Title: A Phase 2b, Double-blind, Randomized, Multi-site, Placebo-controlled Trial to Evaluate the Efficacy, Safety and Immunogenicity of Intramuscular HIL-214 Norovirus Vaccine in Healthy Children 5 Months of Age at Initial Vaccination

Trial No.: NOR-212

NCT: 05281094

HILLEVAX

A Phase 2b, Double-blind, Randomized, Multi-site, Placebo-controlled Trial to Evaluate the Efficacy, Safety and Immunogenicity of Intramuscular HIL-214 Norovirus Vaccine in Healthy Children 5 Months of Age at Initial Vaccination

(Efficacy and Safety of Two Doses of HIL-214 in Children)

Sponsor: HilleVax

[redacted]

Trial Identifier: NOR-212

IND Number: 014421 **EudraCT Number:** Not Applicable

Investigational Medicinal Product(s):
- Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine
- Placebo

Protocol Date: 1 September 2023

Version: 3.0

[redacted]

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

[redacted]

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure (IB) [26], 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 Protocol Version V3.0 Summary of Changes

This document describes the changes in reference to protocol version 2.0 (14 October 2022).

The primary purpose of this amendment is to reduce the number of primary endpoint cases and to define the observation periods. [redacted]. Full details on changes to the text are given in Section 1.3.2.

1.3.1 Version History

Table must include all approved versions, including the current version.

Date	Version	Change Type	Region
6 October 2021	1.0	Not applicable	Global
14 October 2022	2.0	Substantial	Global
1 September 2023	3.0	Substantial	Global

1.3.2 Summary of Changes

Summary of changes for protocol amendment 2 dated 1 September 2023 to protocol version 2.0 dated 14 October 2022		
Section	**Description of Change**	**Rationale for Change**
2.0	Various changes.	Consistent with the body of the protocol.
2.1, 2.2, 2.3	[redacted]	
4.2	[redacted]	
5.0	Adjustment of the objectives and endpoint section for the primary endpoint cases, and analysis set and primary observation period definitions.	Replace the expected number of endpoint cases (64), with the minimum number of cases for 80% power (24 cases). Define the analysis sets and the primary observation period.

6.1	**Arm 1** (N = 1500): One dose of HIL-214 ~~on~~***at Visit 1 (***Day 1***)*** and one dose of HIL-214 ~~between Day 29 and Day 57~~.***at Visit 2 (28 to 56 days post dose 1)***. **Arm 2** (N = 1500): One dose of placebo ~~on~~***at Visit 1 (***Day 1***)*** and one dose of placebo ~~between Day 29 and Day 57~~.***at Visit 2 (28 to 56 days post dose 1)***.	Change in the naming convention (applies throughout the protocol).
	The subject's legally-authorized representative (LAR) (all subjects) will ~~be contacted~~***receive*** weekly ~~by phone, text messages or~~ ***notifications via*** eDiary~~, or home visits by trained field workers for~~ ***to complete the*** AGE ~~surveillance, which should be made daily~~***report*** if ***the subject has*** AGE ~~is confirmed, and until the~~ symptoms ~~disappear.~~***(episodes of vomiting and/or liquid stools)***.	Correction to the description of method used for notifying subjects.
	~~The subject's LARs will contact the site if the~~ ***If the*** child has liquid/loose stools or vomiting, ***the LAR will enter the number of episodes in the eDiary to inform the site. The subject's LARs will be requested to record AGE symptoms and their frequency, and body temperature in the eDiary (AGE symptom log) from the first day of AGE onset until the symptoms have resolved. This log will be activated automatically if the number of episodes of vomiting and loose/liquid stools satisfies the AGE case definition.*** All subjects who meet the criteria for the AGE case definition will provide ~~a~~***one*** AGE onset stool sample. ~~Subjects' LARs~~ ***and two AGE follow-on stool samples. AGE cases*** will be ~~requested to enter the AGE into the Vigilant-e mobile app collected~~ ***starting*** from the ~~first day~~***Day 1 (Dose 1*** of ~~AGE symptoms onset~~***trial vaccine)*** until ~~the symptoms~~***all subjects*** have ~~resolved.~~***reached 2 years of age (end of trial). The number of AGE cases including primary endpoint AGEs will be monitored during the trial in a blinded way. The process is described in the AGE monitoring charter.***	Clarification and further description of the process.
	• All AGE onset stool samples will be assayed for the presence of norovirus and norovirus-positive samples will be sequenced for genotype identification. Only norovirus-positive samples will be analyzed for the presence of co-pathogens. Follow-~~up~~***on*** stool samples collected ~~weekly for up to~~ ***2 and*** 3 weeks post-onset will be analyzed for norovirus presence and genogroup only.	Clarification.
	[redacted]	

[redacted]

	[redacted]
6.2	[redacted]
7.5	'There are circumstances … LAR is encouraged to allow the child to continue in trial participation for safety follow-up ***and efficacy and immunogenicity data collection.***' 'Early termination of a subject's trial participation … may apply in which subjects may continue participating in the trial (e.g., contributing safety ***and other*** data according to protocol) but investigational 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 protocol.'
9.1.2	Demographic information to be obtained will include ~~age/~~date of birth ~~(if applicable)~~, sex, race (and ethnicity) as described by the subject's LAR. All medications, vaccines and blood products taken or received by the subjects ***prior to Visit 1 (Day 1)*** are to be collected as prior ~~and concomitant~~ medications. a) Medications: 2 months prior to ***Visit 1 (***Day 1, ~~(~~day of vaccination).

	b) Vaccines: From birth up to ***Visit 1 (***Day 1, ~~(~~day of vaccination). c) Blood products: 3 months prior to ***Visit 1 (***Day 1, ~~(~~day of vaccination). ***Concomitant medications and vaccines will be collected from Visit 1 (Day 1) to Visit 3 (28 days after the second dose).***	
9.1.8	Safety assessments are planned ~~on~~ ***at Visit 1 (***Day 1~~,~~***),*** Day 3 (phone contact), Day 8 (phone contact or visit), ~~Day 29, 7~~***Visit 2 (28 to 56*** days post-~~Day 29~~ ***dose 1), 7 days post dose 2*** (phone contact) and ~~Day 57~~***Visit 3 (28 days post dose 2)***, then when the subjects reach the age of 1 year~~,~~ ***(Visit 4),*** 18 months ***(Visit 5)*** and 2 years. ***(Visit 6). The safety assessments*** will include collection and recording of solicited local (injection site) and systemic AEs (for 7 days post- vaccination), unsolicited AEs and AEs (serious and non-serious, for 28 days ~~following~~***post*** vaccination~~).~~***), and SAEs***. Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.5.	Clarification (stylistic change).
9.1.10	[redacted]	
	[redacted]	
9.3.3	• The eDiary should be reviewed ~~with~~ ***by*** the ~~subject's LAR~~ ***site***.	Clarification and further description of the process.

	• No corrections or additions to the eDiary will be allowed after ~~it is reviewed with the investigator/designee~~. • ~~Any~~ ***the end of each day (midnight) in the solicited*** data ~~that are identified as implausible or incorrect, and confirmed by the subject's LAR to be an error should be corrected by the subject's LAR on the eDiary.~~ ***collection period (for 7 days post vaccination).*** • Any blank fields on the eDiary ~~not otherwise corrected~~ will be missing in the eCRF. • ~~The site must enter all entries on the eDiary into the eCRF.~~ • ~~Any newly described solicited safety information should be added to the eDiary by the subject's LAR.~~ Any new unsolicited safety information would be recorded in the subject source documents as a verbally reported event and therefore captured as an AE and recorded on the AE eCRF. • Starting on the day of vaccination, the subject's LAR will check for specific types of events at the injection site, any specific generalized symptoms (solicited systemic AEs), body temperature (any method), any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs and body temperature will be recorded in the eDiary. ***Other symptoms and medications will be recorded in the memory aid section of the eDiary.*** Assessments should preferably take place in the evening. • Temperature measurement is to be performed ***daily*** using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject's LAR should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the eDiary. • The collection on the eDiary of body temperature, solicited local (injection site) reactions, and solicited systemic AEs will continue for a total of 7 days following vaccine administration (***including day of administration***). The ~~collection~~ ***recording of other symptoms*** ~~on the eDiary of unsolicited AEs~~ and medications ***in the memory aid section of the eDiary*** will continue for 28 days following vaccine administration ~~by eDiary~~ ***(including day of administration)***.	
	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 eDiary daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is	Clarification.

	medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All ***site*** contact details will be provided to the subject***'s LAR***.	
9.3.5	Site visits that do NOT include a vaccination will be performed ~~on Day 57, age 1 year, age 18 months and age 2 years~~ ***at Visit 3 (28 days post Dose 2), Visit 4*** (age 1 year***), Visit 5 (***age 18 months***)*** and ***Visit 6 (***age 2 years***)***. At the site visit, the eDiary will be reviewed. The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject's LAR and will determine if any additional diagnoses and/or AEs are present and/or if concomitant medications have been used. The investigator will check vital signs and perform a physical examination at age 18 months and age 2 years. Blood (~~up to~~***approximately*** 5 mL) should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing ~~Day 57,~~ Visit 3 (28 days post dose 2), Visit 4 (age 1 year~~,~~***), Visit 5 (***age 18 months***)*** and ***Visit 6 (***age 2 years~~.~~***)***~~.~~	Clarification for the blood volume.
9.3.8	The procedures for subjects who meet ~~age~~ case definition criteria ~~and consenting symptomatic household members of AGE case~~ are described in Section 2.2. ~~The subject's LAR will be requested to complete the healthcare resource utilization questionnaire 7 to 14 days after resolution of each AGE episode.~~	Clarification and cross-referencing to the relevant section.
9.3.9	[redacted]	

[redacted]

9.4	[redacted]	
10.1.2	Table 10.a Solicited Local (Injection Site) Reactions and Systemic AEs	Inclusion of pain as a solicited reaction.
10.4.1	All AEs, whether considered related to the use of the trial vaccine or not, must be monitored by the investigator until symptoms subside and any abnormal laboratory values have returned to Baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full autopsy report should be supplied, if possible. All findings must be reported on the AE eCRF and on the SAE form*, if necessary (see Section 10.4.4). All findings in subjects experiencing AEs must also be documented in the subject's source documents. Any unsolicited AE will be collected ~~by the subject's LAR~~ for 28 days ~~via~~ ***after each dose of trial vaccine. The subject's LAR will use the*** eDiary (~~using~~***memory aid to record unsolicited symptoms for reporting in*** the ~~Vigilant e-mobile app).~~site. AEs leading to discontinuation (from the trial or from the vaccination regimen) are 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 protocol.	Clarification and further description of the process.
10.4.4	Collection of SAEs will commence from the time that the ~~subject is first administered the trial vaccine (Day 1).~~***subject's LAR signs the ICF***. Routine collection of SAEs will continue until the end of the trial (up to 2 years of age).	Clarification of when SAE collection actually begins.
11.0	~~A case adjudication committee (CAC) will assess the severity of individual confirmed AGE cases. Details are provided in the CAC charter.~~	Removal of text concerning the CAC. A CAC will not be used for this trial.
13.1	A blinded data review will be conducted prior to unblinding of subject's ***assignment to a*** trial arm. This review will assess the accuracy and completeness of the trial**,** database ***and*** subject evaluability~~, and appropriateness of the planned statistical methods~~.	Text adjusted.
13.1.1	Safety Set (SAF): The SAF will consist of all subjects who ***are randomized and*** received at least one dose of HIL-214 or placebo. ***Subjects will be analyzed***	Inclusion of additional analysis sets.

	according to the treatment which they actually received. ***Full-Analysis Set (FAS): The FAS will include all subjects who are randomized and received at least 1 dose of HIL-214 or placebo. Subjects will be analyzed according to their randomized treatment. Modified*** Full-Analysis Set ([***m***FAS] – Efficacy-evaluable ~~S~~***s***ubjects): The ***m***FAS will include all subjects who are randomized and received 2 doses of HIL-214 or placebo. ***Subjects will be analyzed according to their randomized treatment.*** ***Efficacy*** Per-Protocol ***Analysis*** Set (PPS-***E***): The PPS will include all subjects in the FAS who have no ~~major~~***important*** protocol deviations~~. The major~~ ***which may affect the evaluation of efficacy. These important*** protocol deviation criteria will be defined as part of the blinded data review~~.~~ ***prior to the unblinding of subject's assignment to a trial arm***. The categories of ~~major~~***important*** protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial product (3) receiving prohibited therapies, and (4) other ~~major~~***important*** protocol deviations that may impact the main efficacy endpoint. ***Subjects will be analyzed according to the treatment which they actually received.*** ***Immunogenicity Per-Protocol Analysis Set (PPS-I): The PPS-I will include all subjects in the FAS who have no important protocol deviations which may affect evaluation of immunogenicity. These important protocol deviation criteria will be defined as part of the blinded data review. The categories of important protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial product (3) receiving prohibited therapies, and (4) other important protocol deviations that may impact the immunogenicity endpoints. Subjects will be analyzed according to the treatment which they actually received.*** [redacted]	

13.1.2	Age, sex, race, and other baseline characteristics will be summarized descriptively by trial arm for all randomized subjects for the FAS ***and mFAS***.	
13.1.3	***AGE cases will be collected starting from the Day 1 (Dose 1 of trial vaccine) until the 2nd birthday of each subject (end of trial). The number of AGE cases including primary endpoint AGEs will be monitored during the trial in a blinded way. The process is described in the AGE monitoring charter.*** ~~The primary surveillance period will start 4 weeks after the second dose. The end of the surveillance period for the primary efficacy objective will be conditional on the number of primary endpoint cases and the subject's age. If there are less than 64 primary endpoint cases then the surveillance period will finish at the end of the trial (i.e., when the last subject reaches 2 years of age). If the first 64 primary endpoint cases are for subjects who have not reached 1 year of age then the surveillance period will finish when each subject reaches 1 year of age; otherwise, the surveillance period will finish when each subject has reached the age set by the maximum age of the first 64 primary endpoint cases (e.g. if the maximum age of the first AGE case is 15 months, the surveillance period will finish when all subjects have reached 15 months of age).~~***The primary objective will be evaluated using primary endpoint cases which occurred during the 6-month primary observation period starting at 28 days post-Dose 2. If the number of AGE events collected during the 6-month follow-up predicts less than 80% power (which translates into 24 predicted primary endpoint cases) for the evaluation of the primary objective, the primary observation period will be extended to 8 months, starting 28 days post-Dose 2.*** The event of interest for the primary endpoint is the first occurrence during the ~~surveillance~~ ***primary observation*** period, of ~~a~~ moderate/severe AGE ~~case~~ associated only with GI.1 or GII.4 ***norovirus genotypes*** ~~for a subject. The primary endpoint~~ ***Time-to-event*** will be ***computed from the start of the observation period until the date of AGE onset*** ~~measured and analyzed by determining VE; defined as~~ the ***date of last contact/discontinuation, the end date of the observation period, whichever is earlier. VE will be calculated as*** ~~function~~ 100%[1– (λV/λC)], where λV and λC denote the hazard rates for the HIL-214 and placebo arms, respectively. The primary analysis method will be a time-to-event Cox proportional hazards (CPH) model with trial arm as a factor and stratified by country, using the ~~efficacy~~ ***m***FAS. ~~Subjects without event will be censored at their last information date.~~ The confidence interval (CI) for VE	Adjustment made for 1) the change in number of primary endpoint cases from 64 to 30; 2) removal of the optional interim analysis and 3) clarification of the exploratory efficacy analyses.

	will be derived from the CI of the hazard ratio obtained from the CPH model. The primary efficacy objective will be met if the lower bound of the 95~~.4~~% CI* for the VE is above 0%. ~~The same model will be used to analyze the single event secondary and exploratory VE (only the event definition will be different).~~ The proportional-hazards assumption will be ~~tested~~***assessed*** and an alternative method of analysis will be detailed in the SAP ~~in the case of violation of this assumption.~~. A ~~sensitivity~~***supplementary*** analysis based on the PPS***-E*** will also be provided. ***Analyses for recurrent events (all primary endpoint AGEs, not only the first experienced by a subject) will be performed using proportional intensity (Andersen-Gill) models with treatment as a factor and stratified by country.*** ~~Other sensitivity analyses~~***The same CPH model will be used to analyze the single event secondary and*** [redacted] ***(only the event definition will be different).*** ~~will be described in the SAP, in order to handle subjects with only one vaccine dose or subjects having taken immunosuppressive drugs or blood products during the surveillance period.~~ [redacted]	

	[redacted]	
13.1.4	Immunogenicity results will be summarized using descriptive statistics including 95% CIs for all available assays at all relevant time points. ***These summaries will be provided for the FAS and PPS I.***	Clarification.
13.1.5	In general, data imputation will not be performed for any missing safety data. ~~Any SAE of interest leading to trial vaccine dose withdrawal, and AEs leading to trial withdrawal collected throughout the trial for all subjects in the SAF will be included.~~ ***All safety data summaries will be prepared using the SAF.***	Removal of redundant text and clarification.
13.1.6	[redacted]	Clarification of when the analyses will be performed and where they will be described in detail.

	[redacted]	
13.1.7	***Sequence of Analyses*** ***Primary and secondary efficacy objectives will be evaluated at the end of the primary observation period. Immunogenicity data collected up to Visit 4 (subject aged 1 year) and safety data collected up to the end of the primary observation period will also be analyzed at this time point.*** [redacted]	Inclusion of an additional section describing the sequence of analyses.
13.2	~~The optional IA may occur at the time where a total of 32 primary endpoint cases is expected to be observed according to the current accrual rate assumptions. Thirty-two available cases will provide a power of 78.8% to rule out the null hypothesis of no effect of vaccine (with a one-sided significance level of 0.5%) on the primary endpoint. Only necessary staff will be unblinded, to make decisions on the phase 3 design~~. ~~The final analysis for the main endpoint will be performed at alpha (Type I error) level of 4.6% (bilateral) in order to take into account the 0.1% alpha spent at the IA. The calculation uses gamma spending function (gamma = -3) for analyses at approximately half information (32 cases/64 cases).~~ ~~Efficacy and futility rules are non-binding as the trial is expected to continue, in order to collect sufficient data for evaluation of all trial objectives.~~	Clarification.

	~~More details on the IA will be provided in the DMC charter and in the SAP.~~ ~~All calculations were performed using East® version 6.5 (Cytel Inc., Boston, MA).~~ ~~Safety Interim Analysis (lead-in cohort)~~ ~~A safety data review will be performed by the DMC for the first 200 subjects based on 1) solicited events for 7 days following the first dose of trial vaccine (first DMC analysis) and 2) unsolicited and all other safety data collected from Day 1 through Day 57 (28 days post-dose 2) (second DMC analysis). Recruitment beyond 200 subjects will be paused until both first and second DMC analyses for safety have been performed.~~ ~~Immunogenicity Interim Analysis (lead-in cohort)~~ ~~Immunogenicity data review will be performed when the pan-Ig data up to 28 days post-dose 2 for the first 200 subjects is available.~~ ~~More details on the analyses will be provided in the SAP.~~ ***A formal interim analysis (interim evaluation of the study objectives) is not planned for this trial.***	
13.3	~~It is anticipated that an enrolment of approximately 3000 subjects (ratio 1:1)~~ ***collection of 24 primary endpoint cases*** will provide a power greater than 80% in comparing active vaccine versus placebo in the rate of evaluable first-confirmed AGE cases (moderate or severe) associated with norovirus GI.1 or GII.4 without co-pathogens during the 6 months period if the true VE is 70%. The underlying assumptions are a 7% annual incidence of moderate to severe AGE attributable to norovirus GI.1 or GII.4, hypothesizing that 40% of norovirus AGE cases are moderate to severe, and 30% are associated with norovirus GI.1 or GII.4 ***resulting in*** ~~. Therefore,~~ the 6-month incidence of evaluable primary endpoint AGE ~~is~~ ***cases of*** 3.5%~~, providing at the end of observation (6 months for all subjects) a target events final number of 64 cases. The assumption is a 20% subject drop-out rate~~. ***It is expected that enrollment of 3000 subjects will provide sufficient number of cases to demonstrate efficacy, accounting for various rates of drop-out/non-evaluable samples (20% to 30%), and possible lower incidence rate or underreporting of cases.***	Adjustment of the sample size calculation text.
Appendices	[redacted]	

[redacted]

Minor editorial changes were made throughout the document in light of the modifications made with this amendment. These include the naming convention for the timing of procedures (Visit/Day) and are not listed in each instance.

Summary of changes for protocol amendment 1 dated 14 October 2022 to protocol version 1.0 dated 6 October 2021 are provided in protocol version 2.0 dated 14 October 2023.

Rationale for the amendment:

- To update the protocol to address requests from the [redacted]

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2.0 TRIAL SUMMARY

Name of Sponsor: HilleVax, Inc.		**Product Name:** HIL-214
Trial Title: A Phase 2b, Double-blind, Randomized, Multi-site, Placebo-controlled Trial to Evaluate the Efficacy, Safety and Immunogenicity of Intramuscular HIL-214 Norovirus Vaccine in Healthy Children 5 Months of Age at Initial Vaccination		
IND No.: 014421		**EudraCT No.:** Not applicable
Trial Identifier: NOR-212	**Phase:** 2b	**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 trans-placental 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, genotype II.4 (GII.4) causes the vast majority of norovirus cases in children worldwide, including Latin America, where this trial will be primarily performed.

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

The composition of HIL-214 (50/150 µg GI.I/GII.4) to be used in this phase 2b efficacy trial is based on the results of trial NOR-202, a phase 2 dose-finding, safety and immunogenicity trial in 840 children aged 6 weeks to <9 years. The results of trial NOR-202 show that HIL-214 is immunogenic and had a generally good safety profile in children aged 6 weeks to <9 years for all GI.1/GII.4c VLP compositions adjuvanted with 500 µg of aluminum as $Al(OH)_3$ as (1) a one or two-dose regimen in children aged 6 to 12 months, and (2) as a two or three-dose regimen in children 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 less than 9 years.

The rationale for the inclusion of children 5 months (±14 days) of age at the time of initial vaccination is based on epidemiological data which shows that the risk of norovirus AGE increases in infants aged ~6 months old and allows enrolment either before or after the required routine childhood vaccines in the participating countries per national guidelines.

[redacted]

Primary hypothesis:

The primary hypothesis for this phase 2b proof-of-concept trial is that HIL-214, administered as 2-dose regimen, provides protection against moderate and severe AGE associated only with GI.1 or GII.4 vaccine-represented norovirus genotypes in the targeted population of infants.

This phase 2b trial aims to demonstrate the vaccine efficacy (VE) of two doses of HIL-214 administered up to 8 weeks apart, against moderate or severe AGE due to GI.1 or GII.4 norovirus genotypes in approximately 3000 healthy children aged 5 months at the time of the first dose up to when they reach the age of 2 years, as well as the safety and immunogenicity of HIL-214. A placebo arm is included to allow an unbiased evaluation of efficacy and safety. Placebo will be used in this trial because there is no single active comparator vaccine that is available across all participating sites.

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

Objectives of the Trial:

Objectives and endpoints are presented in Section 2.4.

Trial Design:

This is a phase 2b, double-blind, randomized, multi-site, placebo-controlled trial to evaluate the efficacy, safety, and immunogenicity of two doses of the IM HIL-214 vaccine compared to placebo in approximately 3000 children, 5 months of age (-14/+14 days) at the time of the first dose of trial vaccine.

The second dose of trial vaccine should be administered 28 days (and up to 56 days) after the first dose. Trial vaccine doses will be given at least 14 days before or after non-live and orally administered live vaccines, and at least 28 days before or after parenterally administered live vaccines which are given in accordance with country pediatric immunization guidelines. Subjects will be allocated (1:1) into 1 of 2 trial arms by interactive response technology (IRT) and stratified by country:

- **Arm 1 (N = 1500)**: One dose of HIL-214 at Visit 1 (Day 1) and one dose of HIL-214 at Visit 2 (28 to 56 days post dose 1).
- **Arm 2 (N = 1500):** One dose of placebo at Visit 1 (Day 1) and one dose of placebo at Visit 2 (28 to 56 days post dose 1).

The schematic of NOR-212 is shown in Section 2.1.

- All subjects will be followed for solicited local and systemic adverse events (AEs) up to 7 days after each dose of trial vaccine (including day of dose) and unsolicited AEs for up to 28 days after each dose of trial vaccine (including day of dose).
- All subjects will be followed throughout the trial (from Day 1) for serious adverse events (SAEs), AEs leading to trial vaccine dose withdrawal, and AEs leading to trial withdrawal.
- The subject's legally-authorized representative (LAR) (all subjects) will receive weekly notifications via eDiary to complete the AGE report if the subject has AGE symptoms (episodes of vomiting and/or liquid stools).
- All subjects will have six blood draws (pre-dose 1 at Visit 1 [Day 1], pre-dose 2 at Visit 2 [28 to 56 days post dose 1], at Visit 3 [28 days post dose 2], at Visit 4 [1 year of age], at Visit 5 [18 months of age] and at Visit 6 [2 years of age]), to measure anti-norovirus total immunoglobulin (pan-Ig) and histoblood group antigen (HBGA) blocking antibodies and [redacted]
- All subjects will have two safety phone/home contacts 2 days (Day 3) and 7 days (Day 8) post dose 1, and one safety phone/home contact 7 days post dose 2.
- The first 200 subjects (cohort 1) will have a site visit on Day 8 post dose 1; the remaining subjects

[redacted]

(cohort 2) will have a safety phone/home contact on this trial day.

- Enrolment beyond the first 200 subjects will be paused until safety data up to 28 days post dose 2 has been analyzed by the sponsor and assessed to be satisfactory by the data monitoring committee (DMC). If applicable, the DMC will also evaluate immunogenicity data up to 28 days post dose 2 to support recommendation to continue enrolment.
- If the child has liquid/loose stools or vomiting, the LAR will enter the number of episodes in the eDiary to inform the site. Subject's LARs will be requested to record AGE symptoms and their frequency, and body temperature in the eDiary (AGE symptoms log) from the first day of AGE onset until the symptoms have resolved. This log will be activated automatically if the number of episodes of vomiting and loose/liquid stools satisfies the AGE case definition. All subjects who meet the criteria for the AGE case definition will provide one AGE onset stool sample and two AGE follow-on stool samples. AGE cases will be collected starting from the Day 1 (Dose 1 of trial vaccine) until all subjects have reached 2 years of age (end of trial). The number of AGE cases including primary endpoint AGEs will be monitored during the trial in a blinded way. The process is described in the AGE monitoring charter.
- All AGE onset stool samples will be assayed for the presence of norovirus and norovirus-positive samples will be sequenced for genotype identification. Only norovirus-positive samples will be analyzed for the presence of co-pathogens. Follow-on stool samples collected 2 and 3 weeks post-onset will be analyzed for norovirus presence and genogroup only.
- [redacted]
- [redacted]

Trial procedures are shown in Section 2.2 [redacted]

Subject Population:

Healthy Subjects: Yes.

Age at 1st vaccination: 5 months (-14/+14 days).

Planned Number of Subjects: 3000.

Planned Number of Trial Arms: 2.

- **Arm 1** (1500 subjects): HIL-214.
- **Arm 2** (1500 subjects): Placebo.

Estimated total: 3000 randomized.

Key Inclusion Criteria:

- The subject is aged 5 months (-14/+14 days).
- Male or female.
- Children who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
- The subject's LAR signs and dates a written 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.

- Children whose LARs can and are willing to comply with trial procedures and are available for the duration of follow-up.

Key Exclusion Criteria:

- Clinically significant abnormality in growth by height, weight, or head circumference (according to local guidelines).
- Gastrointestinal abnormalities or any chronic gastrointestinal disease, including any uncorrected congenital malformation of the gastrointestinal tract according to medical history and/or physical examination.
- Known hypersensitivity or allergy to any of the investigational vaccine components (including excipients).
- Any clinically significant active infection (as assessed by the investigator) or temperature ≥38.0°C (>100.4°F), within 3 days of intended trial vaccination.
- Any serious chronic or progressive disease according to the judgment of the investigator (e.g., cardiac, renal or hepatic disease).
- Individuals with history of, e.g., convulsions/febrile convulsions, or any illness, that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
- Known or suspected impairment/alteration of immune function.
- Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
- Subjects who received or are scheduled to receive any routine or authorized vaccine within 14 days (for non-live or orally administered live vaccines) or 28 days (for parenterally administered live vaccines) before or after any dose of trial vaccine.
- Subjects participating in any clinical trial with another investigational product 30 days prior to first trial visit or intend to participate in another clinical trial at any time during the conduct of this trial.
- Subjects known to be positive for or in evaluation for possible human immunodeficiency virus infection.
- Subject's LAR or subject's first-degree relatives involved in the trial conduct.

The full list of exclusion criteria is included in the protocol (Section 7.2).

Trial Vaccine and Placebo:

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

Placebo: 0.9% sodium chloride (saline) for injection is provided by HilleVax Inc. or designated vendor 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:

The overall duration of the trial and subject participation will be up to 20 months.

Criteria for Evaluation and Analyses:

Objectives and endpoints are presented in Section 2.4.

Statistical Considerations:

Analysis sets

Safety Set (SAF): The SAF will consist of all subjects who are randomized and received at least one dose of

HIL-214 or placebo. Subjects will be analyzed according to the treatment which they actually received.

Full-Analysis Set (FAS): The FAS will include all subjects who are randomized and received at least 1 dose of HIL-214 or placebo. Subjects will be analyzed according to their randomized treatment. Modified Full-Analysis Set ([mFAS] – Efficacy-evaluable subjects): The mFAS will include all subjects who are randomized and received 2 doses of HIL-214 or placebo. Subjects will be analyzed according to their randomized treatment.

Efficacy Per-Protocol Analysis Set (PPS): The PPS will include all subjects in the mFAS who have no important protocol deviations which may affect the evaluation of efficacy. These important protocol deviation criteria will be defined as part of the blinded data review prior to the unblinding of subject's assignment to a trial arm. The categories of important protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial product (3) receiving prohibited therapies, and (4) other important protocol deviations that may impact the main efficacy endpoint. Subjects will be analyzed according to the treatment which they actually received.

Immunogenicity Per-Protocol Analysis Set (PPS-I): The PPS-I will include all subjects in the FAS who have no important protocol deviations which may affect evaluation of immunogenicity. These important protocol deviation criteria will be defined as part of the blinded data review. The categories of important protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial product (3) receiving prohibited therapies, and (4) other important protocol deviations that may impact the immunogenicity endpoints. Subjects will be analyzed according to the treatment which they actually received.

[redacted]

Analysis of demographics and other baseline characteristics

Age, sex, race, and other baseline characteristics will be summarized descriptively by trial arm for all randomized subjects for the FAS and mFAS.

Efficacy analysis

AGE cases will be collected starting from the Day 1 (Dose 1 of trial vaccine) until the 2nd birthday of each subject (end of trial). The number of AGE cases including primary endpoint AGEs will be monitored during the trial in a blinded way. The process is described in the AGE monitoring charter.

The primary objective will be evaluated using primary endpoint cases which occurred during the 6-month primary observation period starting at 28 days post-Dose 2. If the number of AGE events collected during the 6-month follow-up predicts less than 80% power (which translates into 24 predicted primary endpoint cases) for the evaluation of the primary objective, the primary observation period will be extended to 8 months, starting 28 days post-Dose 2.

The event of interest for the primary endpoint is the first occurrence during the primary observation period, of a moderate/severe AGE case associated only with GI.1 or GII.4 norovirus genotypes. Time-to-event will be computed from the start of the observation period until the date of AGE onset, the date of last contact/discontinuation, the end date of the observation period, whichever is earlier. VE will be calculated as $100\%[1-(\lambda V/\lambda C)]$, where λV and λC denote the hazard rates for the HIL-214 and placebo arms, respectively. The primary analysis method will be a time-to-event Cox proportional hazards (CPH) model with trial arm as a factor and stratified by country, using the mFAS. The confidence interval (CI) for VE will be derived from the CI of the hazard ratio obtained from the CPH model.

The primary efficacy objective will be met if the lower bound of the 95% CI for the VE is above 0%.

The proportional-hazards assumption will be assessed and an alternative method of analysis will be detailed in the SAP. A supplementary analysis based on the PPS-E will also be provided. Analyses for recurrent events (all primary endpoint AGEs, not only the first experienced by a subject) will be performed using

proportional intensity (Andersen-Gill) models with treatment as a factor and stratified by country.

The same CPH model will be used to analyze the single event secondary and [redacted]

Missing data will be handled by the time to event analysis itself, as subjects prematurely withdrawn from the trial will be censored at their last information date.

Immunogenicity analysis

Immunogenicity results will be summarized using descriptive statistics including 95% CIs for all available assays at all relevant time points. These summaries will be provided for FAS and PPS I.

Safety analysis

In general, data imputation will not be performed for any missing safety data. All safety data summaries will be prepared using SAF.

Solicited AEs

Safety will be assessed daily for 7 days after each vaccination (including the day of vaccination) via collection of solicited local and systemic AEs. Body temperature by the actual route taken will be summarized with no adjustment or conversion for route of measurement. For each solicited AE, the percentage of subjects will be summarized by event intensity for each day from Day 1 to Day 7 (including the day of vaccination) and overall. Summaries of the day of first onset of each event and the number of days subjects reported experiencing each event will also be provided. For subjects with more than 1 episode of the same event, the maximum intensity will be used for tabulations.

Unsolicited AEs

Any unsolicited AEs up to 28 days after each vaccination (including the day of vaccination), SAEs and AEs leading to trial vaccine dose withdrawal and AEs leading to trial withdrawal (all subjects), will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by system organ class (SOC) and preferred term (PT) for each trial arm. In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least one AE), and by SOC and PT. Subjects reporting more than one occurrence for a term (level) being summarized will be counted only once with maximum intensity recorded. Unless otherwise specified, unsolicited AEs after each vaccination will be summarized in the following 3 ways: 1) overall for Day 1 (day of vaccination) to 28 after each vaccination, 2) with onset between Day 1 (day of vaccination) and Day 7 after each vaccination, and 3) with onset between Day 8 and Day 28 after each vaccination.

AEs leading to trial or trial dose discontinuation

AEs leading to trial dose discontinuation collected up to the last planned trial dose administration and AEs leading to withdrawal from the trial collected throughout the trial will also be summarized.

SAEs

SAEs will be collected throughout the trial. SAEs will be coded using MedDRA and summarized by SOC and PT for each trial arm.

[redacted]

[redacted]

[redacted]

Sample Size Justification: Collection of 24 primary endpoint cases will provide a power greater than 80% in comparing active vaccine versus placebo in the rate of evaluable first-confirmed AGE cases (moderate or severe) associated with norovirus GI.1 or GII.4 without co-pathogens during the 6 months period if the true VE is 70%. The underlying assumptions are a 7% annual incidence of moderate to severe AGE attributable to norovirus GI.1 or GII.4, hypothesizing that 40% of norovirus AGE cases are moderate to severe, and 30% are associated with norovirus GI.1 or GII.4 resulting in the 6-month incidence of evaluable primary endpoint AGE cases of 3.5%. It is expected that enrollment of 3000 subjects will provide sufficient number of cases to demonstrate efficacy, accounting for various rates of drop-out/non-evaluable samples (20% to 30%), and possible lower incidence rate or underreporting of cases..
Interim Analyses: A formal interim analysis (interim evaluation of the study objectives) is not planned for this trial.
Data Monitoring Committee: An independent DMC has been established for the HIL-214 clinical development program. The role and responsibilities of the DMC are presented in the DMC charter.
NOR-212 Version 3.0 (1 September 2023)

[redacted]

2.1 Trial Design Diagram


[redacted]

[redacted]

2.2 Schedule of Trial Procedures for all Subjects (N = 3000)

Procedure	Visit 1[a]	Safety Contact 1[b]	Safety Contact 2[b]	Visit 2[a]	Safety Contact 3[b]*	Visit 3[a]	Visit 4[a]	Visit 5[a]	Visit 6[a] (ET/ Trial End)
Timing		Dose 1 + 2d	Dose 1 +7d	Dose 1 + 28 to 56d	Dose 2 + 7d	Dose 2 + 28d	Age: 1 year	Age: 18 months	Age: 2 years
Visit/safety contact window		+2	+2	+2	+2	±3	±10	±10	±10
Reminder via eDiary for AGE detection	Weekly throughout the trial								
Signed informed consent[c]	X								
Assessment of eligibility criteria[d]	X			X					
Assessment of criteria for delay of vaccination[e]	X			X					
Demographics	X								
Medical history	X								
Medication/Vaccination history	X			X					
Randomization	X								
Physical examination[f]	X			X					X
Vital signs[g]	X			X					X
Blood draw[h]	X			X		X	X	X	X
Trial vaccine administration[i]	X			X					
eDiary training[j]	X			X					
Solicited AEs[k]	X	X	X	X	X				
Unsolicited AEs[l]	X	X	X	X	X	X			
Concomitant medications[l]	X		X	X	X	X			
SAEs[m]	Throughout the trial								
AEs leading to trial vaccine withdrawal	X	X	X	X	X				
AEs leading to withdrawal from trial	Throughout the trial								
Assessments for AGE for subjects who meet AGE case definition criteria									
AGE onset stool	Each new onset of AGE (as soon as possible after the start of the episode but up to 6 days after onset of AGE)								
Follow-on stool			2 follow-on stool samples should be collected (7-14 days and 15-21 days after onset of AGE)						
AGE symptoms log[n]			With each new onset of AGE (daily until resolution of the AGE episode)						
AGE-related healthcare provider visits and AGE treatment	With each new onset of AGE (after resolution of the AGE episode)								

[redacted]

Abbreviations: AE, adverse event; AGE, acute gastroenteritis; d, day; ET, early termination; serious adverse event, SAE.
Footnotes are on the following page.

[redacted]

Footnotes:

(a) At each of the visits or phone contacts, the investigator should ask and record whether the child is breastfeeding or not. Home visits may be planned where local regulations and customs permit.

(b) Safety phone/home contacts occur at 2 days (all subjects) and 7 days (the first 200 subjects) post dose 1, and 7 days post dose 2 (all subjects The subjects will be reminded of the next planned trial activity. The safety contact will be a visit for the first 200 subjects.

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

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

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

(f) Complete physical examination prior to trial vaccine dose administration will be performed for all subjects at Visit 1 (Day 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 Visit 2 (28 to 56 days post dose 1) prior to dose 2, and when the subject reaches 1 year of age (Visit 4) and 2 years of age (Visit 5).

(g) Vital signs include (but are not limited to heart rate and temperature) prior to each trial vaccine dose administration and when the subject reaches 1 year of age (Visit 4) and 2 years of age (Visit 6).

(h) The maximum volume of blood taken at any single visit is approximately 5 mL and the approximate total volume of blood taken during the trial is maximum 30 mL for all subjects. Samples will be taken for all subjects prior to trial vaccine administration.

(i) Administration of trial vaccine Dose 1 occurs at Visit 1 (Day 1; subjects aged 5 months -14/+14 days) and trial vaccine Dose 2 occurs at Visit 2 (28 to 56 days post dose 1). Trial vaccine doses will not interfere with the timing of administration of the routine childhood vaccines per the national guidelines. Trial vaccine doses will be given at least 14 days before or after non-live and orally administered live vaccines, and at least 28 days before or after parenterally administered live vaccines. Subjects will be observed for at least 30 minutes following vaccine administration, including observation for unsolicited AEs, solicited local reactions and solicited systemic AEs.

(j) Careful training of the subject's legally-acceptable representative (LAR) on how to measure solicited local reactions, solicited systemic AEs and body temperature, how and how often to complete the eDiary for solicited AE and AGE data collection.

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

(l) Unsolicited AEs and concomitant medications for 28 days after each trial vaccine dose will be recorded on the memory aid section of the eDiary, and reviewed with the site staff/investigator. Full information on these AEs and medications will be collected and entered in the EDC by site staff/investigator.

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

(n) AGE symptoms and body temperature measurements for all subjects with AGE to be entered in the eDiary by the subject's LAR.

(o) [redacted]

[redacted]

E

[redacted]

2.4 OBJECTIVES AND ENDPOINTS

Primary Objective	Endpoints	Summary Statistics and Analysis Sets
• To demonstrate the efficacy of HIL-214 vaccine against mod/sev AGE associated only with GI.1 or GII.4 NoV genotypes.	• Time to first occurrence during the primary observation period*, of mod/sev AGE case associated only with GI.1 or GII.4 NoV genotypes.	• VE estimate** (VE; calculated as 100X [1 minus the risk ratio of AGE cases according to the endpoint definition in the vaccine group over that in the placebo group]) in the mFAS.
Secondary Objectives		
Key Secondary Efficacy Objective		
• To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated only with any NoV (GI or GII) genotypes.	• Time to first occurrence during the primary observation period* of mod/sev AGE case associated only with any NoV (GI or GII) genotypes.	• VE estimate according to the endpoint definition, in the mFAS.
Secondary Efficacy Objectives		
• To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated with GI.1 or GII.4 NoV genotypes, irrespective of other GE pathogens.	• Time to first occurrence during the primary observation period* of mod/sev AGE case associated with GI.1 or GII.4 NoV genotypes, irrespective of other GE pathogens.	• VE estimate according to the endpoint definition, in the mFAS.
• To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated with any NoV genogroup (GI or GII), irrespective of other GE pathogens.	• Time to first occurrence during the primary observation period* of mod/sev AGE case associated with any NoV genogroup (GI or GII), irrespective of other GE pathogens.	• VE estimate according to the endpoint definition, in the mFAS.
Secondary Immunogenicity Objectives		
• To evaluate the immunogenicity of HIL-214.	Pre-dose 1, 28 days post dose 1, and 28 days post dose 2: • HBGA blocking antibody titers. • Pan-Ig antibody titers.	• GI.1 GMTs, GMFRs and SRRs at relevant time points. • GII.4 GMTs GMFRs and SRRs at relevant time points. In the FAS and PPS-I.

[redacted]

OBJECTIVES AND ENDPOINTS (continued)

Secondary Safety Objectives		
• To assess the safety of HIL-214 compared to placebo.	• Solicited local AEs up to 7 days after each dose of trial vaccine. • Solicited systemic AEs up to 7 days after each dose of trial vaccine. • Unsolicited AEs for up to 28 days after each dose of trial vaccine. • AEs leading to trial vaccine dose withdrawal. • AEs leading to the subject's withdrawal from the trial from Day 1 to the end of the trial. • SAEs throughout the trial.	Proportion of subjects with, and number of: • Local reactions. • Systemic solicited AEs. • Unsolicited AEs. • AEs leading to trial vaccine dose withdrawal. • AEs leading to the subject's withdrawal from the trial. • SAEs. In the SAF.
Exploratory Objectives		
[redacted]		

[redacted]

OBJECTIVES AND ENDPOINTS (continued)

Abbreviations: AE, adverse event; AGE, acute gastroenteritis; CI, confidence interval; FAS, Full-Analysis Set; GE, gastroenteritis; GMFR, geometric mean fold rise; GMT, geometric mean titer; HBGA, histoblood group antigen; [redacted]; mod, moderate; mFAS, modified Full-Analysis set; NoV, norovirus; pan-Ig, total immunoglobulin; PPS, Per-Protocol set; SAE, serious adverse event; SAF, Safety-Analysis set; sev, severe; SRR, seroresponse rate.
Notes on the next page.

Subject age at trial entry is 5 months (-14/+14 days).
*The duration of the primary observation period is 6 months starting at 28 days post-Dose 2. Time-to-event will be computed from the start of the observation period until the date of AGE onset; the date of last contact/discontinuation; the end of the observation period, whichever is earlier.
**Vaccine efficacy will be demonstrated if the lower limit of the 95.0% CI is above 0%.

AGE Case Definition and Severity Assessment:

All subjects meeting the following criteria indicating clinical illness (AGE) will be included in the efficacy analysis:

- Individuals presenting with at least three loose or liquid stools OR at least two or more episodes of vomiting OR one or more loose or liquid stools plus one or more vomiting episodes in any 24-hour period.

The severity assessment of AGE episodes will be determined based on a modified Vesikari score (MVS) [Appendix C].

Recurrent norovirus AGE in a subject is considered a new illness according to the clinical AGE definition if:

- The subject has been free from clinical symptoms for at least 5 consecutive days.

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 investigational 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 and by doing so agree(s) that it accurately describes the results of the trial.

3.3 List of Abbreviations

AESI	adverse event of special interest
AE	adverse event
AGE	acute gastroenteritis
$Al(OH)_3$	aluminum hydroxide
CPH	Cox proportional hazards
CTM	clinical trial material
DMC	data monitoring committee
eCRF	electronic case report form
eDiary	electronic diary card
FAS	Full-Analysis Set
FDA	Food and Drug Administration
GI	genogroup (e.g., GI, GII, GIII, etc.)
GI.1	genotype (e.g., GI.1, GII.2, GII.4, etc.)
GII.4c	consensus GII.4
GCP	good clinical practice
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
IEC	Independent Ethics Committee
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
pan Ig	total immunoglobulin
PPS	Per-Protocol Set
PT	Preferred Term
QTL	quality tolerance limits
SAE	serious adverse event
SAF	Safety-Analysis Set
SAP	statistical analysis plan
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
VE	vaccine efficacy
VLP	virus-like particle

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 [4-6]. 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 trans-placental 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, genotype II.4 (GII.4) causes the vast majority of norovirus cases in children worldwide, including Latin America, where this trial will be primarily performed [20-25].

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

Refer to the IB for a summary of known and potential risks and benefits [26].

4.2 Rationale for the Proposed Trial

The rationale for the proposed trial in children aged approximately 5 months is based primarily on epidemiological data which shows that the risk of norovirus AGE increases in infants aged ~6 months old [14].

The composition of HIL-214 (50/150 µg GI.I/GII.4) to be used in this phase 2b efficacy trial is based on the results of trial NOR-202, a phase 2 dose-finding, safety and immunogenicity trial in 840 children aged 6 weeks to <9 years. The results of trial NOR-202 show that HIL-214 is immunogenic and had a generally good safety profile in children aged 6 weeks to <9 years for the 50/150 µg GI.1/GII.4c VLP composition adjuvanted with 500 µg of aluminum as $Al(OH)_3$ as (1) a one or two-dose regimen in children aged 6 to 12 months, and (2) as a two or three-dose regimen in children 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 less than 9 years.

The rationale for the inclusion of children 5 months (±14 days) of age at the time of initial vaccination is based on epidemiological data which shows that the risk of norovirus AGE increases in infants aged ~6 months old and allows enrollment either before or after the required routine childhood vaccines in the participating countries per national guidelines.

[redacted]

Primary hypothesis:

The primary hypothesis for this phase 2b proof-of-concept trial is that HIL-214, administered as 2-dose regimen, provides protection against moderate and severe AGE associated only with GI.1 or GII.4 vaccine-represented norovirus genotypes in the targeted population of infants.

This phase 2b trial aims to demonstrate the vaccine efficacy (VE) of two doses of HIL-214 administered up to 8 weeks apart, against moderate or severe AGE due to GI.1 or GII.4 norovirus genotypes in approximately 3000 healthy children aged 5 months at the time of the first dose up to when they reach the age of 2 years, as well as the safety and immunogenicity of HIL-214. A placebo arm is included to allow an unbiased evaluation of efficacy and safety. Placebo will be used in this trial because there is no single active comparator vaccine that is available across all participating sites.

The trial will be conducted in accordance with this protocol, ICH and GCP Guidelines, and applicable regulatory requirements [2].

[redacted]

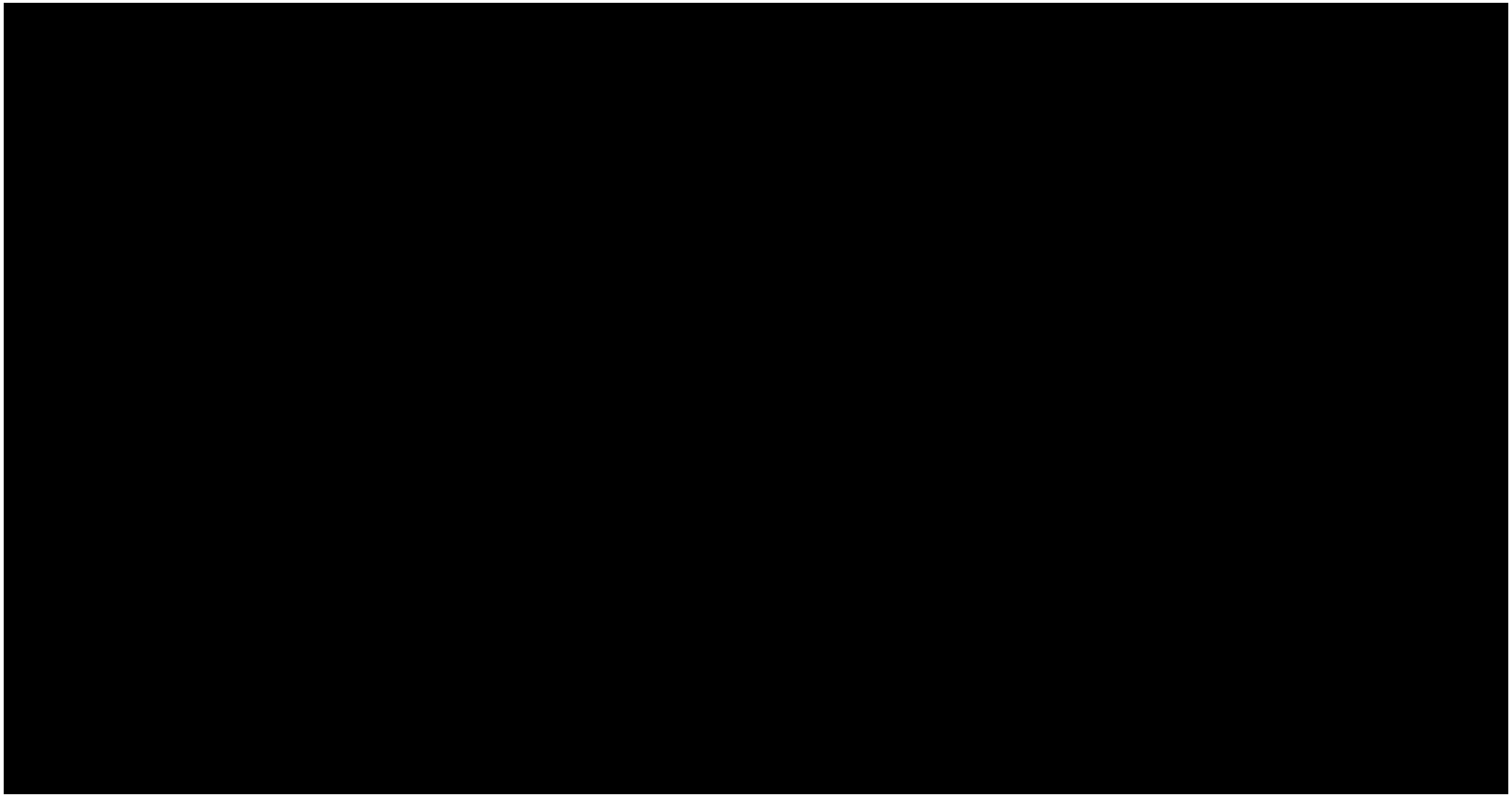
5.0 OBJECTIVES AND ENDPOINTS

Primary Objective	Endpoints	Summary Statistics and Analysis Sets
• To demonstrate the efficacy of HIL-214 vaccine against mod/sev AGE associated only with GI.1 or GII.4 NoV genotypes.	• Time to first occurrence during the primary observation period*, of mod/sev AGE case associated only with GI.1 or GII.4 NoV genotypes.	• VE estimate** (VE; calculated as 100X [1 minus the risk ratio of AGE cases according to the endpoint definition in the vaccine group over that in the placebo group]) in the mFAS.
Secondary Objectives		
Key Secondary Efficacy Objective		
• To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated only with any NoV (GI or GII) genotypes.	• Time to first occurrence during the primary observation period* of mod/sev AGE case associated only with any NoV (GI or GII) genotypes.	• VE estimate according to the endpoint definition, in the mFAS.
Secondary Efficacy Objectives		
• To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated with GI.1 or GII.4 NoV genotypes, irrespective of other GE pathogens.	• Time to first occurrence during the primary observation period* of mod/sev AGE case associated with GI.1 or GII.4 NoV genotypes, irrespective of other GE pathogens.	• VE estimate according to the endpoint definition, in the mFAS.
• To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated with any NoV genogroup (GI or GII), irrespective of other GE pathogens.	• Time to first occurrence during the primary observation period* of mod/sev AGE case associated with any NoV genogroup (GI or GII), irrespective of other GE pathogens.	• VE estimate according to the endpoint definition, in the mFAS.
Secondary Immunogenicity Objectives		
• To evaluate the immunogenicity of HIL-214.	Pre-dose 1, 28 days post dose 1, and 28 days post dose 2: • HBGA blocking antibody titers. • Pan-Ig antibody titers.	• GI.1 GMTs, GMFRs and SRRs at relevant time points. • GII.4 GMTs GMFRs and SRRs at relevant time points. In the FAS and PPS-I.

OBJECTIVES AND ENDPOINTS (continued)

Secondary Safety Objectives		
• To assess the safety of HIL-214 compared to placebo.	• Solicited local AEs up to 7 days after each dose of trial vaccine. • Solicited systemic AEs up to 7 days after each dose of trial vaccine. • Unsolicited AEs for up to 28 days after each dose of trial vaccine. • AEs leading to trial vaccine dose withdrawal. • AEs leading to the subject's withdrawal from the trial from Day 1 to the end of the trial. • SAEs throughout the trial.	Proportion of subjects with, and number of: • Local reactions. • Systemic solicited AEs. • Unsolicited AEs. • AEs leading to trial vaccine dose withdrawal. • AEs leading to the subject's withdrawal from the trial. • SAEs. In the SAF.
Exploratory Objectives		
[redacted]		

OBJECTIVES AND ENDPOINTS (continued)



Abbreviations: AE, adverse event; AGE, acute gastroenteritis; CI, confidence interval; FAS, Full-Analysis Set; GE, gastroenteritis; GMFR, geometric mean fold rise; GMT, geometric mean titer; HBGA, histoblood group antigen; [redacted] mod, moderate; mFAS, modified Full-Analysis set; NoV, norovirus; pan-Ig, total immunoglobulin; PPS, Per-Protocol set; SAE, serious adverse event; SAF, Safety-Analysis set; sev, severe; SRR, seroresponse rate. Notes on the next page.

Subject age at trial entry is 5 months (-14/+14 days).
*The duration of the primary observation period is 6 months starting at 28 days post-Dose 2. Time-to-event will be computed from the start of the observation period until the date of AGE onset; the date of last contact/discontinuation; the end of the observation period, whichever is earlier.
**Vaccine efficacy will be demonstrated if the lower limit of the 95.0% CI is above 0%.

AGE Case Definition and Severity Assessment:

All subjects meeting the following criteria indicating clinical illness (AGE) will be included in the efficacy analysis:

- Individuals presenting with at least three loose or liquid stools OR at least two or more episodes of vomiting OR one or more loose or liquid stools plus one or more vomiting episodes in any 24-hour period.

The severity assessment of AGE episodes will be determined based on a modified Vesikari score (MVS) [Appendix C].

Recurrent norovirus AGE in a subject is considered a new illness according to the clinical AGE definition if:

- The subject has been free from clinical symptoms for at least 3 consecutive days.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase 2b, double-blind, randomized, multi-site, placebo-controlled trial to evaluate the efficacy, safety, and immunogenicity of two doses of the intramuscular (IM) HIL-214 vaccine compared to placebo in approximately 3000 children, 5 months of age (-14/+14 days) at the time of the first dose of trial vaccine.

The second dose of trial vaccine should be administered 28 days (and up to 56 days) after the first dose. Trial vaccine doses will be given at least 14 days before or after non-live and orally administered live vaccines, and at least 28 days before or after parenterally administered live vaccines which are given in accordance with country pediatric immunization guidelines. Subjects will be allocated (1:1) into 1 of 2 trial arms by interactive response technology (IRT) and stratified by country:

- **Arm 1** (N = 1500): One dose of HIL-214 at Visit 1 (Day 1) and one dose of HIL-214 at Visit 2 (28 to 56 days post dose 1).
- **Arm 2** (N = 1500): One dose of placebo at Visit 1 (Day 1) and one dose of placebo at Visit 2 (28 to 56 days post dose 1).

A schematic of the trial design is shown in Section 2.1 and included as Figure 6.a.

Figure 6.a: Schematic of Trial Design

- All subjects will be followed for solicited local and systemic adverse events (AEs) up to 7 days after each dose of trial vaccine (including day of dose) and unsolicited AEs for up to 28 days after each dose of trial vaccine (including day of dose).
- All subjects will be followed throughout the trial (from Day 1) for serious adverse events (SAEs), AEs leading to trial vaccine dose withdrawal, and AEs leading to trial withdrawal.

- The subject's legally-authorized representative (LAR) (all subjects) will receive weekly notifications via eDiary to complete the AGE report if the subject has AGE symptoms (episodes of vomiting and/or liquid stools).
- All subjects will have six blood draws (pre-dose 1 at Visit 1 [Day 1], pre-dose 2 at Visit 2 [28 to 56 days post dose 1], at Visit 3 [28 days post dose 2], at Visit 4 [1 year of age], at Visit 5 [18 months of age] and at Visit 6 [2 years of age]), to measure anti-norovirus total immunoglobulin (pan-Ig) and histoblood group antigen (HBGA) blocking antibodies and [redacted]
- All subjects will have two safety phone/home contacts 2 days (Day 3) and 7 days (Day 8) post dose 1, and one safety phone/home contact 7 days post dose 2.
- The first 200 subjects (cohort 1) will have a site visit on Day 8 post dose 1; the remaining subjects (cohort 2) will have a safety phone/home contact on this trial day.
- Enrolment beyond the first 200 subjects will be paused until safety data up to 28 days post dose 2 has been analyzed by the sponsor and assessed to be satisfactory by the data monitoring committee (DMC). If applicable, the DMC will also evaluate immunogenicity data up to 28 days post dose 2 to support recommendation to continue enrolment.
- If the child has liquid/loose stools or vomiting, the LAR will enter the number of episodes in the eDiary to inform the site. The subject's LARs will be requested to record AGE symptoms and their frequency, and body temperature in the eDiary from the first day of AGE onset until the symptoms have resolved. This log will be activated automatically if the number of episodes of vomiting and loose/liquid stools satisfies the AGE case definition. All subjects who meet the criteria for the AGE case definition will provide one AGE onset stool sample and two AGE follow-on stool samples. AGE cases will be collected starting from the Day 1 (Dose 1 of trial vaccine) until all subjects have reached 2 years of age (end of trial). The number of AGE cases including primary endpoint AGEs will be monitored during the trial in a blinded way. The process is described in the AGE monitoring charter.
- All AGE onset stool samples will be assayed for the presence of norovirus and norovirus-positive samples will be sequenced for genotype identification. Only norovirus-positive samples will be analyzed for the presence of co-pathogens. Follow-on stool samples collected 2 and 3 weeks post-onset will be analyzed for norovirus presence and genogroup only.
- [redacted]
- [redacted]

[redacted]

The trial procedures are described in Section 2.2, and procedures for the country-specific household transmission ancillary study are shown in Section 2.3 and Section 9.0.

6.2 Justification for Trial Design, Dose, and Endpoints

Trial NOR-212 will be performed in children aged approximately 5 months at receipt of the first dose as this age corresponds to waning protection by maternal antibodies found in breast milk [14]. This phase 2b trial will evaluate the efficacy of HIL-214 against AGE associated with norovirus up to the time that the vaccinated subjects reach 2 years of age. Safety and immunogenicity will also be assessed throughout the trial. The sample size calculation for this efficacy trial considers the number of subjects required for the primary endpoint (Section 13.3).

HIL-214 will be administered intramuscularly as previously done in the NOR-202 pediatric trial. Based on NOR-202, the dose used during NOR-212 will be 50/150 GI.1/GII4c adjuvanted with 500 µg $Al(OH)_3$, administered as two doses, 28 days apart (at Day 1 and between Day 29 and Day 57). HIL-214 and placebo will be administered separately from the routine infant/childhood vaccines. Placebo will be used in this trial because there is no single active comparator vaccine that is available across all participating sites.

Please refer to the IB for further details [26].

6.3 Planned Duration of Subject's Participation in the Trial

The overall duration of the trial and subject participation will be up to 20 months.

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

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

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

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

6.4.3 Procedures for Premature Termination or Suspension of the Trial or the Participation of Investigational Site(s)

In the event that the sponsor, an Independent Ethics Committee (IEC)/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, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is aged 5 months (-14/+14 days).
2. Male or female.
3. Children who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
4. The subject's LAR signs and dates a written ICF and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
5. Children whose LARs can and are willing to comply with trial procedures and are available for the duration of follow-up.

7.2 Exclusion Criteria

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

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

9. Subjects who received or are scheduled to receive any routine or authorized vaccine within 14 days (for non-live or orally administered live vaccines) or 28 days (for parenterally administered live vaccines) before or after any dose of trial vaccine.
10. Subjects participating in any clinical trial with another investigational product 30 days prior to first trial visit or intend to participate in another clinical trial at any time during the conduct of this trial.
11. Subjects known to be positive for or in evaluation for possible human immunodeficiency virus infection.
12. 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 Investigational Medicinal Product Administration and/or Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of 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.
- Subjects who received any other vaccines within 14 days (for non-live or orally administered live vaccines) or 28 days (for parenterally administered live vaccines) prior to planned trial vaccine administration or blood sampling.
- Subjects who have been given antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. Investigational medicinal product administration should be delayed to allow for at least 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.

For screen failure subjects, refer to Section 9.1.9.

1. **Adverse Event:** The subject has experienced an AE (irrespective of being related/unrelated to the trial vaccine or trial-related procedures) that requires early termination because continued participation imposes an unacceptable risk to the subject's health and/or the subject's LAR is unwilling to allow the child to continue participation because of the AE. If the subject's LAR is unwilling to allow the child to continue because of the AE, the primary reason for early termination of trial participation in this case will be withdrawal due to AE and not withdrawal of consent, see below.
2. **Lost to follow-up**: The subject did not return to the clinic and at least three attempts to contact the subject's LAR were unsuccessful.
3. **Withdrawal of consent**: The subject's LAR wishes to withdraw the child from the trial. The primary reason for early termination will be withdrawal of consent if the subject's LAR withdraws the child from participation due to a non-medical reason (i.e., reason other than 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 IEC/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 local IEC/IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be trial termination.
5. Subject's **death** during trial participation.
6. **Other** reason for early termination that is not captured by the above prespecified categories.

7.5 Criteria for Premature Discontinuation of Investigational Medicinal Product 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 following the initial vaccination. 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 in trial participation for safety follow-up and efficacy and immunogenicity data collection.

Early termination of a subject's trial participation will by default prevent the subject from receiving further doses of investigational vaccine, as the subject will no longer be participating in the trial. In addition to criteria for early termination of a subject's participation (see Section 7.4), other situations may apply in which subjects may continue participating in the trial (e.g.,

contributing safety and other data according to protocol) but investigational 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 data according to protocol.

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

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

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

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

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Investigational Products

Descriptions for the investigational vaccine and the placebo are provided in the following sections.

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

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% sodium chloride (saline)] for injection is provided by HilleVax, Inc. or designated vendor, in a container allowing delivery of a 0.5 mL dose). The placebo does not contain any preservatives.

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

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

8.2 Labeling

A clinical label will be affixed to trial vaccine containers in accordance with local regulatory requirements.

8.3 Inventory and Storage

Vaccines will be shipped in refrigerated, temperature-controlled containers with a temperature monitor. The trial vaccine must be stored, kept away from light, and maintained at a controlled temperature of 2°C to 8°C (36°F to 46°F), as specified on the label. The trial vaccine must be kept in an appropriate, limited access, secure place until it is used or returned to the sponsor or

designee for destruction. The trial vaccine must not be frozen. Each kit is intended for single use only.

Receipt and dispensing of trial vaccine must be recorded by authorized personnel at the trial site. All sponsor-supplied trial 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 every day. 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 trial vaccine dose of 50 µg GI.1/ 150 µg GII.4c VLPs and 500 µg of aluminum as $Al(OH)_3$ or placebo will be administered intramuscularly at Visit 1 (Day 1) and Visit 2 (28 to 56 days after the first dose) in the anterolateral thigh muscle.

8.5 Investigational Medicinal Product Assignment and Dispensing Procedures

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

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

The investigator or designee will be responsible for overseeing the administration of vaccine to subjects enrolled in the trial according to the procedures stipulated in this trial protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable laws and regulations for that specific trial.

Expired vaccines must not be administered.

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

8.5.1 Precautions to Be Observed When Administering the Investigational Medicinal Product

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

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

Standard immunization practices are to be observed and care should be taken when administering a trial vaccine intramuscularly. In addition, World Health Organization (WHO) recommendations to reduce anxiety and pain at the time of vaccination should be followed [27].

Before administration of trial vaccine/placebo, the vaccination 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 post vaccination. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

8.6 Randomization Code Creation and Storage

The investigator or investigator's designee will access the IRT at Visit 1 (Day 1) to obtain the subject number.

The investigator or investigator's designee will utilize the IRT to randomize all subjects into either the HIL-214 or placebo arms. During this contact, the investigator or designee will provide the necessary subject identifying information.

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

8.7 Investigational Medicinal Product Blind Maintenance

The blind will be maintained by the unblinded designee.

This is a double-blind trial; the investigator and subject's LAR are blinded to trial vaccine assignment. Trial vaccine identity (label text as HIL-214 or placebo) will be included on the trial vaccine container label.

8.8 Unblinding Procedures

The trial vaccine blind shall not be broken by the investigator unless information concerning the 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 vaccine blind is broken to discuss the need for unblinding. For unblinding a subject, the trial vaccine blind can be obtained by the investigator, by accessing the IRT.

The sponsor's pharmacovigilance department must be notified as soon as possible if the trial vaccine 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 blind is broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

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

8.9 Accountability and Destruction of Sponsor-Supplied Trial Vaccines, and Other Clinical Trial Materials

The investigator or designee must ensure that the sponsor-supplied trial vaccines and placebo are used in accordance with the approved protocol and is/are administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied trial vaccine or placebo, the investigator must maintain records of all sponsor-supplied trial vaccine or placebo 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 vaccines or placebo, 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 or placebo 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 trial vaccines and placebo, 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 trial vaccine/placebo ID or job number) used to prepare each dose.
- Verifying that all kits used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

The investigator must record the current inventory of all sponsor-supplied trial vaccines or placebo (list all that apply) on a sponsor-approved trial vaccine 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 vaccines or placebo, date, and amount. The log (IRT) should include all required information as a separate entry for each subject to whom sponsor-supplied trial vaccine or placebo is administered.

Include the following if manual system is used for vaccine shipment.

The investigator will be notified of any expiry date or retest date extension of trial vaccine or placebo during the trial conduct. On expiry date notification from the sponsor or designee, the

site must complete all instructions outlined in the notification, including segregation of expired CTM for return to the sponsor or designee for destruction.

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

9.0 TRIAL PLAN

9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The schedule of trial procedures is located in Section 2.2 and 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

The requirements of the ICF are described in Section 15.2.

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

A unique subject number will be assigned to each subject by the IRT after informed consent is obtained. If all eligibility criteria are fulfilled (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

Demographic information to be obtained will include date of birth, 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 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 informed consent and the first administration of 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.

All medications, vaccines and blood products taken or received by the subjects prior to Visit 1 (Day 1) are to be collected as prior medications.

a) Medications: 2 months prior to Visit 1 (Day 1, day of vaccination).

b) Vaccines: From birth up to Visit 1 (Day 1, day of vaccination).

c) Blood products: 3 months prior to Visit 1 (Day 1, day of vaccination).

Concomitant medications and vaccines will be collected from Visit 1 (Day 1) to Visit 3 (28 days after the second dose).

The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be documented. Administration of the trial vaccine should be delayed if subjects have received antipyretics within 24 hours prior to vaccine administration.

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

These data must be written in the source documents.

9.1.3 Documentation of Trial Entry/Randomization

Only subjects who's LAR have a signed ICF and 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 and controlled by the IRT provider. The randomization specification will be approved by the sponsor's trial statistician, or designee.

If the subject is ineligible for randomization, 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: 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 and height/length and head circumference. A complete physical exam will be performed at Visit 1 (Day 1) according to the investigator's standard practice. Additional physical examinations may be performed if indicated by review of the subject's medical history. The findings should be documented in the subject's source document.

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. Follow standard of care for trial population and operational feasibility.

9.1.6 Immunogenicity Assessments

Subjects in all trial arms will undergo blood sampling for serological immunogenicity testing at Visit 1 (Day 1), Visit 2 (28 to 56 days post dose 1 - prior to dose 2) and Visit 3 (28 days post

dose 2); then when the subjects reach the age of 1 year (Visit 4), 18 months (Visit 5) and 2 years (Visit 6). All samples must be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken at any single visit is approximately 5 mL, and the approximate total volume of blood for the trial is maximum 30 mL.

9.1.7 Processing, Labeling and Storage of Biological Samples

All biological samples (e.g., blood, serum, and stool) 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 are planned at Visit 1 (Day 1), Day 3 (phone contact), Day 8 (phone contact or visit), Visit 2 (28 to 56 days post dose 1), 7 days post dose 2 (phone contact) and Visit 3 (28 days post dose 2), then when the subjects reach the age of 1 year (Visit 4), 18 months (Visit 5) and 2 years (Visit 6). The safety assessments will include collection and recording of solicited local (injection site) and systemic AEs (for 7 days post vaccination), unsolicited AEs and AEs (serious and non-serious, for 28 days post vaccination), and SAEs. 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 an 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 subject's LAR.
- Trial terminated by the sponsor.

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

9.1.10 [redacted]

[redacted]

[redacted]

[redacted]

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 for all trial-related procedures for all evaluations is shown in Section 2.2 and Section 2.3. Assessments should be completed at the designated time points.

9.3.1 Pre-Vaccination Procedures (Day 1)

1. Informed consent or ICF (Section 9.1.1).
2. Assessment of eligibility criteria (Section 7.1 and Section 7.2).
3. Demographics (Section 9.1.2).
4. Medical history (Section 9.1.2).
5. Medication/vaccination history (Section 9.1.2).
6. Randomization (Section 8.5).
7. Concomitant medications (Section 9.1.2).
8. Documentation of trial entrance/randomization (Section 9.1.3).
9. Complete physical examination (Section 9.1.4).
10. Vital signs (Section 9.1.5).
11. Blood sampling (~ 5 mL) (Section 9.1.6).

9.3.2 Vaccination Procedures (Visit 1 [Day 1]; Visit 2 [28 to 56 days post dose 1])

After confirming eligibility and randomizing the subject (on Day 1) and blood sampling, perform trial vaccine administration according to the procedures described in Section 8.5. At the next clinic visit that involves vaccination (Visit 2 - between Day 29 and Day 57), confirm that the

[redacted]

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 (Visit 1 [Day 1]; Visit 2 [28 to 56 days post dose 1])

The following post-vaccination procedures will be performed at Visit 1 (Day 1) and Visit 2 (28 to 56 days post dose 1):

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

The eDiary instructions must include the following:

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

Please note:

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

- The eDiary should be reviewed by the site.
- No corrections or additions to the eDiary will be allowed after the end of each day (midnight) in the solicited data collection period (for 7 days post vaccination).
- Any blank fields on the eDiary will be missing in the eCRF.
- Any new unsolicited safety information would be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded on the AE eCRF.
- Starting on the day of vaccination, the subject's LAR will check for specific types of events at the injection site, any specific generalized symptoms (solicited systemic AEs), body temperature (any method), any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs and body temperature will be recorded in the eDiary. Other symptoms and medications will be recorded in the memory aid section of the eDiary. Assessments should preferably take place in the evening.

- Temperature measurement is to be performed daily using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject's LAR should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the eDiary.
- The measurements of solicited local (injection site) reactions are to be performed using the ruler provided by the site.
- The collection on the eDiary of body temperature, solicited local (injection site) reactions, and solicited systemic AEs will continue for a total of 7 days following vaccine administration (including day of administration). The recording of other symptoms and medications in the memory aid section of the eDiary will continue for 28 days following vaccine administration (including day of administration).

After vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited local (injection site) reactions, 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 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 eDiary 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 site contact details will be provided to the subject's LAR.

9.3.4 Phone Contacts - Reminder Calls (2 and 7 days post dose 1 and dose 2 and 7 days post dose 2)

All subjects will have two safety phone/home contacts 2 days (Day 3) and 7 days (Day 8) post dose 1, and one safety phone/home contact 7 days post dose 2. The contact on these days may be a home visit if needed. The purpose is to remind the subject's LAR about completion of the eDiary. If the subject's LAR wishes to describe safety information, this information should only be collected by a trained healthcare professional at the site, and the safety data described must be written down in source documents. The subject's LAR should be reminded to enter the information in the eDiary and to contact the site via the telephone number provided in the ICF to discuss medical questions. The subject's LAR will be asked on Day 8 about any concomitant medications being administered to the child.

9.3.5 Site Visits After Vaccination (Visit 3 [28 days post dose 2], Visit 4 [age 1 year], Visit 5 [age 18 months] and Visit 6 [age 2 years])

Site visits that do NOT include a vaccination will be performed at Visit 3 (28 days post dose 2), Visit 4 (age 1 year), Visit 5 (age 18 months) and Visit 6 (age 2 years). At the site visit, the eDiary will be reviewed. The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject's LAR and will determine if any additional diagnoses and/or AEs are present and/or if concomitant medications have been used.

The investigator will check vital signs and perform a physical examination at age 18 months and age 2 years.

Blood (approximately 5 mL) should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing at Visit 3 (28 days post dose 2), Visit 4 (age 1 year), Visit 5 (age 18 months) and Visit 6 (age 2 years).

The site investigator/personnel should ask and record whether the child is breastfeeding or not.

The site should schedule the next site visit or other trial activity (except at the final visit) with the subject's LAR.

The subject or the subject's LAR will receive a written reminder of the next planned trial activity. The subject or the subject's LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

9.3.6 Final (End of Trial) Visit

The final (end of trial) visit will be performed when the subject has reached 2 years of age. If a subject terminates earlier, the final (end of trial) visit procedures (Section 9.3.5) should be performed at their last trial visit, if possible. The investigator must complete the End of Trial eCRF page for all subjects who received trial vaccine.

9.3.7 Post-Trial Care

No post-trial care will be provided.

9.3.8 Procedures for Subjects who Meet AGE Case Definition Criteria

The procedures for subjects who meet AGE case definition criteria are described in Section 2.2.

[redacted]

9.3.9 [redacted]

[redacted]

[redacted]

[redacted]

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. Stool samples will also be stored at a central repository after the trial has ended for up to but not longer than 20 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

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

The same applies to samples collected from consenting symptomatic household members.

[redacted]

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 investigational 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 following administration of each dose of investigational vaccine (including the day of administration) and will be recorded on the Local and Systemic Reactions eCRF page as applicable and as listed in Table 10.a.

Any solicited local or systemic AEs observed as continuing on Day 8 following each trial vaccination 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:	Erythema
	Induration
	Pain
	Swelling
Systemic adverse events:	Drowsiness
	Irritability/fussiness
	Loss of appetite
	Fever*
	Vomiting
	Diarrhea

Body temperature will be collected and recorded. *Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method used [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)] Subjects are to record greatest surface diameter in mm on the diary.
[(b)] Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method used [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

Not applicable.

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 through 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 AEs 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 Yes 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 No.

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 severity of AEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of 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 ICF are considered as AEs and should be reported as AEs.

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 and on the SAE form*, if necessary (see Section 10.4.4). All findings in subjects experiencing AEs must also be documented in the subject's source documents. Any unsolicited AE will be collected for 28 days after each dose of trial vaccine. The subject's LAR will use the eDiary memory aid to record unsolicited symptoms for reporting to the site. AEs leading to discontinuation (from the trial or from the vaccination regimen) are 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 protocol.

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date, duration.
- Serious (Y/N).

- Severity.
- 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.

**SAE reporting will be done by eCRF. If the eCRF system is unavailable, a paper sponsor SAE form/paper CRF should be completed and the event must be entered into the eCRF once access is restored.*

10.4.2 Collection and Reporting of Solicited Adverse Events

The occurrence of selected indicators of safety will be collected on eDiary by the subject's LAR for 7 days following administration of each trial vaccine dose (including the day of administration) and will be recorded on the Local and Systemic AEs eCRF, as applicable. These will be summarized in the final clinical study report 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 following each trial vaccination will be additionally 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 to withdraw from the trial.
- Solicited local (injection site) reactions or systemic AEs that lead to the subject being withdrawn from the trial 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 and medically-attended AEs (MAAEs) will not be collected.

10.4.4 Collection and Reporting of Serious Adverse Events

Collection of SAEs will commence from the time that the subject's LAR signs the ICF. Routine collection of SAEs will continue until the end of the trial (up to 2 years of age).

SAEs should be reported according to the following procedure:

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

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

The SAE form should be transmitted within 24 hours to [redacted]

If the eCRF system is unavailable, a paper sponsor SAE form/paper CRF should be completed and 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 complete a follow-up SAE form or provide other written documentation immediately. Copies of any relevant data from the hospital notes (e.g., laboratory tests, discharge summary, postmortem results) should be sent to the sponsor after redaction of any personal information for privacy.

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

10.5.3 Safety Reporting to Investigators, Independent Ethics Committees or Investigational Review Boards, and Regulatory Authorities

The sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSAR) and any other SAEs to regulatory authorities, investigators and IEC/IRB, as applicable, in accordance with national regulations in the countries where the trial is conducted. 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 an investigational 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 will also forward a copy of all expedited reports to their IEC/IRB in accordance with national regulations.

10.5.4 Post-Trial Events

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

11.0 TRIAL-SPECIFIC REQUIREMENTS

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

The DMC will be composed with a minimum of 2 members with pediatric infectious disease and/or vaccine expertise, a clinician and statistician.

Two safety data reviews will be performed by the DMC for the first 200 subjects at:

1. Safety Contact 2 (7 days post dose 1) for safety data collected up to 7 days following the first dose of trial vaccine (solicited local reactions and systemic events), and
2. Visit 3 (28 days post dose 2) for safety data collected up to 28 days following the second dose of trial vaccine (unsolicited AEs).

Enrolment beyond the first 200 subjects will be paused until safety data up to 28 days post dose 2 has been analyzed by the sponsor and assessed to be satisfactory by the DMC. If applicable, the DMC will also evaluate immunogenicity data up to 28 days post dose 2 to support the recommendation to continue enrolment.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC can conduct additional analyses of the safety data.

12.0 DATA HANDLING AND RECORD KEEPING

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

12.1 Electronic CRFs

Completed eCRFs are required for each subject for who 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 items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designee[s]) 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 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 agrees to keep the records stipulated in Appendix A and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent), electronic copy 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, International Council on Harmonisation (ICH) E6 [2] Section 4.9.5

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

13.1 Statistical and Analytical Plans

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

A blinded data review will be conducted prior to unblinding of subject's assignment to a trial arm. This review will assess the accuracy and completeness of the trial, database and subject evaluability.

13.1.1 Analysis Sets

Safety Set (SAF): The SAF will consist of all subjects who are randomized and received at least one dose of HIL-214 or placebo. Subjects will be analyzed according to the treatment which they actually received.

Full-Analysis Set (FAS): The FAS will include all subjects who are randomized and received at least 1 dose of HIL-214 or placebo. Subjects will be analyzed according to their randomized treatment. Modified Full-Analysis Set ([mFAS] – Efficacy-evaluable subjects): The mFAS will include all subjects who are randomized and received 2 doses of HIL-214 or placebo. Subjects will be analyzed according to their randomized treatment.

Efficacy Per-Protocol Analysis Set (PPS): The PPS-E will include all subjects in the mFAS who have no important protocol deviations which may affect the evaluation of efficacy. These important protocol deviation criteria will be defined as part of the blinded data review prior to the unblinding of subject's assignment to a trial arm. The categories of important protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial product (3) receiving prohibited therapies, and (4) other important protocol deviations that may impact the main efficacy endpoint. Subjects will be analyzed according to the treatment which they actually received.

Immunogenicity Per-Protocol Analysis Set (PPS-I): The PPS-I will include all subjects in the FAS who have no important protocol deviations which may affect evaluation of immunogenicity. These important protocol deviation criteria will be defined as part of the blinded data review. The categories of important protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial product (3) receiving prohibited therapies, and (4) other important protocol deviations that may impact the immunogenicity endpoints. Subjects will be analyzed according to the treatment which they actually received.

[redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Age, sex, race, and other baseline characteristics will be summarized descriptively by trial arm for all randomized subjects for the FAS and mFAS.

13.1.3 Efficacy Analysis

AGE cases will be collected starting from the Day 1 (Dose 1 of trial vaccine) until the 2nd birthday of each subject (end of trial). The number of AGE cases including primary endpoint AGEs will be monitored during the trial in a blinded way. The process is described in the AGE monitoring charter.

The primary objective will be evaluated using primary endpoint cases which occurred during the 6-month primary observation period starting at 28 days post dose 2. If the number of AGE events collected during the 6-month follow-up predicts less than 80% power (which translates into 24 predicted primary endpoint cases) for the evaluation of the primary objective, the primary observation period will be extended to 8 months, starting 28 days post-Dose 2.

The event of interest for the primary endpoint is the first occurrence during the primary observation period, of moderate/severe AGE associated only with GI.1 or GII.4 norovirus genotypes. Time-to-event will be computed from the start of the observation period until the date of AGE onset, the date of last contact/discontinuation, the end date of the observation period, whichever is earlier. VE will be calculated as 100%[1– (λV/λC)], where λV and λC denote the hazard rates for the HIL-214 and placebo arms, respectively. The primary analysis method will be a time-to-event Cox proportional hazards (CPH) model with trial arm as a factor and stratified by country, using the mFAS. The confidence interval (CI) for VE will be derived from the CI of the hazard ratio obtained from the CPH model.

The primary efficacy objective will be met if the lower bound of the 95% CI for the VE is above 0%.

The proportional-hazards assumption will be assessed and an alternative method of analysis will be detailed in the SAP. A supplementary analysis based on the PPS-E will also be provided. Analyses for recurrent events (all primary endpoint AGEs, not only the first experienced by a subject) will be performed using proportional intensity (Andersen-Gill) models with treatment as a factor and stratified by country.

The same CPH model will be used to analyze the single event secondary and exploratory VE (only the event definition will be different).

[redacted]

[redacted]

[redacted]

Missing data will be handled by the time to event analysis itself, as subjects prematurely withdrawn from the trial will be censored at their last information date.

[redacted]

Further details on efficacy analyses will be provided in the SAP.

13.1.4 Immunogenicity Analysis

Immunogenicity results will be summarized using descriptive statistics including 95% CIs for all available assays at all relevant time points. These summaries will be provided for the FAS and PPS-I.

13.1.5 Safety Analysis

In general, data imputation will not be performed for any missing safety data. All safety data summaries will be prepared using the SAF.

Solicited AEs

Safety will be assessed daily for 7 days after each vaccination (including the day of vaccination) via collection of solicited local and systemic AEs. Body temperature by the actual route taken will be summarized with no adjustment or conversion for route of measurement. For each solicited AE, the percentage of subjects will be summarized by event intensity for each day from Day 1 to Day 7 (including the day of vaccination) and overall. Summaries of the day of first onset of each event and the number of days subjects reported experiencing each event will also be provided. For subjects with more than 1 episode of the same event, the maximum intensity will be used for tabulations.

Unsolicited AEs

Any unsolicited AEs up to 28 days after each vaccination (including the day of vaccination), SAEs and AEs leading to trial vaccine dose withdrawal and AEs leading to trial withdrawal (all subjects), will be coded according to the MedDRA, and summarized by system organ class (SOC) and preferred term (PT) for each trial arm. In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least one AE), and by SOC and PT. Subjects reporting more than one occurrence for the term (level) being summarized will be

counted only once with maximum intensity recorded. Unless otherwise specified, unsolicited AEs after each vaccination will be summarized in the following 3 ways: 1) overall for Day 1 (day of vaccination) to 28 days after each vaccination, 2) with onset between Day 1 (day of vaccination) and Day 7 after each vaccination, and 3) with onset between Day 8 and Day 28 after each vaccination.

AEs leading to trial or trial dose discontinuation

AEs leading to trial dose discontinuation collected up to the last planned trial dose administration and AEs leading to withdrawal from the trial collected throughout the trial will also be summarized.

SAEs

SAEs will be collected throughout the trial. SAEs will be coded using MedDRA and summarized by SOC and PT for each trial arm.

13.1.6 Other Analyses

[redacted]

[redacted]

[redacted]

No imputation will be performed for missing data.

13.1.7 Sequence of Analyses

Primary and secondary efficacy objectives will be evaluated at the end of the primary observation period. Immunogenicity data collected up to Visit 4 (subject aged 1 year) and safety data collected up to the end of the primary observation period will also be analyzed at this time point.

[redacted]

13.2 Interim Analysis and Criteria for Early Termination

A formal interim analysis (interim evaluation of the study objectives) is not planned for this trial.

13.3 Determination of Sample Size

Collection of 24 primary endpoint cases will provide a power greater than 80% in comparing active vaccine versus placebo in the rate of evaluable first-confirmed AGE cases (moderate or severe) associated with norovirus GI.1 or GII.4 without co-pathogens during the 6 months period if the true VE is 70%. The underlying assumptions are a 7% annual incidence of moderate to severe AGE attributable to norovirus GI.1 or GII.4, hypothesizing that 40% of norovirus AGE cases are moderate to severe and 30% are associated with norovirus GI.1 or GII.4 resulting in the 6-month incidence of evaluable primary endpoint AGE cases of 3.5%.

It is expected that enrollment of 3000 subjects will provide sufficient number of cases to demonstrate efficacy, accounting for various rates of drop-out/non-evaluable samples (20% to 30%), and possible lower incidence rate or underreporting of cases.

[redacted]

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 (CRO)] and by the IEC or 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 IEC or 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., Medicines and Healthcare products Regulatory Agency (MHRA), Pharmaceuticals and Medical Devices Agency (PMDA)]. 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, 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 sponsor 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 Independent Ethics Committee and/or Institutional Review Board Approval

IECs and 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 IEC or IRB. If any member of the IEC or IRB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IEC or 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 IEC or IRB for approval. The IEC's or 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 IEC or 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 IEC or IRB. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IEC or IRB, and submission of the investigator's final status report to IEC or IRB. All IEC and IRB approvals and relevant documentation for these items must be provided to the sponsor or designee.

Incentives should not be used to exert undue influence on subjects for participation. Payments to subjects must be approved by the IEC or 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 IEC or IRB approval of the ICF and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet must be approved by both the IEC or 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 IEC or 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, 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 informed consent, 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 informed consent, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by the subject's LAR in the same manner as the original informed consent/ form. 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 (e.g., FDA), the sponsor's designated auditors, and the appropriate IECs/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 ICF 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 correspond to last subject last visit (LSLV)].

In line with EC Regulation N° 1901/2006 [5], the sponsor will submit a summary of the results of a pediatric trial within six months of completion and irrespective of whether it is part of a pediatric investigational plan (PIP) (completed or not yet completed) or not, or whether it is intended for submission later on as part of a variation, extension or new stand-alone marketing authorization application or not.

15.4.3 Publication of Trial Results

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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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 IEC/IRB that conforms to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IEC/IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IEC/IRB, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from the LAR of each subject who participates in the trial, and document the date of consent in the subject's medical chart. The valid ICF is the most current version approved by the IEC/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 each 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 following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied vaccines, and return all unused sponsor-supplied vaccines to the sponsor.

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

APPENDIX B INVESTIGATOR CONSENT TO USE OF PERSONAL INFORMATION

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

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

- Assessment of the suitability of investigator for the trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other vaccines used in other clinical trials that may contain the same chemical compound present in the investigational vaccine.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within the sponsor, 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.

APPENDIX C VESIKARI AND MODIFIED VESIKARI SCORING

	Vesikari Clinical Severity Scoring System[(a)]			Modified Vesikari Score[(b)]			
	Score			Points			
	1	2	3	0	1	2	3
Diarrhea duration, days	1-4	5	≥6	0	1-4	5	≥6
Max. n° of diarrheal stools/24h	1-3	4-5	≥6	0	1-3	4-5	≥6
Vomiting duration, days	1	2	≥3	0	1	2	≥3
Max. n° of vomiting episodes/24h	1	2-4	≥5	0	1	2-4	≥5
Max. recorded body temperature, °C	37.1-38.4	38.5-38.9	≥39.0	≤37.0	37.1-38.4	38.5-38.9	≥39.0
Dehydration	N/A	1-5%	≥6%	-	-	-	-
Health care provider visits	-	-	-	None	-	Outpatient[(c)]	ED[(d)]
Treatment	Rehydration	Hospitalization	N/A	None	Rehydration	Hospitalization	-

[(a)] Adapted from rotavirus clinical trials using the Vesikari clinical scoring system [29,30]. Mild: <7; Moderate: 7-10; Severe: ≥11; Maximum score: 20;

[(b)] Adapted from Freedman et al [31]. Mild: <9; Moderate: 9-12; Severe: ≥13 Maximum score: 20;

[(c)] Community-based health care provider visit related to vomiting, diarrhea, fever or fluid refusal;

[(d)] Emergency room health care provider visit related to vomiting, diarrhea, fever or fluid refusal.

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