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

Trial No.: NOR-212

NCT: 05281094

Statistical Analysis Plan (SAP)

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

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(NOTE: Electronic Signatures [redacted]

2.0 Change History

Version/Date	Change Log
1.0 /22-NOV-2023	Final Version
2.0/02-JUN-2024	Details added for correlates of protection analysis; titers changed to concentration throughout, other minor updates for clarification. Missing MVS subscore set to 0 for efficacy analyses; new vendor processing genotype sequencing results added, change to PPS-I definition

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under HilleVax Protocol NOR-212, titled "A Phase 2b, Double-blind, Randomized, Multi-site, Placebo-controlled Trial to Evaluate the Efficacy, Safety and Immunogenicity of Intramuscular HIL-214 Norovirus (NoV) Vaccine in Healthy Children 5 Months of Age at Initial Vaccination".

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Trial Objectives
- Trial Design
- Trial Endpoints
- Applicable Trial Definitions
- Statistical Methods

Additional exploratory analyses not necessarily defined in this SAP may be performed as deemed appropriate. Any post-hoc or unplanned analyses that are performed and not specifically identified in this SAP will be clearly identified as such if they are included in the Clinical Study Report (CSR).

6.0 Introduction

This SAP describes the statistical methods to be used for the reporting and analyses of data collected under Hillevax Protocol NOR-212.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol Version 3.0 dated 1 September 2023 and CRF version 6.0, dated 12 June 2023. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Primary, secondary and exploratory efficacy objectives related to the primary observation period will be evaluated at the end of the primary observation period (see Section **9.2.6**). Immunogenicity data collected up to Visit 4 (subject aged 1 year) and safety data collected up to the end of the primary observation period will also be analyzed at this time point. Safety data summaries will include all solicited safety data, all unsolicited adverse events (AEs), all AEs leading to withdrawal from trial vaccine, serious AEs (SAEs) with start date prior to the end of primary observation period, and AEs leading to the trial withdrawal with start date prior to the end of the primary observation period.

[redacted]

Changes made to the SAP after it has been approved but prior to analyses of the primary and secondary efficacy endpoints data at the end of the primary observation period and unblinding of subject's trial arm will be documented in SAP amendment(s). Important changes to the SAP, along with the justification for the changes, will be described in the CSR. Changes to the protocol will require an SAP amendment ONLY if the changes are to a principal feature of the protocol. Changes that impact the understanding or application of the analytical methodology of endpoints described in this SAP after analysis of the primary and secondary endpoint will also necessitate a protocol amendment.

6.1 Changes from Protocol

A calendar day instead of any 24-hour period will be used to determine the timing of symptoms for acute gastroenteritis (AGE) events.

Antibody titer for both pan-Ig and HBGA will be reported as a concentration using the units AU/mL.

Subjects will be excluded from the immunogenicity per-protocol set if not in Modified Full Analysis and baseline blood sample not collected.

7.0 Trial Objectives

7.1 Primary Objective

The primary objective of the trial is:

- To demonstrate the efficacy of HIL-214 vaccine against moderate/severe (mod/sev) AGE associated only with GI.1 or GII.4 NoV genotypes.

7.2 Secondary Objectives

7.2.1 Key Secondary Efficacy Objective

The key secondary efficacy objective of the trial is:

- To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated only with any NoV (GI or GII) genotypes.

7.2.2 Secondary Efficacy Objectives

The other secondary efficacy objectives of the trial include:

- To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated with GI.1 or GII.4 NoV genotypes, irrespective of other gastroenteritis (GE) pathogens.
- To evaluate the efficacy of HIL-214 vaccine against mod/sev AGE associated with any NoV genogroup (GI or GII), irrespective other GE pathogens.

7.2.3 Secondary Immunogenicity Objectives

- To evaluate the immunogenicity of HIL-214 vaccine.

7.2.4 Secondary Safety Objective

The secondary safety objective of the trial is:

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

7.3 Exploratory Objectives

7.3.1 Exploratory [redacted]

[redacted]

- [redacted]
- [redacted]

7.3.2 Exploratory [redacted]

7.3.3 Exploratory [redacted]

7.3.4 Exploratory [redacted]

7.3.5 Exploratory [redacted]

7.3.6 Exploratory [redacted]

7.3.7 [redacted]

8.0 Trial Design

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

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

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

A schematic of the Trial Design can be found in Section 6.1 of the protocol.

8.1 Determination of Sample Size

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

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

8.2 Randomization

Subjects who meet all inclusion criteria and none of the exclusion criteria will be centrally randomized in accordance with a computer-generated randomization schedule. Approximately 3000 subjects will be allocated (1:1) into 1 of 2 trial arms, HIL-214 vaccine and placebo, by IRT. Randomization will be stratified by country.

9.0 Objectives and Endpoints

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

OBJECTIVES AND ENDPOINTS (continued)

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

OBJECTIVES AND ENDPOINTS (continued)

[redacted]

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

Notes on the next page.

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

AGE Case Definition and Severity Assessment:

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

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

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

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

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

9.1 Analysis Sets

9.1.1 Safety Analysis Set (SAF)

The SAF will consist of all subjects who are randomized and received at least one dose of HIL-214 or placebo. Subjects will be analyzed according to the trial vaccine which they actually received.

Data from subjects who received one dose of HIL-214 and one dose of placebo will be analyzed in the HIL-214 group for summaries after corresponding HIL-214 dose and summaries after any dose, and in placebo group for summaries after the dose of placebo.

A subject may be excluded from the SAF due to major Good Clinical Practice violations.

9.1.2 Full Analysis Set (FAS)

The FAS will include all subjects who are randomized and received at least 1 dose of HIL-214 or placebo. Subjects will be analyzed according to their randomized trial arm.

A subject may be excluded from the FAS due to major Good Clinical Practice violations.

9.1.3 Modified Full Analysis Set – Efficacy Evaluable Subjects (mFAS)

The mFAS will include all subjects who are randomized and received 2 doses of HIL-214 or placebo. Subjects will be analyzed according to their randomized trial arm.

A subject may be excluded from the mFAS due to major Good Clinical Practice violations.

9.1.4 Efficacy Per-Protocol Analysis Set (PPS-E)

The PPS-E will include all subjects in the mFAS who have no important protocol deviations which may affect the evaluation of efficacy. These categories of important protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial product (3) receiving prohibited therapies, and (4) other important protocol deviations that may affect evaluation of efficacy. Subjects will be analyzed according to the trial vaccine which they actually received.

9.1.5 Immunogenicity Per-Protocol Analysis Set (PPS-I)

The PPS-I will include all subjects in the mFAS with a baseline blood sample collected before administration of first dose and who have no important protocol deviations which may affect evaluation of immunogenicity. These categories of important protocol deviations include: (1) not meeting selected entry criteria, (2) receiving wrong or incomplete trial product (3) receiving prohibited therapies, (4) protocol-described regimen not followed for storage of investigational vaccine or placebo, (5) vaccination regimen described in protocol not followed for administration of investigation vaccine or placebo, (e.g., administered out of window, or in incorrect injection site) and (6) other important protocol deviations that may affect evaluation of the immunogenicity. Subjects will be analyzed according to the trial vaccine which they actually received.

[redacted]

[redacted]

9.2 Conventions and Derivations

9.2.1 Baseline and Change from Baseline

Unless otherwise specified, baseline is defined as the last non-missing value before the first dose of trial vaccine (HIL-214 or Placebo). Baseline values will be collected at the Day 1 visit in this trial, prior to the administration of the study injection. Change from baseline is defined as (value at post-baseline visit – value at baseline). Baseline is set to missing if no dose of trial vaccine is administered.

9.2.2 Prior and Concomitant Medications and Vaccinations

Prior medications are defined as those medications with a start date and end date prior to the date of first dose of trial vaccine.

Concomitant medications are medications with an end date on or after the date of first dose of trial vaccine, or ongoing.

For partial dates, refer to SAP section 9.2.4 for partial dates imputation.

9.2.3 Age at Randomization

Age at randomization will be reported in months and derived in the following way:

$$Age\ (Months) = ((Date\ of\ Randomization - Date\ of\ Birth) + 1) \,/\, 30.4375$$

9.2.4 Imputation of Partial Dates

Partial AE onset and medication start dates will be imputed as follows:

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

If this results in a date that is after the known end date of the AE/medication then use the date of the earliest trial vaccination or January the 1st, whichever is the latest.

If the start date is completely unknown, then use the date of the last trial vaccination. If this results in a date that is after the known end date of the AE/medication, then use the date of the earliest trial vaccination. If this results in a start date after a known or partial end date, do not impute the start date.

Partial medical conditions start dates will be imputed as follows:

- If only the month and year are specified, then use the 1st day of the month or the date of birth, whichever is latest.
- If only the year is specified, then use January 1st of that year or the date of birth, whichever is latest.
- If the start date is completely unknown, do not impute the start date.

Partial AE resolution, medical condition stop dates and medication stop dates will be imputed as follows:

- If the event, condition, or medication is flagged as ongoing, do not impute the stop date.
- If only the month and year are specified, then use the last day of the month or the date of data-cut, whichever is earliest.
- If only the year is specified, then use December 31st of that year or the date of data-cut, whichever is earliest.
- If the stop date is completely unknown, do not impute the stop date.

Dates will be presented in listings as recorded.

9.2.5 Analysis Visit Windows

The study protocol describes the timing of visits and corresponding windows. Visits are not derived for statistical analysis. Measurements from unscheduled visits are excluded from all summaries.

For immunogenicity analysis on the PPS-I analysis set, the following windows will define which results are summarized. Immunogenicity assay results will be excluded if the corresponding blood sample is collected outside of the following windows:

- Visit 2 blood collection must be between 23 days and 70 days from dose 1 vaccination date, and also before second vaccination.
- Visit 3 blood collection must be between -10 and +33 days from 28 days after dose 2 vaccination date.
- Visit 4 blood collection must be between -17 and +40 days from subject's one year of age.
- Visit 5 blood collection must be between -17 and +40 days from subject's 18 months of age.
- Visit 6 blood collection must be between -17 and +40 days from subject's two years of age.

Summaries exclude data outside of allowable visit windows as described here. Data outside of allowable windows and data from unscheduled visits will be listed.

9.2.6 Primary Observation Period

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

9.2.7 Exploratory [redacted]

[redacted]

9.3 Efficacy

9.3.1 Acute Gastroenteritis (AGE)

Clinical definition of the AGE case as per trial protocol: Individuals presenting with at least three loose or liquid stools OR at least two or more episodes of vomiting OR one or more loose or liquid stools plus one or more vomiting episodes in any 24-hour period.

An AGE event is confirmed using records of symptoms (loose or liquid stool and vomiting), reported by subjects legally authorized representative (LAR) in the eDiary: either in the symptoms log, or in the page designed to activate symptoms log once the reported number of symptoms satisfy the clinical definition of AGE event (hereafter referred as "trigger page"). Data from the “trigger page” will be used only in addition to the activated symptom log for an AGE event. The data in symptoms log are collected daily for 8-hour time intervals (00:00 to 08:00, 08:00 to 16:00 and 16:00 to 00:00). The data in the "trigger page" are collected as number of episodes of vomiting or loose/liquid stool in the last 24 hours.

An AGE event is considered confirmed at the calendar day, for which subjects LAR reported any of the following:

- at least three loose or liquid stools,
- at least two episodes of vomiting,
- at least one episode of loose or liquid stool and at least one episode of vomiting.

Only confirmed AGEs are included in the efficacy analyses, with onset date set to the calendar day when the AGE was confirmed.

Per protocol, recurrent norovirus AGE in a subject is considered a new illness according to the clinical AGE definition, if the subject has been free from clinical symptoms for at least 5 consecutive days. Therefore, the end date of an AGE event will be set to the last date with any symptom present, before 5 days of no symptoms reported by the LAR. Missing records are considered as days without symptoms in this calculation.

A day with any symptom present is defined as a calendar day when 'Yes' for symptom occurrence was reported, together with reported number of episodes >0 in any 8-hour time interval in the symptoms log, or when number of episodes >0 was reported in the "trigger page”. If in the symptoms log, the LAR reported ‘Yes’ for the occurrence of a symptom but did not report the number of episodes, 1 will be imputed for the corresponding 8-hour time interval. These imputed data will also be used in determining event severity (Section 9.3.3).

A day of no symptoms is defined as a day when the LAR reported ‘Yes’ for symptom occurrence and 0 for the number of episodes or ‘No’ for symptom occurrence, for all three 8-hour time intervals in the symptoms log.

Derived onset and end dates for an AGE event will be used to compute event duration in days:

Derived End Date – Derived Onset Date + 1 (day).

Derivation of the onset and end date for an AGE event will be based on records within symptoms log for reported AGE event. If there are records reported in the "trigger page" within the following time interval:

> [AGE start date reported in the symptoms log – 5 days; last day with any symptom present in the symptoms log +5 days],

they will also be included in the derivation. For symptoms reported on the same calendar day multiple times, the record with the greatest number of episodes for each symptom will be used.

9.3.2 Recurrent NoV Acute Gastroenteritis (AGE)

Recurrent NoV AGE in a subject is considered a new illness according to the clinical AGE definition (see Section **9.3.1**) if the subject has been free from clinical AGE symptoms for at least 5 consecutive days.

If the symptom log for an AGE event contains records of symptoms after the derived end date (i.e., after 5 consecutive days without symptoms, see Section **9.3.1**), those symptoms are considered as a potential new AGE event. If any of these records confirms an AGE event as per Section **9.3.1**, the date from this record would mark the start of a new AGE event with derived onset and end dates as per Section **9.3.1**. If none of these records confirms an AGE event, they will not be reported as new AGE events, but included in the symptoms data listings (as reported).

9.3.3 Acute Gastroenteritis (AGE) Severity [redacted]

The severity assessment of AGE events will be based on the modified Vesikari scoring (see Appendix A), derived from data collected via the electronic AGE symptoms log, "trigger page" data (both collected in the eDiary), and additional information about the AGE event (treatment and medical attention), collected in the CRF.

If reported start dates for an AGE event differ between the eDiary symptoms log and the Additional Information CRF page, the CRF data with additional information will be attributed to this AGE, if the reported start date on the CRF page is within ±5 days from the start date reported in the eDiary symptoms log.

If more than one Additional Information CRF page is associated with the same AGE event, the page resulting in the worst score (i.e., emergency department visit indicated) will be selected.

The modified Vesikari score (MVS) is composed of seven items:

1. Diarrhea duration (days)
2. Maximum number loose/liquid stools in 24h (calendar day)
3. Vomiting duration (days)
4. Maximum number vomiting episodes in 24h (calendar day)
5. Maximum recorded body temperature
6. Health care provider visits
7. Treatment

Each item attributes a subscore ranging from 0 to 3, except for the subscore for treatment, which contributes a maximum of 2 points. The MVS is computed as sum of subscores, with a maximum MVS of 20. For the efficacy analyses and corresponding summaries of the AGE events data, missing subscore will be set to 0. A summary of the AGE events with non-imputed MVS sub-scores will also be provided.

Symptoms (vomiting, loose/liquid stools) and temperature data collected between derived onset and end date for an AGE will be used to determine duration of the symptom, maximum number of episodes and maximum temperature.

Duration of the symptom is defined as the number of calendar days with this symptom present (see Section **9.3.1**) between derived onset and end dates.

Number of episodes for a symptom will be calculated for each assessment date (calendar day) as the sum of the number of episodes for 3 8-hour time intervals in the symptoms log. Maximum number of episodes will be derived over days with symptom present. For the records where a trigger page and a symptoms log are completed on the same calendar date, the record with the greatest number of episodes will be used.

Maximum for the temperature will be derived over days when temperature was reported without imputation for the missing records.

The following severity categories will be assigned based on the MVS total score: <9 Mild, 9-10 Moderate, ≥11 Severe.

[redacted]

9.3.4 NoV Presence (Genogroup) and Genotypes

The presence of NoV in the AGE onset stool sample, collected from the subject, and genotype of the NoV will be determined by reverse transcription-polymerase chain reaction(RT-PCR) and RT-PCR sequencing assay; sample testing results (presence of NoV, sequencing and presence of co-pathogens) will be provided via data transfer from a Central Lab. Sequencing assay results will be provided by two different laboratory facilities, hereby referred to as PPD and CDC. The CDC sequencing laboratory results will be the primary source of data. Selected summaries will be produced for both sets of sequencing results (i.e., results from CDC and PPD), including a summary of agreement between the two laboratory results. Cohen's Kappa will be used to determine the level of agreement. The Kappa statistic, 95% confidence interval and p-value will be presented for subjects in the mFAS. Sequencing results will be reflected in summaries by genotype or endpoint definitions.

The type of stool sample (onset or follow-on), the sample collection date and reported AGE start date are recorded by the site in electronic data capture (EDC) system. If reported start dates for an AGE event differ among the eDiary symptoms log and EDC Stool Sample page, the stool sample data will be attributed to this AGE, if the reported start date on the CRF page is within ±5 days from the start date reported in the eDiary symptoms log.

The derived AGE onset date will be used to determine the window for the corresponding stool sample collection. Samples labelled as 'Onset' by the site and collected between 0 and 6 days after the derived AGE onset date will be included in the efficacy analyses.
If more than one sample is labelled as 'Onset' and available for the same AGE event, the stool sample with the earliest collection date will be used to determine the presence of NoV.
Samples collected later than 6 days from the derived AGE onset date (i.e., collected out of window) may be used in supplementary or exploratory efficacy analysis, if deemed relevant during blind data review.

If the 'Onset' stool sample is collected before the derived AGE onset date but on or after the reported AGE start date, the sample result will be used only if there is at least one episode of any symptom reported in the aforementioned period (between reported AGE start and derived AGE onset).

If the 'Onset' stool sample for an AGE event is missing (not collected), but the first follow on stool sample is collected within the 0 to 6 days window from the derived AGE onset date, this sample will be tested for the presence of NoV, sequencing and presence of co-pathogens, and test results will be used in efficacy analyses.

9.3.5 Vaccine Efficacy (VE) Point Estimate

The VE point estimate will be calculated as:

- $100 \times [1 - (\lambda V / \lambda C)]$ (%)

where λV and λC denote the hazard rates from a Cox proportional hazards (CPH) model for the HIL-214 and placebo arms, respectively, and λV / λC the hazard ratio.

9.3.6 Total Person-Time at Risk

Person-time will be calculated in days and converted to months by dividing by 30.4375.

9.3.6.1 Last Information Date (Censoring Date)

Censoring date for the primary and secondary efficacy endpoints is defined as the earlier of the last contact date, date of discontinuation from the study, and end of the primary observation period (determined individually for each subjects based on the timing of the second dose). Censoring date for exploratory endpoint analysis will be defined as for the primary and secondary endpoints but assessing the exploratory observation period instead of the primary observation period. For the endpoint of vaccine efficacy between first and second dose, censoring will consider an observation period ending the day before the second dose. AGE event date is defined as the derived date per Section **9.3.1**.

9.3.6.2 Analysis of a Single Event

The total person-time at risk for the analysis of single events will be calculated by summing the subject level time up to censoring or the first event during the relevant observation period.

The subject-level time at risk in days is derived as:

$$Time\ at\ Risk\ (Subject)_S = Date\ of\ Event\ or\ Censoring - Start\ Date\ of\ Relevant\ Observation\ Period + 1$$

See Sections **9.2.6** and **9.2.7** for details on the relevant observation period.

The person-days at risk for both trial arms is derived as:

$$Total\ PersonDays\ at\ Risk_S = \sum Time\ at\ Risk\ (Subject)_S$$

If the start date of the relevant observation period is after the date of censoring, the person-days at risk for that subject is set to zero.

9.3.6.3 Analysis of Multiple Events

The total person-months at risk for the analysis of multiple events will be calculated by summing the subject level time at risk up to the last information date during the relevant observation period and after the last AGE event.

The subject level time at risk is derived as:

$$Time\ at\ Risk\ (Subject)_M = Last\ Information\ Date - Start\ Date\ of\ Relevant\ Observation\ Period + 1$$

See Section **9.2.6** and **9.2.7** for details on the relevant observation period.

The study level person-days for both trial arms at risk is derived as:

$$Total\ PersonDays\ at\ Risk_M = \sum Time\ at\ Risk\ (Subject)_M$$

9.3.7 Unadjusted Event Rate

The unadjusted event rate will be calculated as:

$$Number\ of\ Events\ during\ Relevant\ Observation\ Period\ /\ Total\ PersonDays\ at\ Risk_S$$

9.3.8 Time to Event (Days)

The time to an event or censoring during the relevant observation period for each subject will be derived as:

$$Time\ to\ [Event]\ (Days) = Date\ of\ Event\ or\ Censoring - Start\ Date\ of\ Relevant\ Observation\ Period + 1$$

If a subject's last contact date occurs before the start date of the observation period, the subject's time to event will be set to 0. See Section **9.2.6** and **9.2.7** for details on the relevant observation period.

9.3.9 Incidence Rate

The incidence rate during the relevant observation period will be defined as the number of:

$$Number\ of\ Subjects\ with\ Events\ during\ Relevant\ Observation\ Period / Total\ PersonDays\ at\ Risk_S$$

9.4 Safety

9.4.1 Adverse Events After Vaccine Doses

Unsolicited AEs will be summarized up to 28 days after each vaccine dose if:

$$1 \leq AE\ Start\ Date - Date\ of\ Vaccine\ Dose + 1 \leq 28$$

Unsolicited adverse events starting after 28 days after the first dose of vaccine but before the second dose, or starting 28 days after second dose, will not be included in the safety summaries, but will be included in the listings.

9.4.2 Solicited Adverse Events

Solicited local AEs include Injection Site Pain, Erythema, Induration and Swelling, and solicited systemic AEs include Fever, Drowsiness, Irritability/Fussiness, Loss of Appetite, Vomiting and Diarrhea. Solicited AEs are collected at 30 minutes after vaccine dose and daily for 7 days starting on the day of vaccine dose.

9.5 Other Conventions

9.5.1 Values below the Lower Limit of Quantification (LLOQ)

For the immunogenicity lab concentrations, values that are below the lower level of detection (LLOD) will be set to 0.5 of the LLOD. Values between LLOD and LLOQ are set to mid-point of the interval between LLOD and LLOQ, and values above upper limit of quantification (ULOQ) are set to the ULOQ. The table in Appendix B displays the relevant LLOD and LLOQ values for each assay. The actual reported values will be provided in by-subject listings.

9.5.2 Seroresponse Rate

Seroresponse is defined as a 4-fold increase from baseline in anti-Nov antibody concentrations as measured by histo-blood group antigen (HBGA) blocking assay and pan-immunoglobulin enzyme-linked immunosorbent assay (pan-Ig), to GI.1 and GII.4 and to both GI.1 and to GII.4. If the baseline value is missing, seroresponse will not be calculated. Subjects without a seroresponse will be referred to as non-responders. The seroresponse rate is defined as the ratio of the number of subjects who met the seroresponse criteria, divided by the number of subjects in the relevant group in the analysis set.

9.5.3 Geometric Mean Concentration (GMC)

The GMC will be calculated as the anti-logarithm of ∑ (log transformed concentration/n), i.e. as the anti-logarithm transformation of the mean of the log-transformed concentration, where n is the number of subjects with concentration information in the relevant group. The geometric standard deviation (GSD) will be calculated as the anti-logarithm transformation of the standard deviation of the log-transformed concentration. The 95% confidence interval (CI) for GMC will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the sample mean of the log-transformed concentrations.

9.5.4 Fold Rise in Antibody Concentrations

Fold rise in antibody concentrations is summarized using geometric mean fold rise (GMFR), defined as the geometric mean of the ratio between post vaccination assay result and baseline assay result. The GMFR is calculated as the anti-logarithm of ∑ (log transformed (post-vaccination concentration/ pre vaccination concentration)/number of subjects in the relevant group). GSD for the fold rises and 95% CI for the GMFR are calculated in the same manner as for GMC.

10.0 Interim Analyses

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

11.0 Statistical Methods

All statistical analyses will be performed using SAS® Version 9.4 or higher.

Unless otherwise noted, continuous variables will be summarized using the number of observations (n), mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum, and maximum values. The minimum and maximum values will be displayed to the same level of precision as the raw data; the mean, median, Q1 and Q3 values to one additional decimal place and the standard deviation to two additional decimal places.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places, and percentages will not be displayed for zero counts.

Listings will be provided for relevant summaries.

11.1 Subject Disposition

The number and percentage of subjects screened and who failed screening and the reason for failure, and the number and percentage of subjects randomized and not randomized and the reason for not being randomized will be summarized. Number and percentage of subjects randomized by country and site, as well as the number of subjects included in each analysis set will be summarized overall and by trial arm. For the FAS, mFAS, the trial group will be the randomized trial arm. For all other analysis sets, trial arm will be that actually received by the subject.

The number and percentage of randomized subjects will be summarized by visit completed and randomized trial arm and overall. Number and percentages of subjects who discontinued the vaccination regimen as well as those who discontinued the study, along with the reasons for discontinuation by last visit completed will be reported. [redacted]

11.2 Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized descriptively by trial arm in the SAF, FAS, mFAS, PPS-E, and PPS-I. Demographic information to be obtained in CRF will include date of birth, sex, race, and ethnicity as described by the subject's LAR. Country and age (months) at randomization will also be summarized (see Section **9.2.3**). Weight, length, and head circumference at baseline will be summarized.

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and will be summarized by preferred term (PT) and primary system organ class (SOC) for the SAF. MedDRA version will not be updated during the study.

11.3 Vaccine/Investigational Product

11.3.1 Extent of Exposure

Number and percentage of subjects receiving only one dose or both doses of trial vaccine will be presented by trial arm in the SAF. Time between trial doses in days will also be summarized by trial arm in the SAF. A listing of the vaccine administration will be provided.

11.3.2 Prior and Concomitant Medications and Vaccines

Prior and concomitant medications and vaccines (see Section **9.2.2**) will be summarized by preferred drug name according to World Health Organization Drug Dictionary (WHO-DD) (GLOBAL B3Sep21). Prior and concomitant medications will be summarized separately for the SAF. The number and percentage of subjects administered prior medications, concomitant medications, and vaccines, in each trial arm will be summarized by system organ class and preferred term in the SAF. A by-subject listing of all prior and concomitant medications, and vaccines will be provided.

11.4 Important Protocol Deviations

The number and percentage of subjects with important protocol deviations as described in the protocol deviations guidance and medically reviewed will be summarized overall, by deviation category and by trial arm in the FAS. A listing by-subject listing of important protocol deviations will also be provided.

The categories of important protocol deviations, which may affect evaluation of efficacy or immunogenicity, include:

1. Not meeting selected entry criteria;
2. Receiving wrong or incomplete trial product;
3. Receiving prohibited therapies (e.g., antipyretics and/or analgesic medications administered within 24 hours prior to investigational vaccine or placebo, non-live and orally administered live vaccines within 14 days of investigational vaccine or placebo, parenterally administered live vaccine within 28 days of investigation vaccine or placebo);
4. Protocol-described regimen not followed for storage of investigational vaccine or placebo;
5. Vaccination regimen described in protocol not followed for administration of investigation vaccine or placebo (e.g., administered out of window, or in incorrect injection site);
6. Other important protocol deviations that may affect efficacy evaluation;
7. Other important protocol deviations that may affect immunogenicity evaluation.

Subjects with these deviations will be excluded from PPS-E and/or PPS-I, as appropriate.

The number and percentage of subjects with important protocol deviations, which led to the exclusions of subjects from PPS-E and PPS-I, will be summarized overall, by deviation category and by trial arm, in the FAS and mFAS, respectively.

All protocol deviations are recorded in a system of record, and a subset of those are defined as Important protocol deviations.

The study team and the HilleVax team will conduct periodic blinded reviews of the deviation data from the electronic system of records during the study conduct, and the resulting set of evaluable subjects.

Exclusions from the per protocol sets will be determined programmatically and via medical review of relevant blinded listings prior to the unblinding of the subject's trial vaccine assignments for the primary analyses. The PPS-E and PPS-I will not be revised for the end-of-trial analyses.

11.5 Efficacy Analyses

11.5.1 Hypothesis Testing Strategy and Multiplicity Adjustments

The analysis for the primary efficacy endpoint will be performed at an alpha risk of 5% (two-sided). Statistical analysis of the key secondary efficacy endpoint will be performed only if the primary efficacy endpoint is significant.

11.5.2 AGE Events

An overview of all AGE events will be provided, including the number of subjects with AGE events, number of AGE events, number of AGE events by severity (not available, mild, moderate, severe), number of AGE events per subject by count, number of AGE events by NoV GI genogroup and GII genogroup from first dose until the end of the primary observation period, summarized by trial arm and overall, in the FAS.

For confirmed NoV AGE events with derived onset date from first dose until end of the primary observation period, number of subjects with AGE events, number of AGE events GI positive, and GII positive, number of AGE events by severity (no severity score, mild, moderate, severe, mod/sev), number of AGE events per subjects, number of AGE events by norovirus genotype (genotype, pending, quantity not sufficient, or indeterminate), and without co-infection, with co-infection (each individual pathogen, multiple, any) will be summarized by trial arm and overall, in the FAS and in the PPS-E. This summary will be repeated in the FAS during the primary observation period for medically attended NoV AGEs. It will also be repeated for NoV AGEs from Dose 1 until the end of trial, for NoV AGEs from Dose 1 until Dose 2, and for NoV AGEs from 28 days post dose 2 until the end of the trial in the FAS.

For the first confirmed NoV AGE event with derived onset date in the primary observation period, AGE duration in days, number of days with loose/liquid stools, number of episodes of loose/liquid stools in a day, number of days with vomiting, number of episodes of vomiting in a day, health care provider visits (yes/no), hospitalization for AGE treatment (yes/no), oral rehydration needed (yes/no), subjects treated with IV hydration (yes/no), MVS, severity (not available, mild, moderate, severe) will be summarized descriptively overall and by trial arm using mFAS. This summary will be repeated for primary endpoint AGE events (GI.1 / GII.4 without co-pathogens) and for primary endpoint events in the PPS-E.

11.5.3 Primary Endpoint

The primary endpoint for the study is the time to first occurrence during the primary observation period (see Section **9.3.4**) of a mod/sev AGE event (see Section ERROR! REFERENCE SOURCE NOT FOUND.) associated only with GI.1 or GII.4 NoV genotypes (see Section **9.3.4**). Subjects without an AGE event will be censored at their last information date (see Section **9.3.6.1**). The time to event endpoint will be derived as per Section **9.3.8**. The analyses will be performed using the mFAS.

11.5.3.1 Primary Analysis

The primary analysis method will be a time-to-event stratified CPH model using Efron's method for handling ties. The model will include a term for randomized trial arm and will be stratified by country. In the event that model convergence is not achieved, countries with a smaller number of subjects contributing to the analysis will be pooled by region. The 95% CI for VE will be derived from the CI estimation of the hazard ratio obtained from the CPH model. Kaplan-Meier median time to event and plots will also be presented by trial arm. The primary efficacy objective is met if the lower bound of the 95% CI for the VE is above 0%.

To assess the proportional hazards assumption, the following will be examined as suggested by Therneau & Grambsch, 2000.

For each trial arm (x), a plot of log negative log survival function (i.e., log [-log S_0 (t|x_i)]) versus the log of survival times for each trial arm should produce roughly parallel lines if the hazards are proportional over time.

Analyses of the primary efficacy endpoint will not be adjusted based on these plots. A sensitivity analysis to assess the robustness of the primary analysis will be performed as described in section **11.5.3.3.**

11.5.3.2 Supplementary Analysis

The following supplementary analyses will be performed for the primary efficacy endpoint:

- Analysis based on the PPS-E using the same definition of the AGE events and same statistical methods as for the primary endpoint analysis as described in sections **11.5.3** and **11.5.3.1.**
- Analysis of multiple moderate or severe events per subject will be performed using the Andersen-Gill extension of the Cox model (Andersen & Gill, 1982), stratified by country similarly to the primary endpoint. Recurrent AGE events are described in Section **9.3.2** The total number of events, the total time at risk (see Section **9.3.6.3**) and unadjusted event rate (see Section **9.3.7**) will be presented. Vaccine efficacy will be derived and presented in the same way as the primary analysis in Section **11.5.3.1**.

11.5.3.3 Sensitivity Analysis

A sensitivity analyses of the primary efficacy endpoint will be performed by calculating the

VE as 1 - Incidence Rate Ratio

and corresponding CI based on Poisson distribution. The incidence rate ratio (IRR) is then defined as

$$(s_1 / T_1) / (s_0 / T_0)$$

where

s_1 = number of events in HIL-214 arm,

s_0 = number of events in Placebo arm,

T_1 = total person-time at risk in HIL-214 arm,

T_0 = total person-time at risk in Placebo arm.

Wald confidence limits for the mean IRR will be derived using a Poisson regression model accounting for the log-transformed time at risk of the subject, adjusted for country.

11.5.4 Key Secondary Efficacy Endpoint

11.5.4.1 Vaccine Efficacy Associated with Any GI or GII Genotype

The key secondary efficacy endpoint for the study is the time to first occurrence during the primary observation period (see Section **9.2.6**) of mod/sev AGE case (see Section ERROR! REFERENCE SOURCE NOT FOUND.) associated only with any GI or GII NoV genogroups (see Section **9.3.4**). Subjects without an AGE event will be censored at their last information date (see Section **9.4.6.1**). The time to event endpoint (months) will be derived as per Section **9.3.8** time to event The analysis will be performed on the mFAS and will follow the same analysis as in Section **11.5.3.1**.

11.5.5 Secondary Efficacy Endpoints

The analysis of secondary vaccine efficacy endpoints as described in Section **9.0** will follow the primary analyses specified in Section **11.5.3.1**. The secondary efficacy analyses will be performed on the mFAS.

11.5.5.1 Vaccine Efficacy caused by GI.1 or GII.4 Irrespective of Other GE Pathogens

The first secondary efficacy endpoint for the study is the time to first occurrence during the primary observation period (see Section **9.2.6**) of moderate or severe AGE associated only with GI.1 or GII.4 NoV genotypes (see Section **9.3.4**) irrespective of the presence of other GE Pathogens. Subjects without an AGE event will be censored at their last information date (see Section **9.3.6.1**). The time to event endpoint will be derived as per Section **9.3.8.**

11.5.5.2 Vaccine Efficacy Associated with Any GI or GII Genogroup Irrespective of Other GE Pathogens

The second secondary efficacy endpoint for the study is the time to first occurrence during the primary observation period (see Section **9.2.6**) of moderate or severe AGE associated with any GI or GII NoV genogroups (see Section **9.3.4**) irrespective of the presence of other GE Pathogens. Subjects without an AGE event will be censored at their last information date (see Section **9.3.6.1**). The time to event endpoint will be derived as per Section **9.3.8.**

11.6 Secondary Immunogenicity Endpoint

11.6.1 Immunogenicity of HIL-214

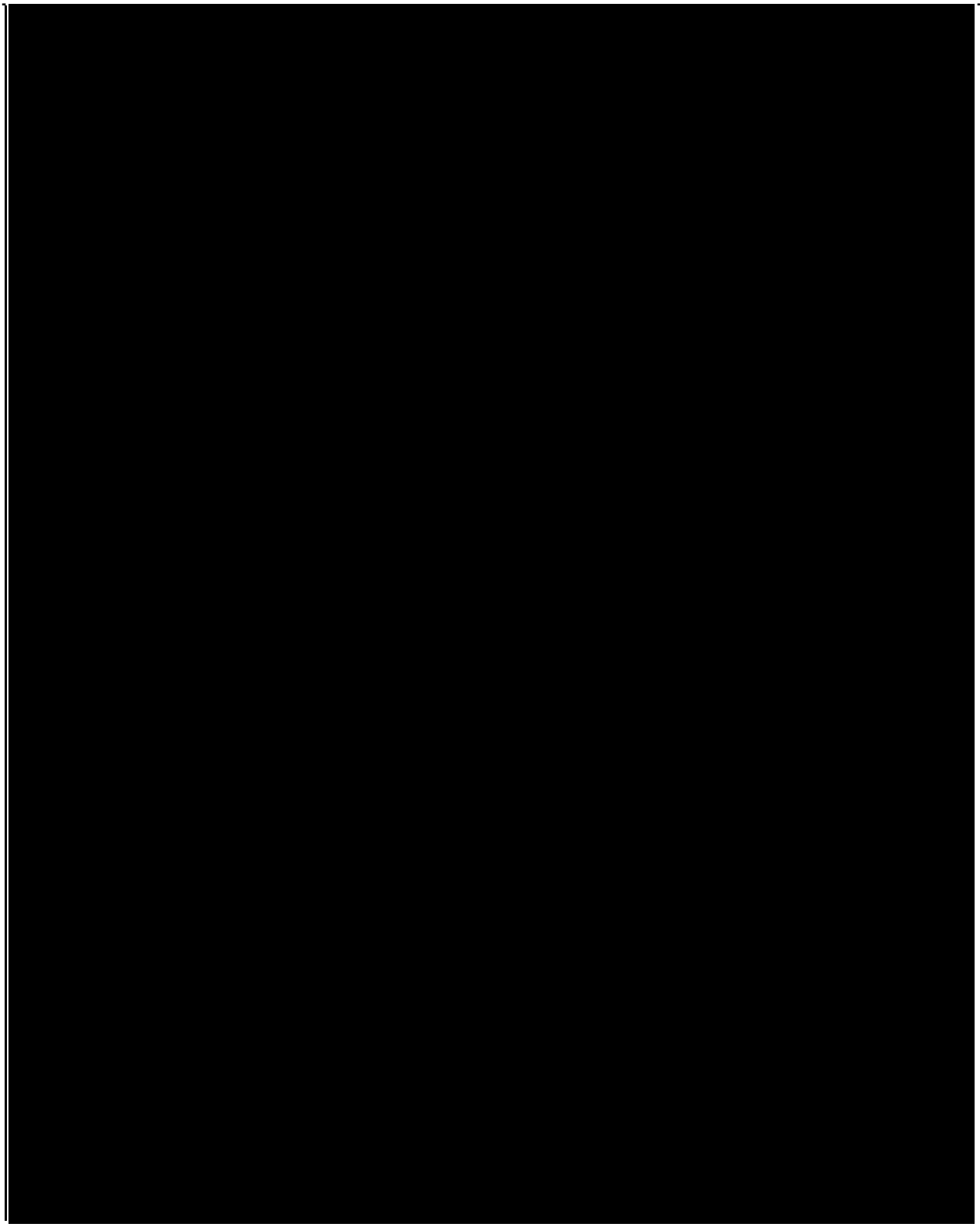
The secondary immunogenicity endpoints for the trial are pan-Ig and HGBA blocking antibody concentrations. These endpoints will be summarized as seroresponse rates (see Section **9.5.3**), GMCs and GMFRs (see Section **9.5.4**) for HBGA blocking antibody concentrations and for pan-Ig antibody concentrations collected at Visit 1(Day 1), Visit 2 (28 to 56 days post dose 1 - prior to dose 2) and Visit 3 (28 days post, and when the subjects reach the age of 1 year (Visit 4), 18 months (Visit 5) and 2 years (Visit 6) (see Section **9.2.5**). These estimates will be presented by trial arm separately for GI.1 and GII.4 NoV genotypes. Summaries of results for Visits 1 through Visit 4 will be included in the primary and secondary efficacy analysis. 18 months (Visit 5) and 2 years (Visit 6) results will be summarized at the end of trial.

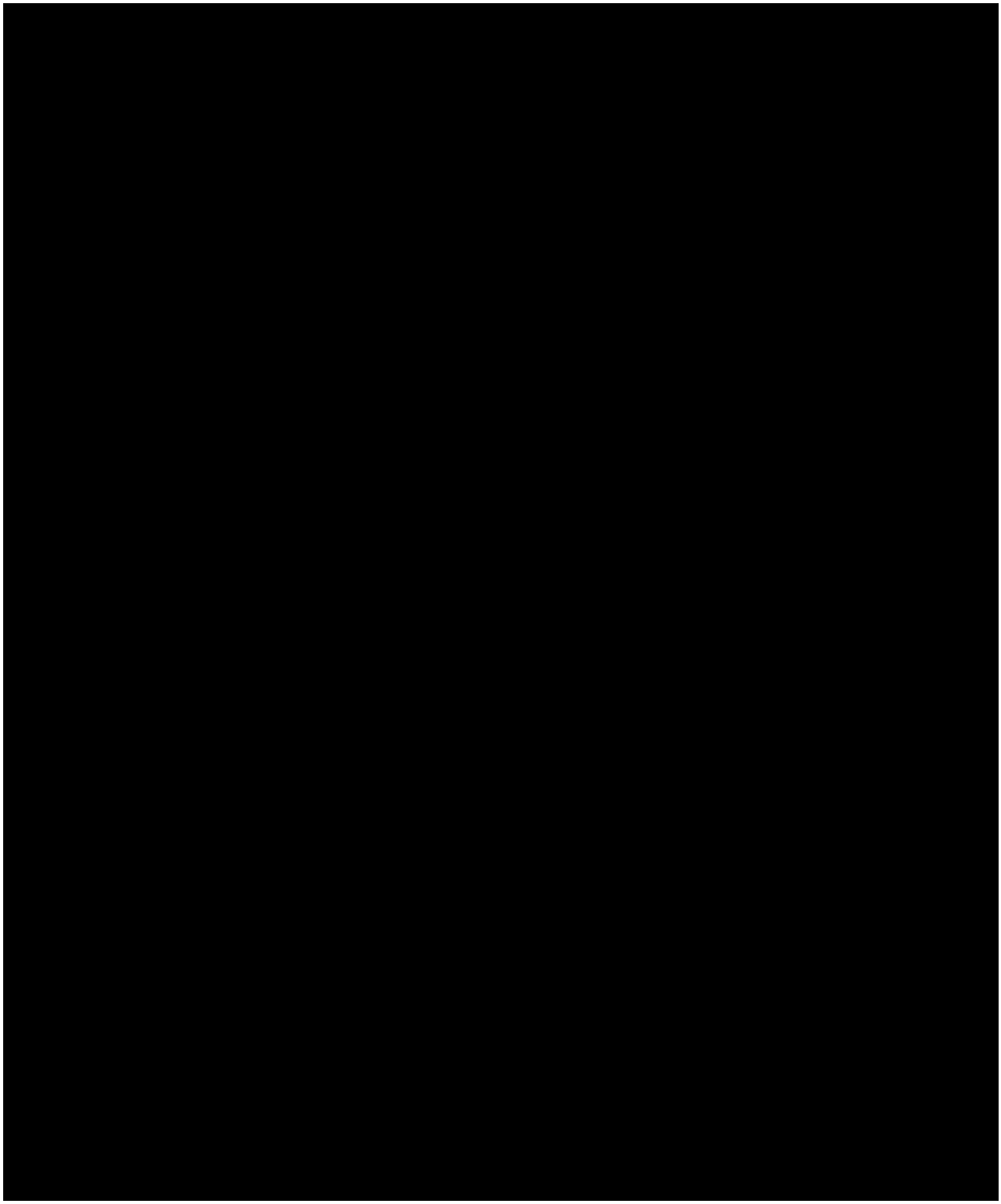
The number of subjects with seroresponse, seroresponse rate and 95% CI on post-dosing visits will be presented. The two-sided exact 95% CI will be estimated using the Clopper-Pearson exact method (Clopper CJ & Pearson ES, 1934). For details of the derivations of GMC and GMFR, see section **9.5.3**. Longitudinal plots and reverse cumulative distribution plots for concentrations will be presented by genotype and trial arm. The secondary immunogenicity analyses will be performed on the FAS and the PPS-I.

11.7 Exploratory [redacted]

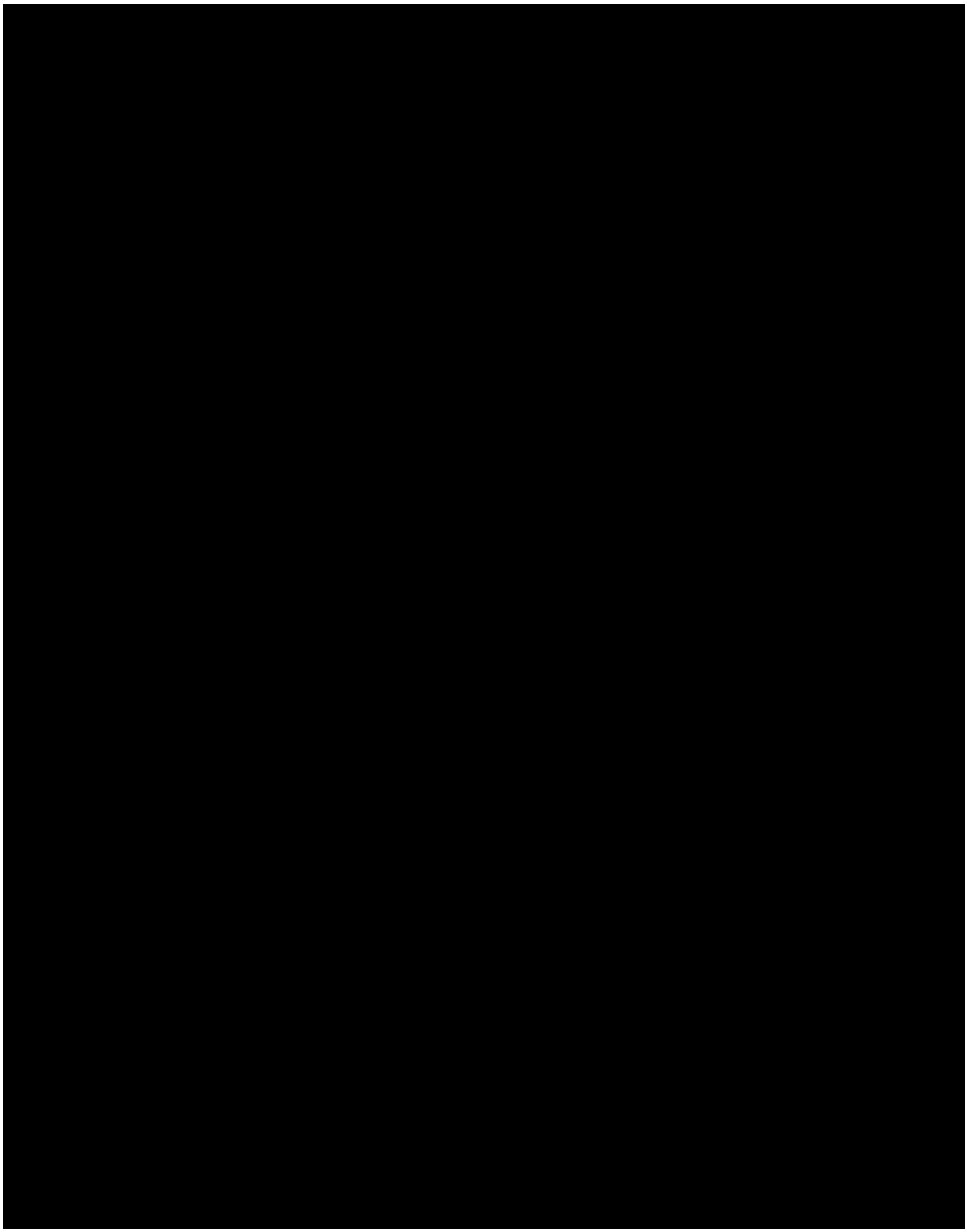
[redacted]

[redacted]





[redacted]



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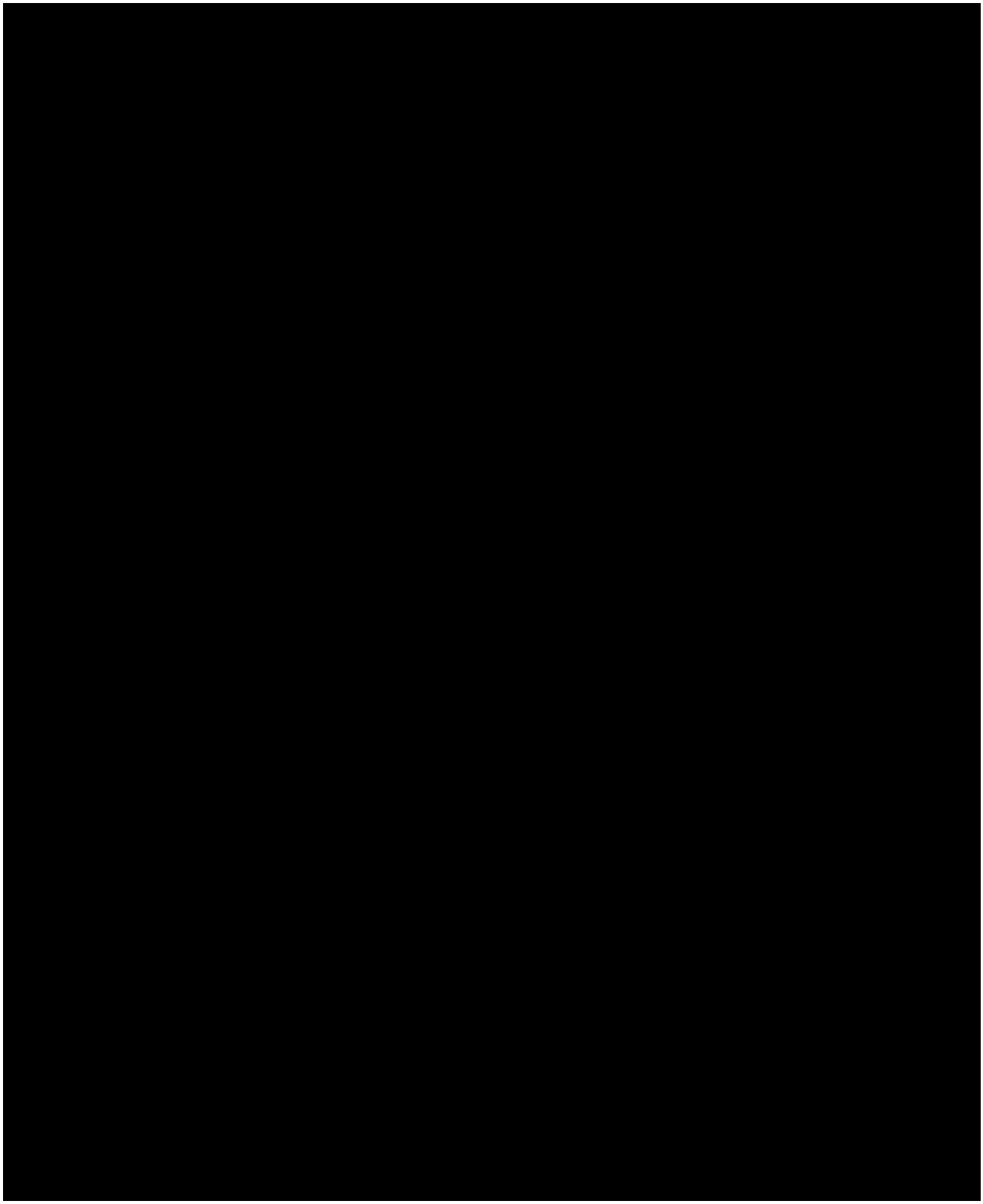

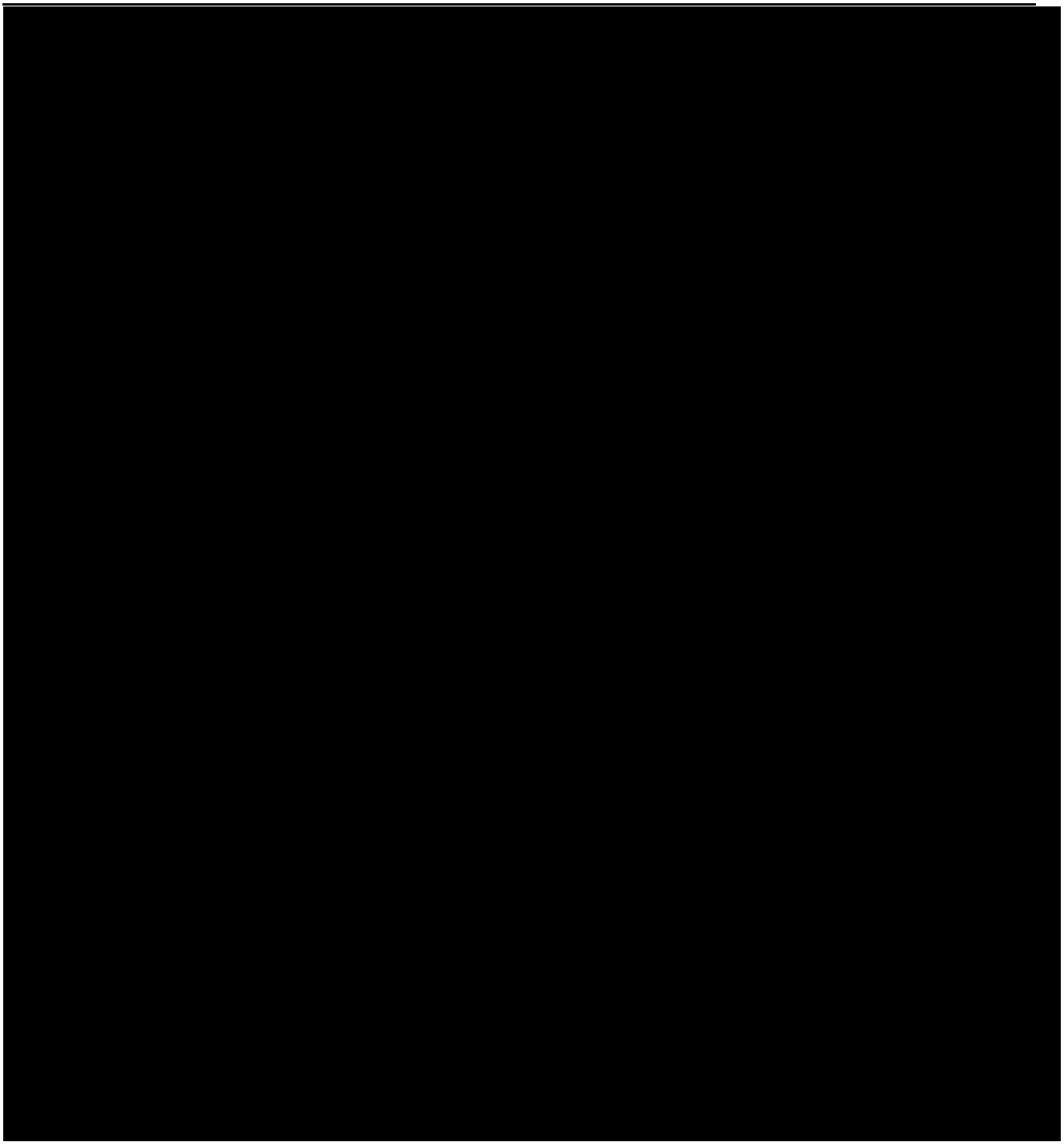

12.0 Safety

The safety analyses will be performed based on the SAF, unless otherwise specified. For the end-of-trial analysis, the overall summary of safety events, and summary of SAEs will be summarized for the complete trial (i.e., first dose through end of trial).

12.1 Adverse Events

Unsolicited adverse events will be coded according to the MedDRA version 24.1.

An overall summary of the number of patients with AEs after first dose of trial vaccine and number of events will be summarized, with line items for each of the following:

- Solicited local AEs
- Solicited systemic AEs
- Unsolicited AEs
- SAEs
- AEs leading to trial vaccine dose withdrawal
- AEs leading to withdrawal from the trial.

12.1.1 Solicited Adverse Events

The following summaries will be prepared for each trial arm and overall after each dose of trial vaccine and after any dose:

- The number and percentage of subjects experiencing solicited local and systemic AEs; overall and by severity
- The number and percentage of subjects experiencing local and systemic AEs, for each of 7 days after vaccination; overall and by severity
- The number and percentage of subjects experiencing solicited local and systemic AEs by day of onset
- The number and percentage of subjects experiencing solicited systemic AEs by relationship to vaccine as determined by the clinical investigator.

Only solicited AEs collected up to 7 days after dosing of vaccine will be summarized. Percentages will be based on the number of subjects who had at least one non-missing assessment for a given event.

Solicited safety data collected 30 min post-vaccination will be summarized separately.

12.1.2 Body Temperature

Body temperature measurements will be summarized for the seven days following each vaccination, by route of measurement and overall. The following categories will be used to report body temperature measurements: below 38°C, 38°C or higher (Fever), 38°C to less than 39°C, 39°C to less than 40°C, and 40°C or higher. The number and of subjects having at least one non-missing measurement will be used as the denominator to calculate percentages. Fever related to trial vaccine will also be presented using the same temperature categories, starting from 38°C or higher.

Body temperature measured 30 min post-vaccination will be summarized separately.

12.1.3 Unsolicited Adverse Events

The number and percentage of subjects experiencing any unsolicited AE (up to 28 days after each vaccine dose) will be summarized by trial arm, and by SOC and PT. Unsolicited AE summaries will include solicited AEs ongoing after 7 days post-vaccination. Percentages will be calculated based on the number of subjects in the SAF.

Unsolicited AEs will further be summarized by relationship to the trial vaccine or trial procedure. Subjects with multiple events coding to the same SOC or PT will be counted only once in that level, according to the most related event.

Unsolicited AEs will similarly be summarized by severity to the trial vaccine. Subjects with multiple events coding to the same SOC or PT will be counted only once in that level, according to the most severe event.

Unsolicited AEs after each vaccination will be summarized in the following 3 ways: 1) overall for Day 1 (day of vaccination) to 28 days after each vaccination, 2) with onset between Day 1 (day of vaccination) and Day 7 after each vaccination, and 3) with onset between Day 8 and Day 28 after each vaccination. Each group will be summarized after each vaccine dose, and any vaccine dose by trial arm and overall.

12.1.4 Deaths and Serious Adverse Events

SAEs and fatal SAEs occurring after each dose and after any dose will be summarized by vaccine dose and overall, by SOC and PT. Summaries will be provided by trial arm and overall. Percentages will be calculated based on the number of subjects in the SAF.

SAEs including fatal SAEs will be included in a subject listing.

SAEs and fatal SAEs will similarly be summarized by relationship and by severity as described for unsolicited events above.

12.1.5 Adverse Events Leading to Trial Vaccine Dose Withdrawal

Adverse events leading to trial vaccine dose withdrawal after the first dose will be summarized by trial arm and overall. Summaries by SOC and PT will be provided by trial arm and overall. Percentages will be calculated based on the number of subjects in the SAF.

The adverse events will be listed.

Adverse events leading to trial dose discontinuation will similarly be summarized by relationship and by severity as described for unsolicited events above.

12.1.6 Adverse Events Leading to Withdrawal from Trial

Adverse events leading to withdrawal from trial occurring after each dose and after any dose will be summarized by vaccine dose and overall, by SOC and PT. Summaries will be provided by trial arm and overall. Percentages will be calculated based on the number of subjects in the SAF.

The adverse events will be listed.

Adverse events leading to withdrawal from the trial will similarly be summarized by relationship and by severity as described for unsolicited events above.

12.2 Vital Signs

Observed and change from baseline values for length (cm), weight (kg), head circumference (cm), body temperature (°C) by measurement route, and heart rate (beats/min) will be summarized (n, mean, std, median, Q1, Q3, minimum, and maximum) at baseline and each post baseline clinic visit until trial end.

Vital signs collected will be listed.

13.0 References

Andersen, P. K., & Gill, R. D. (1982). Cox's regression model for counting processes: a large sample study. *The annals of statistics*, 1100-1120.

Clopper CJ & Pearson ES. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*, 26:404-413.

Therneau, T., & Grambsch, P. (2000). Testing Proportional Hazards. In: Modeling Survival Data: Extending the Cox Model.

14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AGE	Acute Gastroenteritis
CI	Confidence Interval
CPH	Cox Proportional Hazards
CRF	Case Report Form
CSR	Clinical Study Report
EDC	Electronic Data Capture
ET	End of Trial
FAS	Full Analysis Set
GE	Gastroenteritis
GI	Genogroup (GI, GII, GIII etc.)
GII	Genogroup (GI, GII, GIII etc.)
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GSD	Geometric Standard Deviation
HBGA	Histo-Blood Group Antigen
[redacted]	
IM	Intramuscular
IRR	Incidence Rate Ratio
IRT	Interactive response technology
LAR	Legally Authorized Representative
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MVS	Modified Vesikari Score
NoV	Norovirus
Pan-Ig	pan-Immunoglobulin
PPS-E	Efficacy Per-Protocol Analysis Set
PPS-I	Immunogenicity Per-Protocol Analysis Set

PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SOC	System Organ Class
ULOQ	Upper Limit of Quantification
VE	Vaccine Efficacy
WHO-DD	World Health Organization Drug Dictionary

15.0 Appendices

Appendix A Vesikari and Modified Vesikari Scoring

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

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

[b] Adapted from Freedman et al. Mild: <9; Moderate: 9-10; Severe: ≥11 Maximum score: 20;

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

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

Appendix B LLOD and LLOQ values for Assays of Immune Response

Assay	LOD	LLOQ	ULOQ
NW Pan Ig	62.5 AU/mL	100 AU/mL	400000 AU/mL
CN Pan Ig	15.625 AU/mL	100 AU/mL	200000 AU/mL
NW HBGA	19 AU/mL	19 AU/mL	78848 AU/mL
CN HBGA	33 AU/mL	33 AU/mL	149504 AU/mL

[redacted]