[redacted]

STATISTICAL ANALYSIS PLAN

Protocol: NOR-215

Protocol Version: V3.0 25OCT2023

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

SAP/Amendment Number	**Date**
Final SAP v1.0	17JUL2023
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Approved by	Signature	Date
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1 Table of Contents

1.1 Table of Tables

1.2 Table of Figures

2 Abbreviations and Definitions

ADaM	Analysis Dataset Model
AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DP	Decimal Place
GI/GII	Genogroup I/ Genogroup II
GI.1/GII.4	Genotype I.1/ Genotype II.4
GII.4c	GII.4 consensus
GM	Geometric Mean
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
GSD	Geometric Standard Deviation
HBGA	Histo-Blood Group Antigen
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medical Product
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantification
MEDRA	Medical Dictionary for Regulatory Activities
pan Ig	Total Immunoglobulin
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Standard Data Tabulation Model
SOC	System Organ Class
SRR	Seroresponse Rate
TFL	Tables, Figures and Listings
ULOQ	Upper Limit of Quantification
VLP	Virus-Like Particle
WHODD	World Health Organization Drug Dictionary

3 Introduction

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analyses of study NOR-215. It also defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol. The SAP is based upon, and assumes familiarity, with the study protocol, version 3.0, dated 25OCT2023.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. The content of this SAP is compatible with the ICH E9 Guidance document.

4 Study Objectives and Endpoints

4.1 Study Objectives

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]
- [redacted]

Exploratory objectives and endpoints will not be outlined in this SAP and instead will be documented separately.

4.2 Study Endpoints

Primary Endpoints:

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

- GI.1 virus-like particles (VLP).
- GII.4c VLP.

Secondary Endpoints:

- Solicited local adverse events (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]

5 Study Methods

5.1 General Study Design and Plan

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.

As shown in **Figure 1**, the study comprises of 3 scheduled site visits (Day 1, Day 8, and Day 29) and one telephone contact (Day 85). Visits 1, 2, and 3 involve blood draws. **Table 1Table 1: Visit Windows** shows the visit windows for Visits 2 and 3.

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

Throughout this document, trial vaccine will refer to the investigational vaccine administration of HIL-214.

Figure 1: Trial Design Diagram

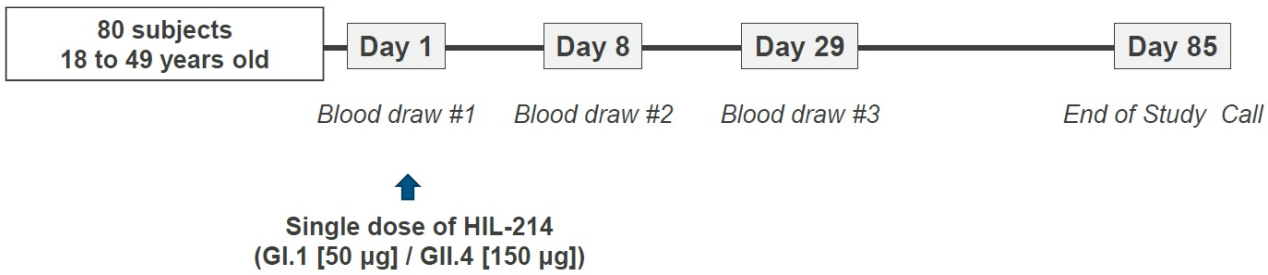

Table 1: Visit Windows

Day	Day 8	Day 29
Visit window	+2 days	+3 days

5.2 Randomization and Blinding

This is a single arm, open-label study with no randomization or blinding.

5.3 Derived variables

5.3.1 General

5.3.1.1 Baseline

Unless otherwise stated, baseline is defined as the last non-missing pre-trial vaccine assessment prior to the administration of the trial vaccine.

5.3.1.2 Relative Day

The relative day of an assessment will be calculated as:

- For measurements performed on or after the date of the trial vaccine dose:
  Date of assessment – date of trial vaccine dose+1.
- For measurements performed before the date of the trial vaccine dose:
  Date of assessment – date of trial vaccine dose.

5.3.1.3 Demographic and Background Data

Age will be calculated in years and will be calculated as follows:

Age (years) = (Visit 1 Date (Day 1) – Date of Birth)/365.25 [Rounded down to the integer].

Weight may be recorded in kilograms or pounds. Weight in pounds will be converted to weight in kilograms as follows:

Weight (kg) = Weight (lb) * 0.4536.

Weight will be presented to 1 dp in the listings.

Height may be recorded in centimetres or inches. Height in inches will converted to height in centimetres as follows:

Height (cm) = Height (inches) * 2.54.

Height will be presented to 1 dp in the listings.

Body mass index (BMI) will be calculated as follows:

BMI (kg/m^2) = Weight (kg) / (Height (m)^2).

BMI will be present to 1dp in the listings.

Temperature may be recorded in Degrees Celsius or Fahrenheit. Temperature in Fahrenheit will be converted to temperature in Degrees Celsius as follows:

Temperature (°C) = (Temperature (°F) – 32) * 0.5556.

Temperature will be presented to 1 dp in the listings.

5.3.2 Immunogenicity

5.3.2.1 Fold Increase

The fold increase is calculated by taking the ratio of assessments from two visits, which for this study will be Visit 1 (Day 1) and Visit 3 (Day 29) assessments.

If v_1 is a subject's Visit 1 record and v_3 is a subject's Visit 3 record then the fold increase is:

$$fi = \frac{v_3}{v_1}.$$

5.3.2.2 Seroresponse Rate

Seroresponse is defined as a fold increase from baseline (Visit 1) greater than or equal to 4.

Seroresponse rate (SRR) is defined as the percentage of subjects with a seroresponse. The 95% confidence intervals (CIs) for the SRR will be computed using the exact Clopper-Pearson method.

5.3.2.3 Immunogenicity Assessments

When summarizing immunogenicity assessments the following rules will apply:

- If a record is below the lower limit of detection (LLOD) then ½ the LLOD value will be used in the summary.
- If a record is below the lower limit of quantification (LLOQ) then the midpoint of the LLOQ value and the LLOD value will be used in the summary.
- If a record is above the upper limit of quantification (ULOQ) then the ULOQ will be used in the summary.

5.4 Statistical Analysis Methods

5.4.1 Geometric Mean

The geometric mean (GM) of a set of numbers $x_1, x_2, \ldots, x_N$ is calculated by taking the exponential of the mean of the logged values, as per the following formula:

$$GM_x = \exp\left\{\frac{\sum_{i=1}^{N} ln(x_i)}{N}\right\}.$$

The geometric standard deviation (GSD) for the same set of numbers is given by

$$GSD_x = exp\left\{\sqrt{\frac{\sum_{i=1}^{n}\left(ln\left(\frac{x_i}{GM_x}\right)\right)^2}{n}}\right\}.$$

The 95% confidence interval (CI) is calculated as per the following formula:

$$95\%\ CI = \exp\left\{ln(GM) \pm Z_{1-\frac{\alpha}{2}}\frac{ln(GSD)}{\sqrt{n}}\right\}$$

where α is the selected level of confidence. All confidence intervals outlined in this SAP will be two sided 95% confidence intervals, i.e. with α = 0.05.

5.4.2 Geometric Mean Fold Rise

The geometric mean fold rise (GMFR) is given by taking the mean of the natural logarithm of the fold increases (**Section 5.3.2.2**). Therefore, for the fold increases $fi_1, \ldots, fi_n$, the GMFR is

$$GMFR = \exp \sum_{j=1}^{n} \left(ln\{fi_j\}/n \right).$$

Which is equivalent to

$$GMFR = \frac{GM_3}{GM_1}$$

where GM_1 is the geometric mean at Visit 1 and GM_3 is the geometric mean at Visit 3.

The 95% confidence interval for GMFR will be calculated using the same method as the 95% CI for GM (outlined in **Section 5.4.1**) but using the log of the fold rises rather than the log of concentrations.

6 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.

7 General Considerations

7.1 Analysis Sets

For the purposes of analysis, the following subject analysis sets are defined in **Table 2**:

Table 2: Subject Analysis Sets

Subject Analysis Set	Description
Enrolled analysis set	• All subjects who signed the informed consent form.
Safety analysis set	• All subjects who received HIL-214.
Per protocol analysis set	• All subjects who received HIL-214 and did not have any major protocol deviations that impact immunogenicity

Protocol deviations will be logged within the clinical trial management system and categorized as important/not important, with important protocol deviations being categorized as major/not major.

Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or the reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Major protocol deviations are a subset of important protocol deviations that might significantly impact the immunogenicity analysis.

Major protocol deviations may include, but are not limited to:

- Fraudulent data
- Inclusion/exclusion criteria not being met but the subject was dosed
- Visit 2 or Visit 3 occurred out of window
- Study treatment impacted by a temperature excursion
- Vaccine administered or blood sample collected while one of the delaying criteria met
- Incorrect volume of IP administered
- IP stored outside of temperature range
- Participant dosed with expired IP

The classification of a major protocol deviation will take place prior to database lock and any subjects deemed to have a major protocol deviation will be excluded from the Per Protocol set.

7.2 Subgroups

There will not be any subgroup analysis for this study.

7.3 Missing Data

7.3.1 Partial Dates/Times

Partial dates and times for AEs, medical conditions, concomitant medications and other vaccinations will be imputed for the purpose of calculating duration. Imputed dates and times should not be shown in the listings.

Partial AE onset, concomitant medication and other vaccinations start dates will be imputed as follows:

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

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

Partial AE start times will be imputed as follows:

- If the actual or imputed start date is the same as the date of the trial vaccination and the start time is completely missing, then use the time of the trial vaccination administration.
- If the actual or imputed start date is not the same as the trial vaccine administration, and the start time is completely missing, then use 00:00.
- If the actual or imputed start date is the same as the trial vaccine administration, and the start time is partially missing (hh:XX) then use the following:
    - If the hour is the same as the hour of the trial vaccine administration time then use the complete time of trial vaccine administration (i.e., both hours and minutes).
    - If the hour is not the same as the hour of the start time than use hh:00.
- If the actual or imputed start date is not the same as the trial vaccine administration date, and the start time is partially missing (hh:XX) then use hh:00.

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.
- If only the year is specified, then use January 1st of that year.
- If the start date is completely unknown, do not impute the start date.

Partial AE resolution, medical conditions and concomitant medications 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.
- If only the year is specified, then use December 31st of that year.
- If the stop date is completely unknown, do not impute the stop date.

7.4 Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

7.5 Multi-center Studies

No multi-center analyses are planned for this study.

8 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In

general, all data will be listed, sorted by site, subject, and when appropriate by visit number within subject.

All summary tables, unless otherwise stated, will be structured with one column for the trial vaccine (HIL-214) and will be annotated with the total population size relevant to that table, including any missing observations.

8.1 Subject Disposition

Completion/withdrawal from the study, together with reasons for withdrawal from the study for subjects in the safety analysis set will be listed and the following will also be tabulated:

- Number and percentage of subjects who completed the study.
- Number and percentage of subjects withdrawn from the study and the principal reason for withdrawal.

For subjects in the enrolled set who fail to meet the eligibility criteria the reasons for failure, including the inclusion/exclusion criteria that were not met will be summarized and listed.

The number and percentage of subjects in the enrolled set with data available for each scheduled visit will be summarized and listed.

The number and percentage of subjects included in each analysis set and the reasons for exclusion will be summarized and listed.

8.2 Protocol Deviations

The number and percentage of subjects in the safety analysis set with at least one important protocol deviation will be summarized by deviation category (major/minor).

The final PD data will be reviewed during the data review meeting and updated by the statistics group to add the important protocol deviations flag and the deviation categories.

All protocol deviations will be listed.

8.3 Demographic and Baseline Variables

Demographic and baseline variables will be summarized descriptively. The variables that will be summarized are:

- Age (years)
- Age (years) by category:
    - 18 to 65 years
- Sex:
    - Male
    - Female
    - Other/Not Recorded
- Race:

  - American Indian or Alaskan Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Other
  - Not Reported
  - Unknown
- Ethnicity:
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
  - Unknown
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

8.4 Concurrent Illnesses and Medical Conditions

Medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®). The dictionary version used will be 25.1.

Concurrent illnesses and medical conditions will be classified as 'current' if the end date is on or after Visit 1 (Day 1), or the condition has been marked as ongoing. Illnesses and medical conditions that start and end before Visit 1 (Day 1) will be classified as past.

Past and current medical history will be summarized and listed for the safety analysis set. All medical history summaries will be ordered by the MedDRA internationally agreed order (**Appendix 1**) for system organ class (SOC), and decreasing frequency of preferred term (PT) within SOC. A subject who has multiple events in the same SOC and PT will be counted only once in the subject counts but all events will be included.

8.5 Prior and Concomitant Medications and Other Vaccinations

Prior medication definition: If a subject takes a medication before Visit 1 (Day 1), this medication will be classified as 'prior medication'. With this definition, any medication recorded that has been taken for at least 1 day and has been stopped before Visit 1 (Day 1) will be considered as prior.

Concomitant medication definition: Prior medication not stopped before Visit 1 (Day 1) will be classified as 'concomitant medication'. Medication will be labelled as 'concomitant medication' when the start date is between Day 1 and the final study visit (Day 85) or, in case of early termination, on the date of the subject's last visit. With this definition, any medication that has been taken for at least 1 day between Visit 1 (Day 1) and Day 85 will be considered as concomitant.

Other vaccinations will be determined as prior or concomitant using the same definitions as medications.

Medications and other vaccinations will be coded according to the 2020 version of the World Health Organization Drug Dictionary (WHODD). Medical procedures will not be coded.

Prior and concomitant medications and other vaccinations will be summarized and listed for the safety analysis set.

9 Immunogenicity Analysis

The primary endpoint will consider the immunogenicity of HIL-214 at Visit 3 (Day 29) and all analysis will be defined in this section. Analyses will be completed for the safety analysis set and per protocol analysis set. Subjects with immunogenicity samples taken outside of the visit windows (as described in **Table 1**) will not be included in analyses which use the per protocol analysis set.

The immunogenicity variables, HBGA-blocking titers and total immunoglobulin (pan-Ig) titers that are specific for GI.1 VLP and GII.4c VLP will be summarized. Along with the following summaries, the immunogenicity data will be listed by subject.

9.1 Main Analytical Approach

For all immunogenicity variables a standard summary of the number of subjects with an assessment (n), mean, standard deviation, median, Q1, Q3, minimum and maximum will be presented alongside the number of assessments below the LLOQ and LLOD and above the ULOQ. The number of subjects that are missing an assessment will also be summarized.

As well as the standard continuous summary of the outcomes, geometric mean titers (GMTs), geometric mean fold rise (GMFR) and seroresponse rate (SRR) will be presented (as defined in **Sections 5.3.2 and 5.4**) for each immunogenicity variable. The 95% confidence intervals (CI) for GM, GMFR and SRR as well as geometric standard deviation (GSD) will also be provided.

In addition, for each immunogenicity variable a reverse cumulative distribution curve will be produced, with titer on the x-axis and the percentage of subjects below the titer value on the y-axis.

Line graphs and boxplots summarizing the GMT for each trial vaccine group for the serotypes GI.1 and GII.4 will also be produced. These outputs will both have the visits of baseline (Day 1) and Visit 3 (Day 29) on the x-axis and the GMT on the y-axis, presenting data on the log scale.

10 Safety Analyses

All safety analysis is defined in this section and will be completed for the safety analysis set. Along with the following summaries, all safety endpoints will be listed by subject.

All safety summaries of continuous variables will present n (non-missing sample size), mean, standard deviation, median, maximum and minimum.

10.1 Adverse Events

All unsolicited AE summaries will be ordered by the MedDRA internationally agreed order (**Appendix 1**) for system organ class (SOC), and decreasing frequency of preferred term (PT) within SOC. A subject who has

multiple events in the same SOC and PT will be counted only once in the subject counts but all events will be included.

10.1.1 Severity of Adverse Event

In summaries including severity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. For the solicited AEs of redness, swelling, and induration the following categories of severity will be summarized: '<25mm', '≤25-50mm', '>50-100mm', '>100mm'. For fever the following categories of severity will be summarized: '<38°C', '≥38-39°C', '≥39-40°C', '≥40°C'. Subjects who experience the same event multiple times will be included in the most severe category. Missing severities are not expected, however if these occur they will not be imputed but will be included in relevant summary tables under a missing category.

10.1.2 Relationship to Trial Vaccine and Procedures

In summaries including relationship to trial vaccine and relationship to trial procedures, the following relationships will be summarized: 'Not Related', 'Related'. Subjects who experience the same event multiple times will be included in the most related category. Missing relationships are not expected, however if these occur they will not be imputed but will be included in relevant summary tables under a missing category.

10.1.3 Solicited Adverse Events

The solicited safety parameters for this study are the local adverse events (injection site reactions) of pain, erythema (redness), induration and swelling and the systemic adverse events of headache, fatigue, myalgia, arthralgia, vomiting, diarrhea and fever (defined as body temperature greater than or equal to 38°C regardless of methods used).

Solicited reactions will be assessed 30 minutes after administration of the trial vaccine, and then daily for 7 days (including the day of administration).

Body temperature measurements will be summarized in categories (including fever), without adjustment for the route of measurement. Summaries of the day of first onset of each event and the maximum number of continuous days subjects experienced each event will also be provided.

Any solicited local or systemic reactions observed as continuing beyond 7 days following the trial vaccine dose will be recorded as an unsolicited AE in the case report form (CRF).

10.1.3.1 Summaries

The summaries for solicited AEs will be:

- The number and percentage of subjects with solicited local and systemic reactions during the first 7 days (including day of administration) after the trial vaccine dose by day and overall.
- The number and percentage of subjects with solicited local and systemic reactions during the first 7 days (including day of administration) after the trial vaccine dose by severity, day and overall.
- The number and percentage of subjects with solicited local and systemic reactions during the first 30 minutes after the trial vaccine dose.

- The number and percentage of subjects with solicited local and systemic reactions during the first 30 minutes after the trial vaccine dose by severity.
- Summary of the day of first onset of each solicited AE.
- Summary of the duration (days) of each solicited AE.

A horizontal stacked bar plot showing the percentage of participants with each solicited AE after the trial vaccine dose. This plot will break down the percentages by maximum severity, with the percentage of mild, moderate and severe events stacked for each solicited AE.

All solicited AEs will also be listed.

10.1.4 Unsolicited Adverse Events

Unsolicited AEs will be collected up to 28 days after administration (including the day of administration) of the trial vaccine. Only unsolicited AEs recorded after the dose of trial vaccine will be summarized. All AEs will be listed with the timing relative to dose of trial vaccine.

Any unsolicited AEs 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,
3) Day 8 to Day 28.

10.1.4.1 Summaries

The summaries for unsolicited AEs will be:

- Overall Overview of the occurrence of all AEs.
- The number and percentage of subjects with any unsolicited AE during the first 28 days (including day of administration) after the trial vaccine dose.
- The number and percentage of subjects with any unsolicited AE during the first 28 days (including day of administration) after the trial vaccine dose by severity.
- The number and percentage of subjects with any unsolicited AE during the first 28 days (including day of administration) after the trial vaccine dose by relatedness to the trial vaccine.
- The number and percentage of subjects with any unsolicited AE during the first 28 days (including day of administration) after the trial vaccine dose by relatedness to the trial procedures.

Listings will be presented for all unsolicited AEs.

10.1.5 Serious Adverse Events

10.1.5.1 Summaries

The summaries for serious adverse events (SAEs) will be:

- The number and percentage of subjects with SAEs during the first 28 days (including day of administration), and overall (up to Day 85).
- The number and percentage of subjects with SAEs during the first 28 days (including day of administration), and overall (up to Day 85) by severity.

- The number and percentage of subjects with SAEs during the first 28 days (including day of administration), and overall (up to Day 85) by relatedness to the trial vaccine.
- The number and percentage of subjects with SAEs during the first 28 days (including day of administration), and overall (up to Day 85) by relatedness to the trial procedures.

All SAEs will be listed.

10.1.6 Adverse Events Leading to Trial Withdrawal

10.1.6.1 Summaries

The summaries for AEs leading to trial withdrawal will be:

- The number and percentage of subjects with AEs leading to trial withdrawal, during the first 28 days (including day of administration), and overall (up to Day 85).
- The number and percentage of subjects with AEs leading to trial withdrawal, during the first 28 days (including day of administration), and overall (up to Day 85) by severity.
- The number and percentage of subjects with AEs leading to trial withdrawal, during the first 28 days (including day of administration), and overall (up to Day 85) by relatedness to the trial vaccine.
- The number and percentage of subjects with AEs leading to trial withdrawal, during the first 28 days (including day of administration), and overall (up to Day 85) by relatedness to the trial procedures.

All AEs leading to trial withdrawal will be summarized and listed.

10.2 Deaths

All AEs that lead to death will be listed.

10.3 Extent of Exposure

Trial vaccine administration details (including date and time and reason for no administration if applicable) will be listed.

The number and percentage of subjects who fulfil any of the criteria for delay of vaccination will be summarized along with the criteria that was satisfied.

10.4 Pregnancies

In women of childbearing potential, pregnancy tests (urine) will be performed on Day 1 before the administration of the trial vaccine. Female subjects who are pregnant or result of the test is indeterminate will not be eligible for the study. Pregnancy data will be listed by subject for women of childbearing potential only.

10.5 Clinical Laboratory Evaluations

There will be no laboratory data collected other than the data needed for the immunogenicity analysis.

10.6 Vital Signs

The vital signs of heart rate and temperature will be summarized descriptively by visit.

Both vital signs parameters will also be listed.

10.7 Physical Examination

Physical examination findings for general appearance, heart and lungs, abdomen, extremities and other at Visit 1 (Day 1) will be summarized for those that are normal, abnormal or not done.

Physical examination findings for all other visits will be listed only along with findings from Visit 1 (Day 1).

11 Reporting Conventions

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfil certain criteria, the percentage value will be displayed as 100.
- For values where the absolute frequency is 0, there will be no percentage presented at all.
- All other percentage displays will use 1 decimal place.

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer.
- Mean (arithmetic and geometric) and median will use 1 decimal place more than the original data.
- SD will use 2 decimal places more than the original data.
- Minimum and maximum will be reported using the same number of decimal places as the original value.
- If no subjects have data at a given timepoint, for example, then only n=0 will be presented. However, if n<3, present the n, min and maximum only. If n=3, n, mean, median, minimum and maximum will be presented only; the other descriptive statistics will be left blank.

12 Technical Details

Statistical evaluation will be performed by Veramed Limited and supervised by the Statistics Department of HilleVax unless otherwise indicated.

The datasets will follow analysis dataset model (ADaM) data specifications and will use the standard data tabulation model (SDTM) data sets. Both SDTMs and ADaMs will be programmed by Veramed.

All analyses will be performed using SAS version 9.2 or higher (SAS Institute, Cary, NC, USA).

13 Summary of Changes to the Protocol

The SAP is based on the latest Protocol which is version 3.0 dated 25th October 2023.

14 References

There are no references in the text of this SAP.

15 Amendment(s) to the Statistical Analysis Plan

15.1 Amendment 1

The SAP amendment 1 was to document changes to the planned safety analysis. All reference to Treatment emergent adverse events has been removed as this definition will not be used on this study, and will match the NOR-206 Study SAP.

Table 3: Summary of Changes to the SAP

SAP Section	Summary and Justification of Change
Section 10.1.4	All reference to Treatment emergent adverse events has been removed. The following has also been added to clarify what will be summarised 'Only unsolicited AEs recorded after the dose of trial vaccine will be summarized. All AEs will be listed with the timing relative to dose of trial vaccine'.
Section 5.3.1.1 and Section 10.1.2	Reference to 'Treatment' removed and instead 'Trial vaccine' is used. Update made to match the NOR-206 SAP and distinguish between a treatment and the trial vaccine.
Section 5.3.1.3	Updated conversion formula for height.
Section 9.1	Line graph and boxplot figures added to visually describe the primary endpoint data.
Section 10.1.3.1	Figure added to visually describe the number of and severity of solicited AEs occurring after the dose of trial vaccine.
Section 7.1	Per protocol set added. This is so that the immunogenicity data can be evaluated only for the subjects that have no major protocol deviations that impact the immunogenicity assessments
Section 8.1	As the per protocol set was added a summary and listing of analysis sets and reasons for exclusion from each analysis set has been added.
Section 5.1	Added Table 1 defining visit windows for visits 2 and 3 as per the protocol.
Section 8.2	Description of how final PD data will be reviewed and updated for important PDs and deviation categories.
Section 9	Description of how immunogenicity samples taken outside the visit windows will be handled in per protocol analyses.

Section 10.1.1	Definitions of the severity categories for solicited AEs; redness, swelling and induration of '<25mm', '≤25-50mm', '>50-100mm', '>100mm' as per table 10.b in the protocol.

16 Appendices

16.1 Appendix 1 – MedDRA Internationally Agreed Order for System Organ Class

Table 4: MedDRA Internationally Agreed SOC Order

Order Number	System Organ Class
1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues