TITLE: Phase 2, Single-arm, Open-label Trial for Serologic Assay Validation, Proficiency Testing, Safety and Immunogenicity of the Intramuscular HIL-214 Norovirus Vaccine in Adults Aged 18 to 49 Years

NCT: NCT05972733

Phase 2, Single-arm, Open-label Trial for Serologic Assay Validation, Proficiency Testing, Safety and Immunogenicity of the Intramuscular HIL-214 Norovirus Vaccine in Adults Aged 18 to 49 Years

(Serologic Assay Validation and Proficiency Testing of HIL-214 in Adults)

Sponsor: HilleVax Inc.
[redacted]

Trial Identifier: NOR-215

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

Trial Vaccine: Norovirus GI.1/GII.4c Bivalent Virus-like Particle Vaccine

Protocol Date: 25 October 2023

Version: 3.0

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

The list of contacts will be provided to the 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.

Approvers:

[redacted]

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki [1].
- ICH, E6 (R2) GCP: Consolidated Guideline [2].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.
- Regulatory requirements for reporting serious adverse events defined in Section 10.4.4 of this protocol.
- Terms outlined in the clinical trial site agreement.
- Appendix A – Responsibilities of the investigator.

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

Signature of the investigator _____ Date _____

Investigator name (print or type) _____

Investigator's title _____

Location of Facility (City, State) _____

Location of Facility (Country) _____

1.3 Protocol Version Summary of Changes

1.3.1 Version History

Date	Version	Change Type	Region
17 November 2022	1.0	Not applicable	Global
31 May 2023	2.0	Non-substantial	Global
25 October 2023	3.0	Non-substantial	Global

1.3.2 Summary of Changes

Summary of changes for protocol amendment 2 dated 25 October 2023 to protocol version 2.0 dated 31 May 2023

Rationale for the amendment:

Alignment with provider procedures.

Section	Description of Change	Rationale for Change
2.2	Indication that vital signs are to be collected during symptom-directed physical examinations.	Clarification.
7.3	• Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration. ~~The reason for their use (prophylaxis versus treatment) must be documented.~~ Trial vaccine administration should be delayed to allow for a full 24 hours to have passed between having used antipyretics and/or analgesic medications and trial vaccine administration.	The reason for the use of antipyretics and/or analgesics will not be documented.
9.3.3	• The use of analgesic/antipyretic medications to treat symptoms associated with trial vaccine administration will be recorded in the diary card ~~daily~~ during the reporting period (Day 1 to Day 7).	Antipyretics and/or analgesics will not be collected daily.
9.3.4	Site visits that do NOT include a vaccination will be performed on Day 8 and Day 29. Procedures include ~~symptom-directed physical examination, vital signs,~~ diary card review (Day 8 visit only solicited AEs) and blood draw. ***If applicable, a symptom-directed physical examination (including vital signs) may be performed.*** Information relating to unsolicited AEs will be obtained by interview at the Day 29 visit. The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present and/or if concomitant medications and vaccines have been used.	Clarification concerning the measure of vital signs during symptom-directed physical examination.

9.3.5	These calls will ~~follow a script, which will~~ facilitate the collection of relevant safety information including concomitant medication, and any AEs/SAEs the subject may have experienced since receiving the trial vaccine. ~~The subject will be interviewed according to the script, and information relating to AEs/SAEs, and concomitant medications or vaccinations associated with those events.~~ All safety information described by the subject must be written down in a designated location within the source documents ~~and not written on the script used for the telephone call~~.	A telephone script will not be used for this trial.
13.1.1	***The Per Protocol Set will consist of all subjects who received HIL-214 and did not have any major protocol deviations that impact immunogenicity. The Per Protocol Set will be used for supportive analyses of the immunogenicity data.***	Per Protocol set is included to see how the immunogenicity is impacted in subjects that complete procedures as planned.

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2.0 TRIAL SUMMARY

Name of Sponsor: HilleVax, Inc.		**Product Name:** HIL-214
Trial Title: Phase 2, Single-arm, Open-label Trial for Serologic Assay Validation, Proficiency Testing, Safety and Immunogenicity of the Intramuscular HIL-214 Norovirus Vaccine in Adults Aged 18 to 49 years.		
IND No.: 014421		**EudraCT No.:** Not applicable
Trial Identifier: NOR-215	**Phase:** 2	**Blinding Schema:** Open label
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. Acute gastroenteritis (AGE) caused by norovirus may sometimes lead to hospitalization and death. There is currently no vaccine against 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.

The trial vaccine, HIL-214 (previously called TAK-214), contains GI.1 virus-like particles (VLPs) and norovirus GII.4 consensus (GII.4c) VLPs which represent 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 trial vaccine used in this trial is adjuvanted with aluminum as aluminum hydroxide [$Al(OH)_3$].

The clinical trials for different compositions of HIL-214 have so far been performed in Europe, the United States and several countries in South America. The composition of HIL-214 to be used in this phase 2 trial is 50/150 µg GI.I/GII.4c, which has been primarily tested in children below the age of 9 years and shown to be immunogenic and have a good safety profile in this population. This same dose level was tested in NOR-107 in adults aged 18 to 64 years, and although 15/50 µg was considered the optimal dose, 50/150 µg was also immunogenic and had an acceptable safety profile in this population.

This single-arm trial serves to obtain serum for proficiency testing to confirm assay validity is maintained. [redacted] Given the large volume of blood required, the pediatric dose will be tested in healthy adults. The main scientific rationale for the trial is to identify immune assays that can assess the generation of serum antibodies [redacted]

In this trial, the HBGA-blocking assay and total immunoglobulin (pan Ig) enzyme-linked immunosorbent assay (ELISA), for the measurement of titers specific to the strains represented in HIL-214 (GI.1 and GII.4c), will provide the positive-control benchmarks for the exploratory objectives, and with respect to comparisons with the

other clinical trials that have evaluated immunogenicity of HIL-214

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

Objectives of the Trial:

Primary Objective

- To assess the immunogenicity of HIL-214 in serum samples that will form a proficiency panel for further analysis.

Secondary Objective

- To assess the safety of HIL-214.

Trial Design:

This is a phase 2, single-arm, open-label trial for serologic assay validation, proficiency testing, safety and immunogenicity of HIL-214, in healthy adults aged 18 to 49 years. Vaccination with a single dose of HIL-214 will occur on Day 1.

There are 3 protocol-scheduled site visits (Day 1, Day 8, and Day 29) and 1 telephone contact (Day 85). Visits 1, 2, and 3 involve blood draws.

The final contact to collect safety data is scheduled on Day 85.

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

Safety assessments

- For 7 days after vaccination (including the day of vaccination), solicited local adverse events (AEs; injection site: pain, erythema, induration and swelling); solicited systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea), and body temperature.
- For 28 days after vaccination (including the day of vaccination), unsolicited AEs.
- Throughout the trial, serious adverse events (SAEs), and AEs leading to withdrawal from the trial.

Immunogenicity assessments

- Blood for the primary endpoint (proficiency panel) will be collected from all 80 subjects at Day 1 and Day 29, corresponding to approximately 100 mL of serum from a total 200 mL of blood from an individual subject.
-

The blood sampling volumes are shown in **Table S1**.

Table S1: Blood Sampling Volumes

Sample	Day 1	Day 8	Day 29	Total volume per Subject	
Blood for serum* and **	100 mL	-	100 mL	200 mL blood	
[redacted]	10 mL	-	10 mL	20 mL blood	(total 110 mL)
[redacted]	30 mL	30 mL	30 mL	90 mL blood	
Total volume per blood draw	**140 mL**	**30 mL**	**140 mL**	**310 mL blood**	

Abbreviations: [redacted]. Notes: *serum-based assays include histoblood group antigen (HBGA)-blocking assay, pan-Ig enzyme-linked immunosorbent assay (ELISA), and [redacted]

Subject Population:

Healthy Subjects: Yes.

Age Range: 18 to 49 years.

Planned Number of Subjects: 80.

Planned Number of Trial Arms: 1.

Inclusion Criteria:

Subject eligibility is determined according to the following criteria:

- Male or female subjects aged 18 to 49 years, inclusive.
- Individuals 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 individual signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any trial procedures after the nature of the trial has been explained according to regulatory requirements.
- Individuals willing and able to comply with trial procedures and are available for the duration of follow-up.

Key Exclusion Criteria:

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

- Females who are pregnant or breastfeeding.
- Known hypersensitivity or allergy to any of the HIL-214 components (including excipients).
- Known or suspected impairment/alteration of immune function, including history of any autoimmune disease or neuro-inflammatory disease.
- Any serious chronic or progressive disease (including hepatitis B or C).
- Previous exposure to an experimental norovirus vaccine.
- Subject or subject's first-degree relatives are involved in the trial conduct.

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

Route of administration:

Intramuscular injection (deltoid muscle, preferably of the non-dominant arm).

Duration of the Trial and Duration of Subject Participation:

Up to 85 days.

Criteria for Evaluation and Analyses:

Primary Endpoints

At Day 1 and Day 29, (i) HBGA-blocking titers and (ii) pan-Ig titers that are specific for:

- GI.1 VLP.
- GII.4c VLP.

Secondary Endpoints

- Solicited local AEs up to 7 days after the dose of trial vaccine.
- Solicited systemic AEs up to 7 days after the dose of trial vaccine.
- Unsolicited AEs for up to 28 days after the dose of trial vaccine.
- AEs leading to the subject's withdrawal from the trial from Day 1 to the end of the trial.
- SAEs from Day 1 to the end of the trial.

Exploratory Endpoints

- [redacted]

Statistical Considerations:

Analysis sets:

Safety Set: The Safety Set will consist of all subjects who received HIL-214. The Safety Set will be used for the analyses of safety and immunogenicity data.

Per-protocol Set: The Per Protocol Set will consist of all subjects who received HIL-214 and did not have any major protocol deviations that impact immunogenicity. The Per Protocol Set will be used for supportive analyses of the immunogenicity data.

Analysis of demographics and baseline characteristics: Demographics, age, sex, race, and other baseline characteristics will be summarized descriptively for all subjects who received HIL-214. Summaries of continuous variables will include mean, standard deviation, median, minimum and maximum values. For categorical variables, count and percentage of subjects in each category will be computed.

Primary analysis – **immunogenicity**:

Descriptive statistics will be computed for HBGA-blocking titers and pan-Ig titers against GI.1 and GII.4c, measured at Day 1 and Day 29. These statistics will include the geometric mean titers (GMTs), geometric mean fold rise in titers (GMFR) from baseline (Day 1), and seroresponse rate (SRR). The SRR is defined as the percentage of subjects with a seroresponse, where seroresponse is a ≥4-fold rise in titer from baseline (Day 1). The 95% confidence intervals (CI) will be provided for geometric means and the SRRs.

Secondary analysis – **safety**:

Safety data will be summarized by computing number and percentage of subjects who experienced an AE.

Solicited AEs

Solicited AEs will be assessed 30 minutes after administration of trial vaccine then daily for 7 days (including the day of administration). Summaries will be provided for each solicited AE, daily from Day 1 to Day 7 after administration of trial vaccine (including the day of dose) and overall. Solicited local and systemic AEs will also be summarized by severity. For subjects with more than 1 episode of the same event within the Day 1 to Day 7 period, the maximum severity will be used for overall tabulations. Body temperature measurements will be summarized in categories (including fever, defined as temperature ≥38°C). Summaries of the day of first onset of each event and the number of days subjects experienced each event will also be provided. Data from the 30-minutes assessment will be summarized separately.

Unsolicited AEs

Unsolicited AEs, SAEs, and AEs leading to withdrawal from the trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred term (PT) and system organ class (SOC). Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once for

this term. Unsolicited AEs collected up to 28 days after administration (including the day of administration) of trial vaccine, will be summarized by severity (mild, moderate, severe) and relationship (not related, related) to trial vaccine or trial procedures. If a subject reported more than one AE within an SOC or PT then the event with the maximum severity and strongest relationship (causality) to trial vaccine or trial procedure will be included in the summaries. Any unsolicited AE will be summarized using the day of onset for the following 3 time intervals: 1) Day 1 to Day 28, 2) Day 1 to Day 7, and 3) Day 8 to Day 28. SAEs and AEs leading to withdrawal from the trial will be summarized for Day 1 to Day 28, and overall (up to Day 85).
Sample Size Justification: A sample size of 80 subjects will provide sufficient serum for the establishment of proficiency panels to confirm assay validation of the validated serology assays planned to support the clinical development plan for HIL-214.
Interim Analysis: No interim analysis is planned for this trial.
Data Monitoring Committee: An independent data monitoring committee (DMC) has been established for the HIL-214 clinical development program. The DMC will review the SAEs throughout the trial and convene as needed.
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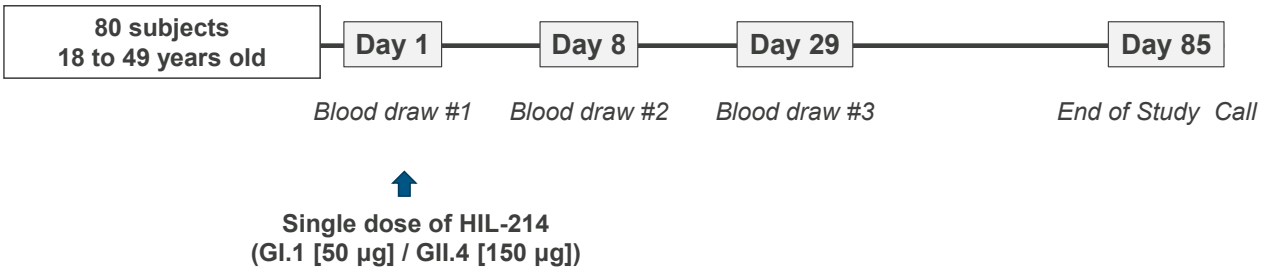
2.1 Trial Design Diagram



2.2 Schedule of Trial Procedures

Day		Day 1	Day 8	Day 29	Day 85 [a]
Visit number		1	2	3	
Visit window			±3 days	+3 days	+ 14 days
Site visit		X	X	X	
Phone contact					X
Signed informed consent form		X			
Pregnancy test [b]		X			
Assessment of eligibility criteria [c]		X			
Demographics		X			
Medical history		X			
Prior medications		X			
Concomitant medications		X	X	X	X
Physical exam	Complete [d]	X			
	Symptom-directed		X	X	
Vital signs [e]		X	X [d]	X [d]	
Vaccine administration		X			
30 min post-vaccination observation period		X			
Solicited AEs		X	X		
Unsolicited AEs		X	X	X	
Diary card provision [f]		X			
Diary card review [f]			X (Days 1–7)		
Serious adverse events [g]		X	X	X	X
AEs leading to withdrawal from trial		X	X	X	
Blood draw (max. 140 mL) [h]		X	X	X	

Notes on the next page.

Notes:
(a) Day 85 corresponds to 84 days after trial vaccine administration at Day 1.
(b) In women of childbearing potential, pregnancy tests (urine) will be performed on Day 1 before trial vaccine administration.
(c) Assessment of eligibility criteria will be documented before trial vaccine administration.
(d) Physical exam on Day 1 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. For any procedures at the site, the investigator shall follow his/her standard practice. If applicable, a symptom-directed physical examination (including vital signs) may be performed at the visits on Day 8 and Day 29.
(e) Vital signs include but are not limited to heart rate and temperature.
(f) Daily diary of solicited local and systemic adverse events (AEs) for 7 days following the trial vaccine administration.
(g) Serious adverse events (SAEs) will be collected from the time the subject is administered the trial vaccine (Day 1) up to the end of the trial (Day 85).
(h) The maximum volume of blood taken at any single site visit is approximately 30 to 140 mL, and the approximate total volume of blood taken during the trial is maximum 310 mL for all subjects. Samples will be taken for all subjects prior to trial vaccine administration on Day 1.

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

Selection criteria for the investigator will include significant knowledge of the trial protocol, the trial vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. The investigator will be required to review and sign the clinical protocol. The investigator will also be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AGE	acute gastroenteritis
$Al(OH)_3$	aluminum hydroxide
CFR	Code of Federal Regulations
[redacted]	
CSR	clinical study report
CTM	clinical trial materials
DMC	data monitoring committee
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
[redacted]	
GCP	good clinical practice
GI/GII	genogroup I/genogroup II
GI.1/GII.4	genotype I.1/genotype II.4
GII.4c	GII.4 consensus
HBGA	histoblood group antigen
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	institutional review board
MAAE	Medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
pan Ig	total immunoglobulin
[redacted]	
PT	Preferred Term
QTL	quality tolerance limit
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SRR	seroresponse rate
SUSAR	suspected unexpected serious adverse reaction
HIL-214	previously TAK-214
VLP	virus-like particle
WHO	World Health Organization

[redacted]

4.0 INTRODUCTION

4.1 Background

Noroviruses have emerged as the single most significant cause of gastroenteritis in both middle-high income countries and low resource settings worldwide [3-6]. Those most at risk of severe illness include the very young, the elderly, and immunocompromised individuals [7-11]. Noroviruses are highly infectious, highly resistant to environmental conditions, and have multiple routes of transmission including person-to-person, food-borne, and contaminated surfaces. Noroviruses can cause acute, mild to severe illness characterized by vomiting, diarrhea, fever, dehydration, and abdominal pain, representing a significant burden to public health [7]. The clinical presentation in adults and older children is similar. Acute gastroenteritis (AGE) caused by norovirus may sometimes lead to hospitalization and death. There is currently no vaccine against 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 [12-14]. 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 [15-20].

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

The clinical trials for different compositions of HIL-214 have so far been performed in Europe, the United States and several countries in South America. The composition of HIL-214 to be used in this phase 2 trial is 50/150 µg GI.I/GII.4c, which has been primarily tested in children below the age of 9 years and shown to be immunogenic and have a good safety profile in this population. This same dose level was tested in NOR-107 in adults aged 18 to 64 years, and although 15/50 µg was considered the optimal dose, 50/150 µg was also immunogenic and had an acceptable safety profile in this population [21].

More detailed information about the known and expected benefits and risks, and the reasonably expected adverse events (AEs) of the trial vaccine can be found in the current IB [21].

4.2 Rationale for the Proposed Trial

This single-arm trial serves to obtain serum for proficiency testing to confirm assay validity is maintained. [redacted]. Given the large volume of blood required, the pediatric dose will be tested in healthy adults. The main scientific

rationale for the trial is to identify immune assays that can assess the generation of serum antibodies [redacted]

The trial will be conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for ICH-GCP Guidelines, and applicable regulatory requirements [2].

5.0 TRIAL OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are listed in the following sections.

5.1 Objectives

The primary, secondary and exploratory objectives of this trial are:

Primary Objective

- To assess the immunogenicity of HIL-214 in serum samples that will form a proficiency panel for further analysis.

Secondary Objective

- To assess the safety of HIL-214.

Exploratory Objectives

[redacted]

5.2 Endpoints

Primary Endpoints

At Day 1 and Day 29, (i) HBGA-blocking titers and (ii) total immunoglobulin (pan-Ig) titers that are specific for:

- GI.1 VLP.
- GII.4c VLP.

Secondary Endpoints

- Solicited local AEs up to 7 days after the dose of trial vaccine.
- Solicited systemic AEs up to 7 days after the dose of trial vaccine.
- Unsolicited AEs for up to 28 days after the dose of trial vaccine.
- AEs leading to the subject's withdrawal from the trial from Day 1 to the end of the trial.
- Serious adverse events (SAEs) from Day 1 to the end of the trial.

Exploratory Endpoints

- [redacted]

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase 2, single-arm, open-label trial for serologic assay validation, proficiency testing, safety and immunogenicity of HIL-214, in healthy adults aged 18 to 49 years. Vaccination with a single dose of HIL-214 will occur on Day 1.

There are 3 protocol-scheduled site visits (Day 1, Day 8, and Day 29) and 1 telephone contact (Day 85). Visits 1, 2, and 3 involve blood draws.

The final contact to collect safety data is scheduled on Day 85.

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

6.2 Justification for Trial Design, Dose, and Endpoints

In this trial, the HBGA-blocking assay and pan-Ig enzyme-linked immunosorbent assay (ELISA), for the measurement of titers specific to the strains represented in HIL-214 (GI.1 and GII.4c), will provide the positive-control benchmarks for the exploratory objectives, and with respect to comparisons with the other clinical trials that have evaluated immunogenicity of HIL-214.

Please refer to the current IB [21].

6.3 Planned Duration of Subject's Participation in the Trial

Expected duration of trial participation for each subject is up to 85 days.

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

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

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

6.4.2 Criteria for Premature Termination or Suspension of the Investigational Site

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to trial vaccine administration.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. Male or female subjects aged 18 to 49 years, inclusive.
2. Individuals who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the investigator.
3. The individual signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any trial procedure after the nature of the trial has been explained according to regulatory requirements.
4. Individuals willing and able 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. Behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the trial.
2. History of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 2 years prior to Visit 1.
3. Female subjects who are pregnant or breastfeeding.
4. Female subjects of child-bearing potential who are sexually active with men and have not used any of the acceptable contraceptive methods for at least 2 months prior to trial entry.
    a) Of childbearing potential is defined as status post-onset of menarche and not meeting any of the following conditions: menopausal for at least 2 years, status after bilateral tubal ligation for at least 1 year, status after bilateral oophorectomy, or status after hysterectomy.
    b) Acceptable birth control methods are defined as one or more of the following:
        I. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).
        II. Double barrier methods (e.g., condom and cervical cap with spermicide or diaphragm with spermicide) every time during intercourse.
        III. Intrauterine device.

IV. Monogamous relationship with vasectomized partner. The partner must have been vasectomized for at least six months prior to the subjects' trial enrollment.

5. Female subjects of childbearing potential who are sexually active and refuse to use an acceptable contraceptive method as outlined in the protocol, from the time of consent throughout the trial period for 6 months after the date of trial vaccine administration.
6. Female subjects who plan to get pregnant or to donate ova before consent, during the trial period for 6 months after the date of trial vaccine administration.
7. Any positive or indeterminate pregnancy test (Section 9.1.10).
8. Chronic use of oral corticosteroids (equivalent to 20 mg/day prednisolone for ≥12 weeks / ≥2 mg/kg body weight /day for ≥2 weeks) within 60 days prior to Visit 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
9. Use of parenteral corticosteroids (equivalent to 20 mg/day prednisolone for ≥12 weeks / ≥2 mg/kg body weight /day for ≥2 weeks. Use of inhaled, intranasal or topical corticosteroid is allowed) within 60 days prior to Visit 1.
10. Receipt of immunostimulants within 60 days prior to Visit 1.
11. Receipt of parenteral, epidural or intra-articular immunoglobulin (Ig) preparations, blood products, and/or plasma derivatives within 90 days prior to Visit 1 or planned during the full duration of the trial.
12. Receipt of immunosuppressive therapy within 6 months prior to Visit 1.
13. Known hypersensitivity or allergy to any of the trial vaccine components (including excipients).
14. Any clinically significant active infection (as assessed by the investigator) or temperature ≥38.0°C (100.4°F), regardless of method used, within 3 days prior to intended trial vaccine administration.
15. Any serious chronic or progressive disease according to the judgment of the investigator (e.g., cardiac, neurological, renal, or hepatic disease).
16. History of 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.
17. Abnormalities of splenic or thymic function.
18. Known or suspected impairment/alteration of immune function.
19. Known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
20. Receipt or scheduled receipt of any approved or authorized vaccines within 14 days (all non-live vaccines) or 28 days (for live vaccines) before or after trial vaccine administration.

21. Previous exposure to an experimental norovirus vaccine.
22. Participation in any clinical trial with another investigational product 30 days prior to first trial visit or intention to participate in another clinical trial at any time during the conduct of this trial.
23. Seropositive for human immunodeficiency virus.
24. Hepatitis B or C infection.
25. Known or suspected impairment/alteration of immune function, including history of any autoimmune disease or neuro-inflammatory disease.
26. Subject or subject's first-degree relatives are involved in the trial conduct.

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

7.3 Criteria for Delay of Trial Vaccine Administration and/or Blood Sampling

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

- Subjects with a clinically significant active infection (as assessed by the investigator).
- Subjects with a body temperature ≥38.0°C (100.4°F), within 3 days of planned trial vaccine administration.
- Subjects who received any approved or authorized vaccines within 14 days (all non-live vaccines) or 28 days (for live vaccines) prior to planned trial vaccine administration or blood sampling.
- Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration. Trial vaccine administration should be delayed to allow for a full 24 hours to have passed between having used antipyretics and/or analgesic medications and trial vaccine administration.

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

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

termination of the subject's trial participation should be documented using the following categories:

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

For screen failure subjects, refer to Section 9.1.11.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding the trial vaccine (HIL-214) and materials provided directly by the sponsor, and/or sourced by other means, that are required by the trial protocol, including important sections describing the management of clinical trial materials (CTM).

8.1 Trial Vaccine

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

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

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

8.2 Labeling

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

8.3 Inventory and Storage

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

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

8.4 Dose and Regimen

The trial vaccine 50 µg GI.1/ 150 µg GII.4c VLPs and 500 µg of aluminum as $Al(OH)_3$ will be administered intramuscularly as a single dose on Day 1 in the deltoid muscle, preferably of the non-dominant arm.

8.5 Trial Vaccine Assignment and Dispensing Procedures

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

Expired trial vaccines must not be administered.

8.5.1 Precautions to Be Observed When Administering the Trial Vaccine

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

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

Standard vaccination practices are to be observed and care should be taken when administering a trial vaccine intramuscularly in the deltoid muscle. In addition, World Health Organization (WHO) recommendations to reduce anxiety and pain at the time of vaccination should be followed [24]. Before administration of the trial vaccine, the injection site must be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. Refer to the pharmacy manual for details on preparation and administration of trial vaccine.

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

8.6 Randomization Code Creation and Storage

Not applicable.

8.7 Trial Vaccine Blind Maintenance

This is an open-label trial.

8.8 Unblinding Procedure

This is an open-label trial.

8.9 Accountability and Destruction of Sponsor-Supplied Clinical Trial Materials

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

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

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 vaccine doses, and other CTM (including ancillary materials, as applicable) received and administered during their entire participation in the trial. Accountability includes, but is not limited to:

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

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

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

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

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

9.0 TRIAL PLAN

9.1 Trial Procedures

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

9.1.1 Informed Consent

The requirements of the informed consent form (ICF) are described in Section 15.2.

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

A unique subject number will be assigned to each subject after informed consent is obtained. If all eligibility criteria are fulfilled (Sections 7.1 and 7.2), this subject number will be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.11).

9.1.2 Demographics, Medical History, Prior Medications and Other Vaccinations

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

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 ICF and 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.

Details of all medications, vaccines and blood products administered or received by the subjects in the following timeframes will be collected as *prior* (prior to Day 1), or *concomitant* (from Day 1 to the end of the trial):

- Medications: from 2 months prior to Day 1 (day of trial vaccine administration), to the end of the trial.
- Vaccines: within 14 days before or after trial vaccine administration, to the end of the trial.
- Blood products: 90 days prior to Day 1 (day of trial vaccine administration), to the end of the trial.
- Antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration and the reason for their use (prophylaxis versus treatment) must be documented. Administration of the trial vaccine should be delayed if the subject has received antipyretics within 24 hours prior to trial vaccine administration.

Medications taken for prophylaxis are those intended to prevent the onset of AEs after trial vaccine administration. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

These data must be recorded in the source documents.

9.1.3 Documentation of Trial Entry

Only subjects for whom there is a signed ICF, who meet all of the inclusion criteria (Section 7.1) and none of the exclusion criteria (Section 7.2) are eligible for entry into the trial. Trial entry will be recorded in the subject screening and enrolment log.

9.1.4 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and as listed within the site responsibility delegation log. A physical examination includes but is not limited to the following: a check of general appearance, auscultation of heart and lungs, palpation of the abdomen, and inspection of extremities (including skin over the intended injection site). A complete physical exam will be performed on Day 1, prior to trial vaccine administration, according to the investigator's standard practice. Additional symptom-directed physical examinations may be performed on Day 8 and Day 29 if indicated by review of the subject's medical history or if deemed necessary.

9.1.5 Vital Signs

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

9.1.6 Immunogenicity Assessments

The immunogenicity assessments will include:

- Blood for the primary endpoint (proficiency panel) will be collected from all 80 subjects at Day 1 and Day 29, corresponding to approximately 100 mL of serum from a total 200 mL of blood from an individual subject.
- [redacted]

The blood sampling volumes are shown in Table 9.a.

Table 9.a Blood Sampling Volumes

Sample	Day 1	Day 8	Day 29	Total volume per Subject
Blood for serum* and **	100 mL	-	100 mL	200 mL blood
[redacted]) **	10 mL	-	10 mL	20 mL blood (total 110 mL)
[redacted]	30 mL	30 mL	30 mL	90 mL blood
Total volume per blood draw	**140 mL**	**30 mL**	**140 mL**	**310 mL blood**

Abbreviations: [redacted]

Notes: *serum-based assays include histoblood group antigen (HBGA)-blocking assay, pan-Ig enzyme-linked immunosorbent assay (ELISA[redacted]

All samples must be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken at any single site visit is approximately 140 mL, and the approximate total volume of blood for the trial is maximum 310 mL.

9.1.7 Processing, Labeling, and Storage of Biological Samples

All biological samples (e.g., blood and serum) will be processed, labeled, and stored according to the laboratory manual or other appropriate guideline provided to the site (Section 9.4).

9.1.8 Safety Assessments

Safety assessments will include:

- For 7 days after vaccination (including the day of vaccination), solicited local AEs (injection site: pain, erythema, induration and swelling); solicited systemic AEs (headache, fatigue, myalgia, arthralgia, vomiting, and diarrhea), and body temperature.
- For 28 days after vaccination (including the day of vaccination), unsolicited AEs.
- Throughout the trial, SAEs and AEs leading to withdrawal from the trial.

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

9.1.9 Contraception and Pregnancy Avoidance Procedure

For female subjects of childbearing potential, pregnancy testing (urine) will be performed on Day 1 prior to trial vaccine administration. All subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is strongly recommended.

Refer to Section 7.2.

9.1.10 Pregnancy

To ensure subject safety and the safety of the unborn child, each pregnancy occurring during the trial in a subject having received the trial vaccine must be reported to the sponsor promptly. If the subject agrees, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. If the subject agrees, this follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

Any pregnancy occurring following trial vaccine administration should be reported immediately, using the paper pregnancy report form, to the contact listed in the investigator site file.

Should the pregnancy occur after administration of the trial vaccine, the investigator must inform the subject of their right to receive information concerning the trial vaccine.

Any SAE occurred during pregnancy should be reported throughout the trial as per timelines and procedures described in Section 10.4.1.

9.1.11 Documentation of Subjects Who Are Not Randomized

This trial is open-label.

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

9.2 Monitoring Subject Compliance

The investigator will record the injection 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. Assessments should be completed at the designated site visit(s)/time point(s).

9.3.1 Pre-Vaccination Procedures (Day 1)

The following procedures must be performed before trial vaccine administration:

1. Informed consent (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. Concomitant medications and vaccines (Section 9.1.2).
7. Documentation of trial entrance (Section 9.1.3).
8. Complete physical examination (Section 9.1.4).
9. Vital signs (Section 9.1.5).
10. Blood sampling (~ 140 mL) (Section 9.1.6).
11. Pregnancy test (Section 9.1.10).

9.3.2 Vaccination Procedures (Day 1)

After completing all pre-vaccination procedures (Section 9.3.1) and assessing the criteria for the delay of trial vaccine administration, the investigator will administer the trial vaccine according to the procedures described in Section 8.5.

9.3.3 Post-Vaccination Procedures (Day 1)

The following post-vaccination procedures will be performed on Day 1:

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

Diary card instructions must include the following:

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

Please note:

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

- The diary card should be reviewed with the subject.
- No corrections or additions to the diary card will be allowed after it is reviewed with the investigator/designee.
- Any data that are identified as implausible or incorrect, and confirmed by the subject to be an error should be corrected by the subject on the diary card.
- Any blank fields on the diary card not otherwise corrected as above will be missing in the eCRF.

The site must enter all readable entries on the diary card into the eCRF.

- Any newly-described solicited safety information should be added to the diary card by the subject. Any new unsolicited safety information would be recorded in the subject's source document as a verbally-reported event and therefore captured as an AE and recorded in the AE eCRF.
- Starting on the day of trial vaccine administration, the subject 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, body temperature, other symptoms and medications will be recorded in the diary card. Assessments should preferably take place in the evening.
- Temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the diary card.
- The measurements of solicited local AEs are to be performed using the ruler provided by the site.
- The collection in the diary card of body temperature, solicited local AEs, and solicited systemic AEs will continue for a total of 7 days after trial vaccine administration (Day 1).
- The use of analgesic/antipyretic medications to treat symptoms associated with trial vaccine administration will be recorded in the diary card during the reporting period (Day 1 to Day 7).

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

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

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

9.3.4 Site Visits After Vaccination (Day 8 and Day 29)

Site visits that do NOT include a vaccination will be performed on Day 8 and Day 29. Procedures include diary card review (Day 8 visit only solicited AEs) and blood draw. If applicable, a symptom-directed physical examination (including vital signs) may be performed. Information relating to unsolicited AEs will be obtained by interview at the Day 29 visit. The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present and/or if concomitant medications and vaccines have been used.

Blood (30-140 mL/visit) should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing.

The site should schedule the next site visit or other trial activity with the subject.

The subject will receive a written reminder of the next planned trial activity. The subject 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.

9.3.5 Phone Contact – Safety Call and Final Contact (Day 85)

The final (end of trial) contact will be a phone contact on Day 85.

These calls will facilitate the collection of relevant safety information including concomitant medication, and any AEs/SAEs the subject may have experienced since receiving the trial vaccine. All safety information described by the subject must be written down in a designated location within the source documents.

The investigator must complete the end of trial eCRF page for all subjects who received trial vaccine.

9.3.6 Post-Trial Care

No post-trial care will be provided.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.6. After blood draw and serum processing, the serum samples will be preserved and retained at a central laboratory that was contracted by the sponsor for this purpose for up to but

not longer than 20 years or as required by applicable law. The sponsor has put into place a system to protect the subject's personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

Serum samples will be used for the analyses defined in this protocol, but can also, with permission from the subject, 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 samples could also be used for further exploratory testing. If the subject does not consent to future testing of samples on the ICF, the subject can still participate in the trial.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

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

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

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

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

10.1.2 Solicited Adverse Events

The occurrence of selected indicators of safety will be measured/collected for 7 days after trial vaccine administration (including the day of administration) and will be recorded on the local and systemic AEs eCRF page as applicable and as listed in Table 10.a.

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

Table 10.a Solicited Local and Systemic AEs

Solicited local AEs:	Erythema
	Induration
	Swelling
	Pain
Systemic AEs:	Headache
	Fatigue
	Myalgia
	Arthralgia
	Vomiting
	Diarrhea
	Fever*

Body temperature will be collected and recorded. *Fever is defined as body temperature ≥38°C (100.4°F) regardless of method used [25].

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

Table 10.b Solicited Safety Parameters

Adverse Event	Severity Grade	Intensity
Pain at injection site	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Erythema at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Induration at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Swelling at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Headache	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Fatigue	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Myalgia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Arthralgia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe Prevents daily activity
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 [25].

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

No medically-attended adverse events (MAAEs) will be collected in this trial.

10.1.5 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that:

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

10.2 Causality of Adverse Events

Relationship (causality) to the trial vaccine will also be assessed by the investigator. The relationship of each AE to the trial vaccine, including solicited systemic AEs (solicited local 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 related to trial procedure if the investigator considers that there is a reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as not related.

10.2.2 Outcome of Adverse Events

The outcome of AEs can be described as follows:

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

10.3 Additional Points to Consider for Adverse Events

An untoward occurrence generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. Intermittent events for pre-existing conditions or underlying disease should not be considered as AEs.

- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require 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 intensity recorded.

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Trial procedures:

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

AEs occurring during pregnancy:

- AEs that are associated with the pregnancy, or worsened by the pregnancy should be reported, as clinically indicated, using the appropriate pregnancy related terms or indicating the AE is during pregnancy by adding 'during pregnancy', 'in pregnancy' or 'antepartum'.

Other:

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

10.4 Procedures

10.4.1 Collection and Reporting Procedures

All AEs, whether considered related to the use of the trial vaccine or not, must be monitored by the investigator until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full autopsy report should be supplied, if possible. All findings must be reported on the AE eCRF and on the paper SAE report form* if necessary (see Section 10.4.4). All findings in a subject experiencing an AE must also be documented in that subject's source documents. Any unsolicited AE will be collected by the subject for 28 days post-dose. AEs leading to withdrawal from the trial are collected throughout the trial.

The following information will be documented for each event:

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

**SAE reporting will be done with a paper SAE form emailed (encrypted) or faxed [redacted]:*
[redacted]

10.4.2 Collection and Reporting of Solicited Adverse Events

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

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

- Solicited local or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local or systemic AEs that lead to the subject being withdrawn from the trial by the investigator.
- Solicited local 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 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 is administered the trial vaccine (Day 1). Routine collection of SAEs will continue until the end of the trial (Day 85).

SAEs should be reported according to the following procedure:

A paper SAE report 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 paper SAE form must be transmitted within 24 hours to [redacted]

10.5 Follow-up Procedures

10.5.1 Adverse Events

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

10.5.2 Serious Adverse Events

If information is not available at the time of the first report becomes available later, the investigator should complete a paper follow-up SAE report form and provide relevant source 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 within the trial until resolution, permanent outcome of the event, or are otherwise explained. The timelines and procedure for follow-up reports are the same as those for the initial report.

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

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

10.5.4 Post-Trial Events

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

11.0 TRIAL-SPECIFIC REQUIREMENTS

An independent DMC has been established for the HIL-214 clinical development program. The DMC will review the SAEs throughout the trial and convene as needed.

12.0 DATA HANDLING AND RECORD KEEPING

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

12.1 Electronic CRFs

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

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

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

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

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

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

12.2 Record Retention

The investigator must agree to keep the records stipulated in Appendix A and those documents that include (but are not limited to) the trial-specific documents, and the log that identifies all the medical records of the participating subjects. The investigator must also agree to keep temporary media, such as thermal sensitive paper (which should be copied and certified), source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICF), eCRFs, including the audit trail, and detailed records of vaccine disposition, to enable evaluations or audits from regulatory authorities, the sponsor or designee. Furthermore, ICH E6 Section 4.9.5 [2] requires the

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

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

13.0 STATISTICAL METHODS

The statistical considerations for NOR-215 are described in the following sections.

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

Analyses will be performed on the Safety Set.

The Safety Set will consist of all subjects who received HIL-214. The Safety Set will be used for the analyses of safety and immunogenicity data.

The Per Protocol Set will consist of all subjects who received HIL-214 and did not have any major protocol deviations that impact immunogenicity. The Per Protocol Set will be used for supportive analyses of the immunogenicity data.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics, age, sex, race, and other baseline characteristics will be summarized descriptively for all subjects who received HIL-214. Summaries of continuous variables will include mean, standard deviation, median, minimum and maximum values. For categorical variables, count and percentage of subjects in each category will be computed.

13.1.3 Primary Analysis - Immunogenicity

Descriptive statistics will be computed for HBGA-blocking titers and pan-Ig titers against GI.1 and GII.4c, measured at Day 1 and Day 29. These statistics will include the geometric mean titers (GMTs), geometric mean fold rise in titers (GMFR) from baseline (Day 1), and seroresponse rate (SRR). The SRR is defined as the percentage of subjects with a seroresponse, where seroresponse is a ≥4-fold rise in titer from baseline (Day 1). The 95% confidence intervals (CI) will be provided for geometric means and the SRRs.

13.1.4 Secondary Analysis - Safety

Safety data will be summarized by computing number and percentage of subjects who experienced an AE.

Solicited AEs

Solicited AEs will be assessed 30 minutes after administration of trial vaccine then daily for 7 days (including the day of administration). Summaries will be provided for each solicited AE, daily from Day 1 to Day 7 after administration of trial vaccine (including the day of dose) and overall. Solicited local AEs and systemic AEs will also be summarized by severity. For subjects

with more than 1 episode of the same event within the Day 1 to Day 7 period, the maximum severity will be used for overall tabulations. Body temperature measurements will be summarized in categories (including fever, defined as temperature ≥38°C). Summaries of the day of first onset of each event and the number of days subjects experienced each event will also be provided. Data from the 30-minutes assessment will be summarized separately.

Unsolicited AEs

Unsolicited AEs, SAEs, and AEs leading to withdrawal from the trial will be coded using the MedDRA and summarized by preferred term (PT) and system organ class (SOC). Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once for this term. Unsolicited AEs collected up to 28 days after administration (including the day of administration) of trial vaccine, will be summarized by severity (mild, moderate, severe) and relationship (not related, related) to trial vaccine or trial procedures. If a subject reported more than one AE within an SOC or PT then the event with the maximum severity and strongest relationship (causality) to trial vaccine or trial procedure will be included in the summaries. Any unsolicited AE will be summarized using the day of onset for the following 3 time intervals: 1) Day 1 to Day 28, 2) Day 1 to Day 7, and 3) Day 8 to Day 28.

SAEs and AEs leading to withdrawal from the trial will be summarized for Day 1 to Day 28, and overall (up to Day 85).

13.1.5 Exploratory Analyses

[redacted]

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned for this trial.

13.3 Determination of Sample Size

A sample size of 80 subjects will provide sufficient serum for the establishment of proficiency panels to confirm assay validation of the validated serology assays planned to support the clinical development plan for HIL-214.

[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 IRB.

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

14.2 Protocol Deviations

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

14.4 Trial Risk Management

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

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

15.0 ETHICAL ASPECTS OF THE TRIAL

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

15.1 Institutional Review Board Approval

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

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

The ICF, subject authorization form (if applicable), and subject information sheet must be written in a language fully comprehensible to the prospective subject. 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. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject 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 determines he or she will participate in the trial, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, at the time of consent and prior to the subject entering into the trial. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to the subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

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

15.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee, representatives from any regulatory authority, the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram (ECG) reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the ICF process (see Section 13.2).

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

15.4 Clinical Trial Registration, Publication, and Disclosure Policy

15.4.1 Clinical Trial Registration

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

15.4.2 Clinical Trial Results Disclosure

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

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

15.4.3 Publication of Trial Results

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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APPENDIX A RESPONSIBILITIES OF THE INVESTIGATOR

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

The investigator agrees to assume the following responsibilities:

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

12. Report AEs to the sponsor promptly. In the event of an SAE, notify PPD Safety within 24 hours.
13. Report pregnancies to PPD Safety promptly.
14. 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.
- 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.

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