Enrolled Set

The All Enrolled set will include all subjects who were enrolled in the study regardless of whether they were randomized or received study vaccine. This set is used for tables and listings such as subject disposition and screen failures.

4.3.2. Full-Analysis Set (FAS)

The Full Analysis Set (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.

4.3.3. Per-Protocol Set (PPS)

The Per-Protocol Set (PPS) will include all subjects in the FAS who have no major protocol deviations. See section 5.2 for definition of major protocol deviations and how these are collected. The PPS will be used as the primary population for analyses of immunogenicity data.

4.3.4. 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.

5. Subject Disposition

5.1. Disposition

Subject disposition will be summarized for the All Enrolled set. A disposition of subjects includes the number and percentage of subjects for the following categories: subjects who were randomized, subjects who completed vaccine regimen, subjects who withdrew from second dose, subjects who completed the study, subjects who discontinued from the study.

The reasons for withdrawal from second dose will also be summarized in this table. The reason for withdrawal from second dose may include any of the following: Adverse Event, Lost to Follow-up, Withdrawal of Consent, Study Terminated, Death, Protocol Deviation, Other.

The reasons for discontinuation of study participation will also be summarized in this table. The reason for discontinuation of study participation may include any of the following: Adverse Event, Lost to Follow-up, Unblinding, Withdrawal of Consent, PI Decision, Study Terminated, Death, Protocol Deviation, Other.

A summary of the analysis sets includes the number and percentage of subjects for the following categories: subjects in the FAS, PPS and SAF**.** All percentages will be based on the number of subjects in the All Enrolled set. Two separate tables will be produced, one performed according to the trial vaccine that the subject was randomized to receive and the other according to the trial vaccine that the subject actually received at Visit 1.

Subject disposition data and analysis sets will be presented in listings on the All Enrolled set.

5.2. Protocol Deviations

This section summarises protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect subject's rights or safety.

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 following subjects will be considered to have major protocol deviations and therefore excluded from the PPS: (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 following categories of protocol deviations will be reviewed on an ongoing basis with the sponsor prior to database lock to determine those which are considered major deviations as outlined above.

- Subjects not meeting selected entry criteria
- Subjects who received the incorrect dose
- Other deviations that may affect subjects' immunogenicity or safety outcomes.

Such subjects will be identified as part of the data review meeting (DRM) process, prior to database lock.

The number and percentage of subjects with major protocol deviations will be summarised by category. All protocol deviations will be listed. Summaries and listings will be based on the FAS.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of demographics and baseline information will be presented. The demographic characteristics consist of age (days), sex, race, and ethnicity. The baseline characteristics consist of baseline length (cm), baseline weight (kg), and baseline head circumference (cm).

Age (days), baseline length (cm), baseline weight (kg), and baseline head circumference (cm) will be summarized using descriptive statistics. The number and percentage of subjects by sex (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown), will also be reported. Percentages will be based on the total number of subjects in the SAF set. Summaries will also be provided for the PPS. If the PPS is less than 0.9 times FAS, demographics and other baseline characteristics will also be summarized based on the FAS.

Subject demographic and baseline characteristics will be presented in a listing for the SAF set.

6.2. Medical History

Medical history will be collected at screening. Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version. The number and percentage of subjects with any medical history will be summarized overall and for each system organ class and preferred term. Percentages will be calculated based on number of subjects in the SAF set.

Subject medical history data including specific details will be presented in a listing.

6.3. Inclusion and Exclusion Criteria

A listing, based on all enrolled subjects, will be included displaying whether the subject met and/or did not meet the inclusion and exclusion criteria.

A table summarizing screen failures and inclusion/exclusion criteria that subjects did or did not meet will be presented for all enrolled subjects.

7. Treatments and Medications

7.1. Prior and Concomitant Medications and Vaccinations

The following medications, vaccines and blood products received by the subjects are collected on the CRF in the following timeframes:

- All medications used within 2 months prior to the day of first trial vaccine administration through to the time specified up to the end of the trial.
- All vaccines within 14 days before or after either dose of the trial vaccine administration thorough to the time specified up to the end of the trial.
- All blood products used 90 days prior to the day of first trial vaccine administration thorough to the time specified up to the end of the trial.
- All antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration.

The name of the medication, treatment start and stop dates (or ‘ongoing’), dose, route of administration, frequency and indication must be recorded. All medications/vaccinations will be coded according to the latest World Health Organization drug dictionary (WHODrug) version.

A prior medication/vaccination is defined as any medication/vaccination that is taken prior to the first dose of study vaccine (prior to Day 1). The medications could have stopped prior to or be ongoing at the time of study vaccination. A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of study vaccination. A concomitant vaccination is defined as any vaccination administered on or after the date of first dose of study vaccination.

For missing and partial dates, medications and vaccinations will be classified in the following way:

Medications:

If the start date/end date is prior to the first date of vaccination classed as prior.
If the start date/end date is after the first date of vaccination, classed as concomitant.
Start and/or end date is on the same date as first vaccination will be classed as concomitant.
Medications for which the end date is missing will be classified as concomitant.
Otherwise if there is a partial date that is clearly before or after the first vaccination date, set to be prior or concomitant as appropriate.

Vaccinations:

If the administration date is prior to the first date of vaccination classed as prior.
If the administration date is after the first date of vaccination, classed as concomitant.
Administration date is the same date as first vaccination date will be classed as concomitant.
Otherwise if there is a partial date that is clearly before or after the first vaccination date, set to be prior or concomitant as appropriate.

The total number of concomitant medications and the number and percentages of subjects with at least one concomitant medication will be summarized by trial arm. The number and percentages of all concomitant medications will be summarized by trial arm and listed by medication class (Anatomical Therapeutic Chemical (ATC) level 4, if this is not available, the closest ATC level is presented) and preferred term. Prior medications and prior and concomitant vaccinations will be presented similarly to concomitant medications. All summaries will be performed using the SAF.

Prior and concomitant medications and prior and concomitant vaccinations data will be presented in listings. Medication will be flagged as prior (P), concomitant (C) or prior and concomitant (P/C).

7.2. Study Vaccine

Subjects will receive the first vaccine at Visit 1 (Study Day 1) and the second vaccine at Visit 2 (between Study Day 29 to 57). The date and time of administration, kit number, injection site and whether the subject was observed for 30 minutes post injection will all be collected on the CRF. Additionally, whether the dose was delayed and reason for delay will be recorded in the subject's CRF.

The number of subjects who received both doses, a summary of the time between both doses in days and the day of dose 2 administration will be summarized on the SAF.

All study vaccine administration data will be presented in a data listing.

8. Immunogenicity Analysis

All subjects will have four blood draws: pre-dose 1 (Visit 1 - Baseline), 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. Unless otherwise stated the immunogenicity analyses will be performed using the PPS. All immunogenicity data will be listed for the FAS. See section 3.2 for a list of the immunogenicity endpoints and summary measures.

8.1. Immunogenicity Endpoints

The following evaluations will be performed on the Pan-Ig and HBGA assays:

- Geometric mean titer (GMT) with 95% CI, geometric SD, minimum, maximum, Q1 and Q3. at baseline (Visit 1), Visit 2 (pre-dose 2), Visit 3 (28 days post-dose 2) and Visit 4 (6 months post-dose 2). The 95% CI will be calculated based on the t distribution of the log-transformed values for GMTs, then back transformed to the original scale for presentation.
- Geometric mean fold rise (GMFR) with 95% CI at Visit 2 (pre-dose 2), Visit 3 (28 days post-dose 2) and Visit 4 (6 months post-dose 2) relative to baseline. The 95% CI will be calculated based on the t distribution of the log-transformed values for GMFRs, then back transformed to the original scale for presentation.
- Seroresponse rate (SRR) with 95% CI based on the exact Clopper-Pearson method. Seroresponse is defined as a ≥ 4-fold increase at Visit 2 (pre-dose 2), Visit 3 (28 days post-dose 2) and Visit 4 (6 months post-dose 2) relative to baseline, all considered separately. SRR of GI.1, GII.4 and GI.1 and GII.4 will be analyzed.

The GMT will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n} log_{10}(t_i)}{n}\right\}}$$

where t_1, t_2, … t_n are observed immunogenicity titers for n subjects.

The GMFR measures the changes in immunogenicity titers within subjects. The GMFR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n} \log_{10} {}^{v_{ij}}/_{v_{ik}}}{n}\right\}} = 10^{\frac{\{\sum_{i=1}^{n}(\log_{10} v_{ij} - \log_{10} v_{ik})\}}{n}}$$

where, for n subjects, v_{jj} and v_{ik} are observed immunogenicity titers for subject i at time points j and k = 0 (Baseline).

Boxplots of titer and fold rise for the pan-Ig and HBGA assays will be plotted. Reverse cumulative distribution curves for the pan-Ig and HBGA assays will also be plotted.

All endpoints will be summarized by both the PPS and FAS.

9. Safety Analysis

The purpose of this section is to define the safety parameters for the study and to summarise the safety results. All safety analyses will be conducted on the SAF. Safety measurements will include adverse events (AEs), serious AEs (SAEs), medically attended AEs (MAAEs), solicited AEs, physical examinations and vital signs measurements. Individual subject listings will be provided to support the tables. See section 3.2 for a list of the safety endpoints and summary measures.

9.1. Solicited Adverse Events

Solicited AEs are events the subject is specifically asked about. These are measured/collected for 7 days after administration of trial vaccine (including the day of administration). These are to be collected by the subject's legally acceptable representative (LAR) in diary cards. All solicited AEs will be assessed by severity. Solicited systemic AEs will also be assessed by relationship to vaccine.

The local (injection site) AEs collected include: pain, erythema, induration and swelling at the injection site.

The systemic AEs collected include: drowsiness, irritability/fussiness, loss of appetite, fever, vomiting, diarrhea.

Any solicited AEs observed as continuing on or after Day 8 after the trial vaccine administration will be recorded as an AE on the AE eCRF for follow-up. The start date entered will be the initial start date of the solicited AE.

The number and percentage of subjects who report local solicited AEs on the day of vaccination and through the 7 subsequent days will be tabulated by severity, day and trial arm. See appendix 13.1 for severity categories. Fever will be categorized in the following way for severity:

0 None: <38°C
1 Mild: ≥38-<39°C
2 Moderate: ≥39-<40°C
3 Severe : ≥40°C.

Percentages will be based upon the number of participants in the SAF within each trial arm who reported data for the respective category and day. Each table will be repeated for systemic AEs post-dose 1, post-dose 2 and overall. A separate summary for the data from 30 minutes post-dose will also be provided.

The number and percentage of subjects who reported a systemic AE will be presented by trial arm, day, grade, and relationship to the study vaccine (solicited local AEs are considered related to the vaccine). Each table will be repeated for local AEs post-dose 1, post-dose 2 and overall. A separate summary for the data from 30 minutes post-dose will also be provided.

Additional overall summaries will be provided for all solicited AEs reported between Day 1 and Day 7, between Day 1 and Day 3 and between Day 4 and Day 7 presented by trial arm and repeated for post-dose 1, post-dose 2 and overall.

Body temperature measurements will be summarized in the following categories by day and trial arm on the SAF:

<37°C
≥37°C-<38°C
≥38°C-<39°C
≥39°C-<40°C
≥40°C

Summaries of the day of first onset of each event and the number of days subjects experienced each event will also be provided by event and trial arm on the SAF.

All solicited local and systemic AEs will be presented in a listing.

9.2. Unsolicited 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.

Unsolicited AEs are collected through 28 days post-first and second vaccination. AEs leading to trial vaccine withdrawal are collected up to the second trial vaccine dose administration. SAEs, AEs leading to withdrawal from trial and MAAEs are collected for the entire study period.

The reported term for the unsolicited AE, start and end date, seriousness, severity, relationship to trial vaccine or trial procedure, action taken and outcome of event will be collected on the eCRF.

Summaries of the total number of unsolicited AEs and the number and percentage of subjects with at least one AE will be provided by trial arm. AEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the SAF. The summary of AEs will be presented in descending order from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

Summaries of unsolicited AEs will be presented as follows after both vaccines (individually and combined):

1. Overall up to 28 days after trial vaccine administration;
2. With onset between Day 1 and Day 7 after each dose (including the day of trial vaccine administration);
3. With onset between Day 8 and Day 29 after each dose (including the day of trial vaccine administration).

Any AE reported between Day 29 and the second vaccination (up to Day 57) will be included in the listed.

Unsolicited AEs will be coded by PT and SOC using the latest MedDRA version.

For missing/partial start and end dates, the rules stated in Section 4 will be followed.

All AEs will be presented in a listing.

9.2.1. Relationship of Unsolicited Adverse Events to Vaccine and Study Procedure

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

Related: There is suspicion that there is a relationship between the trial vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the trial vaccine contributed to the AE.

Not Related: There is no suspicion that there is a relationship between the trial vaccine and the AE; there are other more likely causes and administration of the trial vaccine is not suspected to have contributed to the AE.

A summary of unsolicited AEs by relationship (i.e. “Related” and “Not Related”) to trial vaccine will be presented in a table by incidence of occurrence. If a subject reports multiple occurrences of the same AE, only the most related occurrence will be presented. AEs that are missing a relationship will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship. Percentages will be calculated out of the number of subjects in the SAF.

The unsolicited AE data will be categorized and presented by SOC, PT, and relationship up to 28 days after both vaccinations separately.

Relationship to trial procedures should also be determined for all unsolicited AEs. Relationship to trial procedures will be summarized in the same way as relationship to trial vaccine.

9.2.2. Severity of Unsolicited Adverse Event

A summary of unsolicited AEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are “Mild”, “Moderate”, and “Severe”. In the unsolicited AE severity table, if a subject reported multiple occurrences of the same AE, only the most severe will be presented. Unsolicited AEs that are missing severity will be presented in tables as “Severe” but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the SAF.

The unsolicited AE data will be categorized and presented by SOC, PT, and severity up to 28 days after both vaccinations separately.

9.2.3. Serious Adverse Events (SAE)

The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. An SAE is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, leads to congenital anomaly/birth defect, requires in-patient hospitalization or prolongation, or results in significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may expose the subject to danger or may require medical or surgical intervention to prevent one of the outcomes listed above.

SAEs will be presented in a table. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the SAF. The SAE data will be categorized and presented by SOC and PT up to 28 days after second dose and overall.

9.2.4. Medically-Attended Adverse Events (MAAEs)

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. MAAEs will be collected throughout the entire study period and will be presented in a summary table for each trial arm and total by SOC and PT up to 28 days after second dose and overall for the SAF.

9.2.5. Adverse Events Leading to Trial Vaccine Withdrawal

A summary of AEs with a study vaccine action taken of "Subject Withdrawn from Subsequent Dose" will be presented in a table. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the SAF. Counts and percentages will be presented by SOC and PT up to the planned time of the second dose administration.

9.2.6. Adverse Events Leading to Trial Withdrawal

A summary of AEs where the answer to "Caused Study Discontinuation" is "Yes" will be presented in a table. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the SAF. Counts and percentages will be presented by SOC and PT up to 28 days after the second dose, and for the overall trial period.

9.2.7. Death

A summary of AEs where the answer to Outcome is 'Fatal' will be presented in a table. Percentages will be calculated out of the number of subjects in the SAF.

All subjects who have an AE with an outcome of Fatal will be presented in a listing.

9.3. Vital Sign Measurements

Vital signs are collected prior to each trial vaccine at Visit 1 (Day 1), Visit 2 (Day 29) and at the end of the trial at Visit 4 (End of Trial). These will include heart rate and body temperature.

Vital sign data will be summarized on the SAF by visit for each parameter. All vital sign data will be listed on the SAF.

9.4. Physical Examination

A complete physical exam will be performed on Day 1, prior to trial vaccine administration. Additional targeted physical examinations may be performed if indicated by review of the subject's medical history. 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 also be measured.

Summary tables for physical examinations will be included on the SAF by visit. Weight, length and head circumference will be presented using summary statistics. For other parameters, number and percentages will be presented by abnormality. Physical examination results will be presented in a listing on the SAF.

10. Primary Analysis

Per the protocol, 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. The study database will be monitored, cleaned and locked through the data cut-off time point per data management plan.

11. Changes in the Planned Analysis

- The All Enrolled Set is included for summarizing the screen failures and analysis sets. This set was not defined in the protocol.

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13. Appendices

13.1. Severity Categories for Solicited Safety Parameters

Adverse Event	Severity Grade	Severity
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.

13.2. Schedule of Study Procedures

	Visit 1	Post-dose 1			Post-dose 2			
	Day 1	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

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.

[redacted]

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**HilleVax**
Protocol Number:	**NOR-109**

Document Description:	Statistical Analysis Plan
SAP 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
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DocuSign

Certificate Of Completion

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Record Tracking

[redacted]

Signer Events	Signature	Timestamp
[redacted]		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**

[redacted]

[redacted]

Envelope Summary Events	Status	Timestamps

[redacted]

Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

[redacted]

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