A Phase 3, Randomized, Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of Serum Institute of India's 10-Valent Pneumococcal Conjugate Vaccine (PNEUMOSIL®) Administered in a 2+1 Schedule to Healthy Infants in The Gambia

Statistical Analysis Plan

Version 5.0

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STATISTICAL ANALYSIS PLAN

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ABBREVIATIONS AND DEFINITIONS:

AE	Adverse Event (unsolicited)
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CVIA	Center for Vaccine Innovation and Access
DSMB	Data and Safety Monitoring Board
EPI	Expanded Program on Immunization
FIP	Full Immunogenicity Population
GMC	Geometric Mean Concentration (where present, subscripts designate treatment)
GMT	Geometric Mean Titer (where present, subscripts designate treatment)
IgG	Immunoglobulin G
IPD	Invasive Pneumococcal Disease
LLOQ	Lower limit of quantification
OPA	Opsonophagocytic Assay
PCV	Pneumococcal Conjugate Vaccine
PP_IMM	Per Protocol Immunogenicity Population
RCD	Reverse cumulative distribution curve
RE	Reactogenicity Event (solicited Adverse Event)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings, and Figures
ULOQ	Upper Limit of Quantification
V	Visit number (e.g. V1 ≡ first study visit)
WHO	World Health Organization

REVISION HISTORY

Document Version	Changes Made	Document Date
Version 1.0	Approved prior to unblinding, and addressing versions 1.0 and 2.0 of the protocol	07FEB2020
Version 2.0	To address changes in version 3.0 of the protocol. Approved before unblinding of patient-level data.	11DEC2020
Version 3.0	Added language to describe how OPA specimens were selected and additional details regarding TEAE summaries. Approved before unblinding of patient-level data.	12JAN2021
Version 4.0	Relevant safety analyses changed from onset of AEs within 14 days of each injection to onset within 28 days of each injection. Documented that unblinding for non-immunogenicity analyses may occur before final immunogenicity results are available. Version 4 was approved before unblinding of patient-level data.	5APR2021
Version 5.0	Modified comparative analysis of reactogenicity events to be consistent with AE summaries (use of 95% CIs for differences in proportions). Specified how to report 95% CIs when the response rate is 0% or 100% in both groups being compared. Version 5 was approved before unblinding of patient-level data.	06JUL2021

1. INTRODUCTION

The bacterium *Streptococcus pneumoniae* kills half a million children before their fifth birthday annually, mostly in low-resource areas of the world. The most common cause of childhood morbidity and mortality due to the bacterium is pneumonia, which in 2013 was estimated to be the cause of roughly 900,000 under-five deaths worldwide, making it the deadliest infectious disease of young children today.

The Serum Institute of India (SIIPL), in collaboration with the PATH Center for Vaccine Innovation and Access (CVIA), has been working since 2006 to develop a multivalent pneumococcal conjugate vaccine (PCV) designed to be affordable for use in low resource countries. PNEUMOSIL, SIIPL's 10-valent candidate PCV, incorporates those pneumococcal serotypes most prevalent prior to PCV introduction in cases of invasive pneumococcal disease (IPD) in Africa, Asia, and Latin America (types 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F), thus offering comparable coverage to currently licensed PCVs in these settings.

Previous clinical studies have provided the necessary immunogenicity, safety, and tolerability data to support the World Health Organisation (WHO) prequalification of PNEUMOSIL when delivered in a 3-dose primary schedule (3+0). The current study (CVIA 074) is intended to provide additional data to assist the WHO Prequalification Programme and regulatory authorities in making recommendations regarding the immunogenicity and safety of PNEUMOSIL when delivered in a 2-dose primary and booster (2+1) schedule, and to compare immunogenicity to that of currently licensed second-generation PCVs (Prevenar 13 and Synflorix) when administered in the same 2+1 schedule.

Version 4.0 of the statistical analysis plan (SAP) is an expanded version of the summary plan included in Protocol CVIA 074 (version 3.0). Cumulative changes made to the SAP since approval of protocol Version 1.0 are documented in the Appendix. Mock tables, listings, and figures (TLFs) designed to capture results of analyses will be approved by the Study Clinical Lead prior to un-blinding and maintained in a separate document.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

Immunogenicity:

1. To evaluate the serum IgG antibody responses (geometric mean concentrations [GMCs]) to the 10 serotypes in PNEUMOSIL, alone and in comparison to IgG antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (administered at 9-18 months of age)

Safety and Tolerability:

1. To assess the safety and tolerability of a 2-dose primary series and booster dose of PNEUMOSIL co-administered with routine pediatric vaccines, through 4 weeks post booster dose.

2.1.2. Secondary Objectives:

Immunogenicity:

1. To evaluate the functional serum antibody responses (geometric mean titers [GMTs]) to the 10 serotypes in PNEUMOSIL as measured by Opsonophagocytic Assay (OPA), alone and in comparison to the responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (subset of 50 subjects per group)
2. To assess seroresponse rates (IgG antibody levels and functional responses) to the 10 serotypes in PNEUMOSIL, alone and in comparison to seroresponse rates for these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (subset of 50 subjects per group for functional response rates)
3. To evaluate the serum IgG antibody responses (seroresponse rates and GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post completion of primary vaccination (administered at 6 and 14 weeks of age)
4. To evaluate the functional serum antibody responses (seroresponse rates and GMTs) to the 10 serotypes in PNEUMOSIL as measured by OPA, alone and in comparison to the functional antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post completion of primary vaccination (subset of 50 subjects per group)
5. To evaluate the persistence of the post-primary serum IgG antibody responses (seroresponse rates and GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to IgG antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 9-18 months of age (prior to a booster dose)
6. To evaluate the persistence of post-primary functional serum antibody responses (seroresponse rates and GMTs) to the 10 serotypes in PNEUMOSIL as measured by OPA, alone and in comparison to the functional antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 9-18 months of age (subset of 50 subjects per group prior to booster)
7. To evaluate the booster responses [(serum antibody concentrations (GMC) and functional responses (GMT)] to PNEUMOSIL, alone and in comparison to booster responses to Prevenar 13 and Synflorix, from 4 weeks after completion of primary vaccination to 4 weeks after a booster dose (subset of 50 subjects per group for functional responses)

2.2. Study Endpoints

2.2.1. Primary Endpoints:

Immunogenicity:

1. Serotype-specific serum IgG GMCs measured 4 weeks post booster dose

Safety and Tolerability:

1. Number and severity of solicited local and systemic adverse events (AEs) through Day 6 post each vaccination
2. Number, severity and relatedness of all unsolicited AEs until 9 months of age, and from booster vaccination through a 4-week follow-up period
3. Number, severity, and relatedness of all serious adverse events (SAEs) through the entire study period

2.2.2. Secondary Endpoints:

Immunogenicity:

For Secondary Objective 1 (post-booster OPA GMTs):

- Serotype-specific serum OPA GMTs measured 4 weeks post booster dose

For Secondary Objective 2 (post-booster seroresponse rates):

- Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 µg/mL measured 4 weeks post booster dose
- Percentage of subjects with serotype-specific serum IgG concentrations ≥ 1.0 µg/mL measured 4 weeks post booster dose
- Percentage of subjects with serotype-specific serum OPA titers ≥ 8 measured 4 weeks post booster dose

For Secondary Objective 3 (post-primary IgG responses):

- Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 µg/mL measured 4 weeks post completion of primary vaccination
- Serotype-specific serum IgG GMCs measured 4 weeks post completion of primary vaccination

For Secondary Objective 4 (post-primary OPA responses):

- Percentage of subjects with serotype-specific serum OPA titers ≥ 8 measured 4 weeks post completion of primary vaccination
- Serotype-specific serum OPA GMTs measured 4 weeks post completion of primary vaccination

For Secondary Objective 5 (persistence of post-primary IgG responses):

- Percentage of subjects with serotype-specific serum IgG concentrations ≥ 0.35 µg/mL measured prior to booster dose
- Serotype-specific serum IgG GMCs measured prior to booster dose

For Secondary Objective 6 (persistence of post-primary OPA responses):

- Percentage of subjects with serotype-specific serum OPA titers ≥ 8 measured prior to booster dose
- Serotype-specific serum OPA GMTs measured prior to booster dose

For Secondary Objective 7 (booster effects):

- Ratio of serotype-specific serum IgG GMCs measured 4 weeks post booster dose to serotype specific IgG GMCs measured 4 weeks post completion of primary vaccination
- Ratio of serotype-specific serum OPA GMTs measured 4 weeks post booster dose to serotype specific serum OPA GMTs measured 4 weeks post completion of primary vaccination

3. STUDY DESIGN

This is a prospective, single center, randomized, active-controlled, observer-blind, Phase 3 descriptive study in which 660 healthy Gambian PCV-naïve infants will be randomized 1:1:1 to receive 3 doses of PNEUMOSIL, Synflorix, or Prevenar 13.

3.1. Visit Schedule and Evaluations

Study vaccinations will be scheduled to occur at 6 weeks of age (+2 week visit window; Visit 1 [V1]), 14 (+2) weeks of age (V3), and 9-18 (+1) months of age (V5). Standard Expanded Program on Immunization (EPI) vaccinations in The Gambia (except Prevenar 13) will be given concomitantly with each primary dose of study vaccine, at 10 (+2) weeks of age (V2), and at 9 months of age where reasonable (recognizing the impact of SARS-CoV-2 on the feasibility of clinic visits). Blood draws for immunogenicity assessments will occur 4 (+2) weeks after the second study vaccination (V4), immediately prior to booster vaccination (V5) at 9-18 months of age, and at 4 (+2) weeks after booster vaccination (V6), which serves as the end-of-study visit. All subjects with evaluable specimens will be assessed for serum IgG responses. For functional antibody responses, 50 subjects who completed V4 per protocol and intended to continue to V6

were selected from each treatment group for OPA specimen testing. Subjects who did not complete V5 or V6 per protocol were replaced with new subjects from the same field site and treatment group to contribute V5 and V6 OPA data (see Section 3.5). The study schema is presented in Table 1.

Table 1. Study Schema

Visit / Age (with length of visit window in parentheses)					
V1	**V2**	**V3**	**V4**	**V5**	**V6**
6 (+2) wks	**10 (+2) wks**	**14 (+2) wks**	**V3+4 (+2) wks**	**9-18 (+1) mo**	**V5+4 (+2) wks**
X, E	E	X, E	B	B, X, E	B

wks = weeks, mo = months, X = study vaccination, E= EPI vaccines, B = blood sample for immunogenicity testing

Solicited reactogenicity events (REs) and vital signs will be assessed at 30 (+/- 10) minutes following each study vaccination. Solicited local REs include tenderness, erythema/redness, and induration/swelling at the injection site. Solicited systemic REs include cutaneous rash, fever, irritability, drowsiness, and decreased appetite. In addition to in-clinic assessments on the day of vaccination, all subjects will be monitored by field workers for local and systemic reactogenicity events during the 6 days after each study vaccination administration.

3.2. Sample Size and Power Calculations

Sample size considerations are based on expected precision of immunogenicity-related parameter estimates, rates of Treatment Emergent Adverse Events (TEAEs), and descriptive comparisons between treatment groups in these measures. All sample size calculations assume the use of descriptive 95% confidence intervals (CIs), with no adjustment for multiple comparisons. Unless otherwise noted, asymptotic Wald-type CIs will be used when describing proportions, and likelihood Score-type intervals for differences in proportions. Log-normality will be assumed when computing CIs for GMCs, GMTs, and their ratios. All sample size calculations were performed using SAS (v9.4).

3.2.1. Primary Immunogenicity Objective: IgG GMCs 4-weeks Post Booster

The previous pivotal Phase 3 study of PNEUMOSIL (VAC-056) in infants observed coefficients of variation (CV) that ranged from 0.89 to 1.46 for serotype-specific serum IgG antibody concentrations 4-weeks after a booster dose. Assuming the CVs for all PNEUMOSIL serotypes measured 4-weeks after booster in the current study are at most 1.5, the lower and upper 95% confidence bounds for each serum IgG GMC are expected to be at most 14% below and 16% above the observed GMC based on the study size of 220 per group (further assuming no more than 10% of subjects are non-evaluable due to loss to follow-up or other exclusions). For example, if the observed serotype-specific GMC = 1.0 μg/mL then the 95% CI is expected to be no wider than (0.86, 1.16) (Table 2). Similarly, the expected 95% bounds for descriptive GMC ratios (PNEUMOSIL versus either comparator) are expected to be no more than 19% below and

24% above the ratio. For example, if the observed GMC ratio equals 1.0, then the 95% CI is expected to be no wider than (0.81, 1.24), so long as the CV in the comparison group does not exceed 1.5.

Table 2. Expected precision of serotype-specific GMCs and GMC ratios (PNEUMOSIL vs. comparator) for a range of possible true GMCs and GMC ratios

GMC in PNEUMOSIL group	Expected 95% CI for GMC	GMC Ratio (PNEUMOSIL vs. comparator)	Expected 95% CI for GMC Ratio
0.5	0.43-0.58	0.75	0.60-0.93
		1.00	0.81-1.24
		1.33	1.08-1.67
1.0	0.86-1.16	0.75	0.60-0.93
		1.00	0.81-1.24
		1.33	1.08-1.67
3.0	2.58-3.49	0.75	0.60-0.93
		1.00	0.81-1.24
		1.33	1.08-1.67
5.0	4.29-5.82	0.75	0.60-0.93
		1.00	0.81-1.24
		1.33	1.08-1.67

3.2.2. Primary Safety Objective

With a sample size of 220 per group, there is 89% or greater chance of observing at least 1 safety endpoint (e.g., a solicited RE) which occurs with probability 0.01 or more. If no events of a specific classification occur, then the 95% upper confidence bound for the event rate will be at most 0.017.

3.2.3. Secondary Immunogenicity Objectives

The precision of IgG GMCs 4 weeks post completion of primary vaccination (V4) is expected to be as for the primary objective under the same assumptions about CV of serotype-specific IgGs and follow-up rates as previously described. The expected precision of other secondary immunogenicity objectives (IgG response rates, OPA response rates, and OPA GMTs) are as follows:

With a sample size of 220 per group (up to 10% of whom may not be evaluable), the half-width of 95% CIs for serum IgG response rates (IgG ≥ 0.35 μg/mL or IgG ≥ 1.0 μg/mL) will be no more than 0.07, and the half-width of 95% CIs for differences in proportions should not exceed 0.10.

With a sample size of 50 per group (and no more than 10% excluded), the half-width of 95% CIs for OPA response rates (titer ≥ 8) will be no more than 0.15, and the half-width of 95% CIs for differences in proportions responding (PNEUMOSIL versus a comparator) should not exceed 0.21.

The VAC-056 study observed CV values that ranged from 0.97 to 2.11 for serotype-specific OPA titers measured 4 weeks after a booster dose of PNEUMOSIL in infants. Assuming the CVs for all 10 PNEUMOSIL serotypes in the current study are at most 2.11 at V4 and V6, the lower and upper 95% confidence bounds for each GMT are expected to be at most 32% below and 48% above the observed GMT based on the study size of 50 per group (assuming no more than 10% of subjects are not evaluable due to loss to follow-up or other exclusions). For example, if the observed serotype-specific GMT = 100, then the 95% CI is expected to be no wider than (68, 148). Similarly, the expected lower and upper 95% confidence bounds for descriptive GMT ratios (PNEUMOSIL versus either comparator) are expected to be no more than 42% below and 73% above the ratio. For example, if the observed GMT ratio equals 1, then the 95% CI is expected to be no wider than (0.58, 1.73), so long as the CV in the comparison group does not exceed 2.11.

Due to positive within-subject correlation among subjects contributing both V4 and V6 data, the precision of within-group booster-effects (ratios of GMCs and GMTs post-booster versus post-primary series) is expected to be at least as high as that of the between-group contrasts at V4 or V6 described above, under similar assumptions about CV and the percentage of evaluable subjects.

3.3. Randomization and blinding

After a subject is confirmed to have met all study eligibility requirements, he or she will be randomized in a 1:1:1 allocation ratio based on a pre-established randomization scheme stratified on field site, and receive the first dose of either PNEUMOSIL, Synflorix, or Prevenar 13 at 6 (+2) weeks of age (V1).

The eligible subject will be assigned the next numeric randomization ID for the given field site. Treatment assignments will be communicated to the unblinded dosing nurse via sealed, opaque, numerically numbered envelopes identified by a unique randomization ID. If a subject is given the wrong treatment at V1 due to an allocation error, the same vaccine will be administered at V3 and V5 so long as the error is identified before the timing of the next injection.

Except for staff responsible for preparing and administering study vaccines, performing vaccine accountability, and maintaining the security of the treatment assignments, all study personnel, including the Principal Investigator (PI) and the Sponsor, will remain blinded to subjects'

individual treatment assignments. All CRO personnel will also remain blinded to individual treatment assignments until the last subject completes V6, with the following exceptions: an unblinded monitor, a clinical supplies manager, a statistician implementing the interim analysis of immunogenicity objectives through V4 and any required unblinded analyses for the Data and Safety Monitoring Board (DSMB), and an Executive Secretary for the DSMB (if required). The interim analysis results shared with the Sponsor will include treatment group-level comparisons, but no information which could reveal individual treatment assignments. Unblinding at interim and final analyses will be conducted and documented in accordance with relevant CRO standard operating procedures (SOPs) and documented in the eTMF when the study is complete. Details regarding maintenance of blinding for any DSMB safety analyses are addressed in the separate DSMB Charter.

3.4. Blinded data review

Prior to both the interim and final analysis, data pooled across treatment groups will be reviewed by the PATH Clinical Lead or designee for analysis decisions. The lead statistician will develop specific listings for this review and will document the Clinical Lead's decisions. Reviews will include (but not necessarily be restricted to) protocol deviations (e.g., out of window visits) for inclusion/exclusion of subjects and/or data points. The blinded review may also include clinical evaluation of safety data for reasonableness or to issue clinical queries to the site if needed. Any decisions made in blind review that might affect analysis interpretation will be documented in the Clinical Study Report (CSR).

3.5. Selection of OPA Specimens

Prior to the interim analysis of primary series immunogenicity data, the PI provided the ratio of subject enrolments per field site expected to be achieved at the completion of the trial. Based on this ratio, the independent statistician selected (based on order of entry into the study, not randomly) the first 27 subjects with evaluable V4 specimens in each treatment group from the Brikama field site, and the first 23 subjects with evaluable V4 specimens in each treatment group from the Bundung site, such that a total of 50 subjects per group were selected for OPA analysis proportional to the enrolment total in each site. Selected subjects who did not complete V5 per protocol were later replaced with new subjects from the same field site and treatment group to contribute V5 and V6 OPA data (with replacements also selected in order of enrolment date, not randomly). If more than 10% of subjects fail to contribute evaluable results at a given visit, then additional subjects may have their specimens analysed to help ensure at least 45/group contribute to each secondary functional antibody analysis timepoint. The PATH Clinical Lead will make this determination in blind review of data once the availability of OPA results has been determined for all selected subjects.

3.6. Scheduled Study Unblinding

The requirements for scheduled unblinding for the final analysis are as follows:

1. Statistical Analysis Plan has been finalized and approved.
2. All CRF data have been collected, double-entered, and discrepancies resolved.
3. Blinded review of non-immunogenicity data is complete and corresponding analysis decisions documented.
4. Medical, concomitant medication and other text coding has been completed.
5. Non-immunogenicity analysis data sets have been independently verified.
6. Non-immunogenicity Tables and Figures programmed and verified using dummy treatment codes.

The requirements listed above will be followed to the extent possible for the planned interim analysis, noting that some queries may not be resolved at the time of the interim analysis. Any resulting implications or limitations of an incomplete blinded review will be noted in the interim analysis report. Additional details are provided in a separate Unblinding Plan.

3.7. General Issues

General descriptive statistics for numeric variables include the number of observed values, the mean, SD, median, minimum, and maximum values. For categorical variables, the number and percentage of subjects with a specific level of the variable will be presented. Percentages will be calculated based on subjects with reported values (i.e., subjects with missing data will not contribute to denominators of percentages). Descriptive statistics and tabular summaries will be presented by treatment group and, as relevant, by vaccination number or other subdivision.

General reporting conventions will include the following:

- The baseline values for any measurement will be the last value obtained prior to receiving the first vaccination at V1.
- Unless decided otherwise during blinded data review, nominal time points will be used for analysis; actual assessment times (e.g., blood draws) will not be used to reclassify the time point at which a measure was taken.
- Study days until the occurrence of a specific event (e.g., an AE start date) will be calculated relative to the date of randomization/1st vaccination (study day 0) as Date of event minus Date of randomization/1st vaccination administration. Unless information on the specific time (hours and minutes) of an event onset and resolution are known, event durations will be calculated as date of event resolution minus date of onset, plus 1 day.
- Other than log-transformations for immunogenicity data, no transformations are planned.
- Unless otherwise noted, percentages will be presented to one decimal place; means will be reported using one more decimal place than the raw data; the number of decimal places for medians, minima and maxima will be the same as for the raw data; SDs and confidence limits will be reported to the same number of decimal places as for the corresponding mean or percentage; and p-values will be rounded to four decimal places.

- All data listings will be sorted by treatment group and subject screening ID.
- Except for TEAEs and REs, and unless determined otherwise based on blind review of data (per Section 3.4), post-randomization data from unscheduled (out of window) visits will be excluded from the summary tables but included in listings.

3.8. Analysis Populations

The following analysis populations will be used when performing statistical analyses:

- **Enrolled Population** includes all screened subjects who provide informed consent, regardless of whether the subject is randomized. This population will be used to account fully for subject disposition, starting with the informed consent.
- **Safety Population** includes all subjects who were randomized, received a study vaccination, and provided post-vaccination safety data. Since all subjects are assessed for REs immediately following injection, the Safety Population will include all treated subjects unless a subject's safety data is unevaluable for some reason. Analyses based on this population will be analyzed according to actual treatment received at V1. This population will serve as the primary analysis population for study disposition, baseline demographics and medical history, as well as safety analyses.
- **The Full Immunogenicity Population (FIP)** includes subjects in the enrolled population who were randomized, received at least one study vaccination, and have post-vaccination immunogenicity measurement(s). Analyses based on the FIP will be performed according to randomized treatment assignment, regardless of any randomization or allocation errors. Results will serve as supportive analyses for the Primary and Secondary PP_IMM Population results (see below).
- **The Primary Per Protocol Immunogenicity Population (PP_IMM)** includes subjects in the FIP who received all 3 study vaccinations (including booster), contribute post-booster immunogenicity measurements, and have no major protocol deviations that are determined to potentially interfere with the immunogenicity assessment. This population (or a relevant subset of subjects contributing OPA results) will be used to assess the primary immunogenicity objective and secondary immunogenicity objectives 1, 2, and 7.
- **The Secondary PP_IMM Population** includes all subjects in the FIP who received both primary series study vaccinations, contribute immunogenicity measurements at 4-weeks post primary series and/or immediately prior to receiving the booster dose, and have no major protocol deviations that are determined to potentially interfere with the immunogenicity assessment. This population (or a relevant subset of subjects contributing OPA results) will be used to assess secondary immunogenicity objectives 3, 4, 5, and 6, as well when performing the planned interim analysis.

Any exclusions from the Primary and Secondary PP_IMM populations (e.g., due to out-of-window study vaccinations or other protocol violations which could potentially interfere with

immune responses or the interpretation of results) will be established in blind review by the PATH Clinical Lead. Populations used for each category of analysis described in subsequent sections of this SAP are summarized in Table 3.

Table 3. Summary of Planned Analyses, by Population

ANALYSIS	ENROLLED	SAFETY	FIP	PRIMARY PP_IMM	SECONDARY PP_IMM
Disposition	√	√			
Baseline		√		√	
Safety		√			
Primary Immunogenicity			√ [1]	√	
Secondary Immunogenicity objectives 1, 2, and 7			√ [1]	√	
Secondary Immunogenicity objectives 3, 4, 5, and 6			√ [1]		√

[1] restricted to subjects who contribute immunogenicity results at the relevant visit(s)

3.9. Covariates

Unless otherwise noted, no covariates will be utilized in primary or secondary statistical analyses of immunogenicity, safety, or tolerability. An exploratory analysis of the effect of duration of elapsed time between completion of the primary series and booster vaccination on post-booster responses and booster effect will be performed, and this analysis may control for covariates such as gender and field site. Additional post hoc analyses which explore the effects of covariates on immune responses may also be conducted.

3.10. Pooling of Sites and Evaluation of Site Differences

Information from the population flow chart, demographics and final disposition tables will be reported by field site to inform potential site differences. No statistical tests for differences in characteristics across field sites or between treatment groups within site will be conducted.

Except for tests of treatment-group differences in safety outcomes, which will be stratified on field site, analyses will be performed on data pooled across field sites. However, potential site-level effects will be assessed in exploratory analyses of treatment-by-site interactions for differences in proportions of subjects with TEAE and differences in the distribution of highest grade of reactogenicity observed within Day 6 of any vaccination. Interactions significant at $\alpha = 0.05$ will be described in the CSR. Site-specific tables summarizing treatment-group differences in key TEAE categories may also be produced, but formal statistical testing of treatment-by-site interactions within such categories will not be conducted. Differences in immunogenicity responses between sites may also be explored (e.g., when assessing log-normality assumptions), but no formal statistical tests of treatment by site interactions will be reported.

3.11. Multiple Comparisons

No adjustment for multiple comparisons will be made. All descriptive CIs will be at the 95% level, and all p-values assessed for statistical significance at the two-sided 0.05 level.

3.12. Interim Analyses

A formal interim immunogenicity analysis is planned for when all enrolled subjected have completed V4 (4-weeks post-primary series). The analysis will be performed by an independent statistician and shared with the Sponsor. Only treatment group-level comparisons will be provided, with no data listings which could reveal subject-level treatment assignments.

3.13. Handling missing and incomplete data

3.13.1. Premature Discontinuation and Missing Data

For any subject who withdraws prematurely from the study, all available data up to the time of discontinuation will be included in relevant analyses unless otherwise excluded during blind review. Per protocol, subjects who are discontinued from the study after vaccination (regardless of reason) will not be replaced, but a subject discontinued after randomization but prior to 1st vaccination will be replaced using a new randomization assignment for the replacing subject.

Missing data will be assumed missing at random and ignorable. Except where noted in Section 3.13.2, missing or censored data will not be estimated or imputed. Denominators for percentages will be based only on the number of subjects with non-missing values.

3.13.2. Imputed Data

All immunogenicity assays reported as being below the limit of quantification or below a specified threshold will be assigned a value of one-half the lower limit of quantification (LLOQ) or threshold value, using values of LLOQ or other information provided by the responsible laboratory. Values above an applicable upper limit of quantification (ULOQ) will be assigned the ULOQ value unless determined otherwise in blind review of data.

In the event missing event dates or times are needed to compute durations of outcomes, the following rules will be applied:

- If the month and year are known, but the date is missing, the date will be imputed as the midpoint between the earliest the event could have occurred and the latest the event could have occurred, based on reporting dates and other information in the clinical data base. If data are not available to do this, the 15th will be used for any calculations of relative time (e.g., UNMAY2018, where ‘UN” denoted unknown, would be imputed as 15MAY2018).
- If the minutes of start or stop times are missing, time will be assumed to be on the hour for a 24 hour clock (e.g., 11:UN, is assumed to be 11:00 AM).
- Listings will report unimputed dates or times.

Otherwise, no imputation for missing values is planned.

3.14. Evaluation of Normality Assumption

The assumption of log-normality of immunogenicity data, including the impact of any imputed (below LLOQ or above ULOQ) values, will be assessed by visual inspection of quantile-to-quantile plots and tests of departures from normality. The lead statistician will use these results to determine whether the normality assumption is substantively violated; that is, if the deviation from normality is to a degree that alternative analysis methods should be employed.

If the log-normality assumption is meaningfully violated, an appropriate non-parametric or bootstrap resampling method may be considered. If bootstrap resampling is implemented, point estimates will be calculated directly from the data but CIs will use the bias-corrected and accelerated method (Efron and Tibshairani [1993]; Barker [2005]) using 10,000 bootstrap samples.

3.15. Statistical Software

Version 14.1 or higher of the SAS/STAT® software will be used for all analysis.

4. EVALUATION OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

4.1. Subject Enrolment and Disposition

Subject disposition will be summarized in a flow chart, including the numbers of subjects screened, randomized, contributing to each analysis population, reasons for early discontinuation and other exclusions from analysis populations, the percentage of subjects whose booster vaccination was delayed due to the COVID-19 pandemic, and person-time contributed to analysis, by treatment group. Disposition data (including number of vaccinations received) will also be tabulated by field site.

4.2. Protocol Deviations and Measures of Study Conduct

Protocol deviations will be reviewed during blinded data review and analysis decisions, if any, made as a consequence of these deviations documented prior to unblinding. All protocol deviations will be tabulated and listed, including individual subject unblinding, whether for safety reasons or by accident. The number of vaccination visits or home visits that were missed, and follow-up visits missed or outside of protocol window, will also be summarized.

4.3. Treatment Compliance

Treatment compliance is defined as having received all three doses of study vaccine. Randomized subjects with less than full compliance and reasons why will be listed.

4.4. Demographics and Baseline Characteristics

Demographic characteristics and socioeconomic status will be summarized for the Safety and Primary PP_IMM Populations. No statistical comparisons of treatment-group differences in demographics or baseline data will be performed. Demographic data will also be reported by field site.

4.5. Medical History and Baseline Assessment

Medical history and baseline anthropometrics, vital signs, etc., will be summarized as for demographic data.

4.6. Concomitant Medications

A summary of concomitant medications taken during the study will be presented in listings and tabulated for the Safety Population. Tabulated data will use codes based on a combination of Lexicomp and the on-line Physicians' Desk Reference. Listings will include drug name, dose, route, frequency, indication, and start and end dates, as available.

5. EVALUATION OF IMMUNOGENICITY

Analysis Populations: Primary and secondary immunogenicity will be evaluated within the Primary and Secondary Per Protocol Immunogenicity Populations, as noted in Table 3.

Data Sources: Primary immunogenicity objectives will be based on serotype-specific IgG antibody concentrations measured 4 weeks after the booster vaccination series (V6). Secondary objectives will be based on the serotype-specific IgG concentrations and OPA titers at three time points (4-weeks after completion of the primary series (V4), immediately prior to booster (V5), and V6).

Endpoint Definitions:

1. **GMC [or GMT]:** The geometric mean concentration (or titer) = antilog (mean [$\log_{10}$ x]), where x is the assay result
2. **Response to study vaccine:**
   - IgG concentration ≥ 0.35 µg/mL
   - IgG concentration ≥ 1.00 µg/mL
   - OPA titer ≥ 8

5.1. General Comments on Reporting of Immunogenicity Objectives:

1. Differences in proportions of responders to each serotype in PNEUMOSIL will be reported as the PNEUMOSIL proportion minus the reference group (Synflorix or Prevenar 13) proportion, with 95% confidence intervals calculated using the Miettinen-Nurminin (1985) likelihood score method. If the response rate is 100% in each group, then two non-response records (one for each group) will be included and given a weight of 0.000001 to facilitate computation of the 95% CI. Differences in proportions will be considered statistically significant if the 95% CI excludes 0.
2. Within-group GMCs [GMTs] and 95% CIs for each serotype in PNEUMOSIL will be computed based on the antilog (base 10) of mean log10 concentrations [titers] and the corresponding CI limits for the mean log10 values, based on a log-normality assumption.
3. Between-group GMC [GMT] ratios will be reported as the PNEUMOSIL GMC [GMT] divided by the reference vaccine GMC [GMT]. 95% CIs for between-group GMC [GMT] ratios will be computed based on the antilog (base 10) of the corresponding CI limits for the difference in mean log10 concentrations [titers]. Differences between groups will be considered statistically significant if the 95% CI excludes 1.
4. Within-group (booster response) GMC [GMT] ratios will be computed based on the antilog (base 10) of the mean within-subject differences in log10 concentrations [titers], V6 minus V4, restricted to subjects who contribute evaluable immunogenicity data at each time point. Confidence intervals for within-group GMC [GMT] ratios will be computed as in (3), and booster responses will be considered statistically significant if the CI excludes 1.0.

5.2. Analysis of primary immunogenicity endpoint

The Primary immunogenicity objective is to evaluate the serum IgG GMCs to the 10 serotypes in PNEUMOSIL, alone and in comparison to IgG antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose. For each serotype, two-sided 95% CIs for the within-group GMC and the between-group GMC ratios will be calculated. Differences between groups will be considered statistically significant if the 95% CI for the GMC ratio excludes 1.0.

5.3. Analysis of Secondary Immunogenicity Endpoints

5.3.1. Secondary Objective 1: functional antibody responses at 4 weeks post booster

Secondary objective 1 is to evaluate the functional serum antibody responses (GMTs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to the responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose. This analysis will be done among a subset of 50 subjects per group (see Section 3.5). For each serotype, two-sided 95% CIs for the within-group GMT and the between-group GMT ratios will be calculated. Differences between groups will be considered statistically significant if the 95% CI for the GMT ratio excludes 1.0.

5.3.2. Secondary Objective 2: IgG seroresponse rates 4 weeks post booster

Secondary objective 2 is to assess seroresponse rates (IgG antibody levels and functional responses) to the 10 serotypes in PNEUMOSIL, alone and in comparison to seroresponse rates for these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post booster dose (functional responses assessed in a subset of 50 subjects per group). For each serotype, the proportion of responders (IgG concentrations ≥ 0.35 μg/mL; IgG concentrations ≥ 1.0 μg/mL; and OPA titers ≥ 8) at 4 weeks post booster will be reported, together with 95% CIs for the proportions and for differences between the PNEUMOSIL and comparison groups. Differences between groups will be considered statistically significant if the 95% CI excludes 0.0.

5.3.3. Secondary Objective 3: IgG antibody responses 4 weeks post primary

Secondary objective 3 is to evaluate the serum IgG antibody responses (seroresponse rates and GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post completion of primary vaccination. For each serotype, the proportion of IgG antibody responders (IgG concentrations ≥ 0.35 μg/mL and IgG concentrations ≥ 1.0 μg/mL) and the GMC at 4 weeks post primary series will be reported, together with 95% CIs for the proportions and GMCs. Differences in seroresponse rates and GMC ratios (PNEUMOSIL versus each comparison group) will also be reported with 95% CIs. Differences between groups will be considered statistically significant if the 95% CI excludes 0.0 (for response rates) or 1.0 (for GMCs).

5.3.4. Secondary Objective 4: functional antibody responses 4 weeks post primary

Secondary objective 4 is to evaluate the functional serum antibody responses (seroresponse rates and GMTs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to the functional antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 4 weeks post completion of primary vaccination in a subset of 50 subjects per group. For each serotype, the proportion of functional antibody responders (OPA titers ≥ 8) and the GMT at 4 weeks post

primary series will be reported, together with 95% CIs for the proportions and GMTs. Differences in response rates and GMT ratios (PNEUMOSIL versus each comparison group) will also be reported with 95% CIs. Differences between groups will be considered statistically significant if the 95% CI excludes 0.0 (for response rates) or 1.0 (for GMTs).

5.3.5. Secondary Objective 5: persistence of post-primary IgG responses

Secondary objective 5 is to evaluate the persistence of the post-primary serum IgG antibody responses (seroresponse rates and GMCs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to IgG antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 9 months of age (prior to a booster dose). For each serotype, the proportion of IgG antibody responders (IgG concentrations ≥ 0.35 μg/mL) and the GMC at V5 (just prior to booster) will be reported, together with 95% CIs for the proportions and GMCs. Differences in seroresponse rates and GMC ratios (PNEUMOSIL versus each comparison group) will also be reported with 95% CIs. Differences between groups will be considered statistically significant if the 95% CI excludes 0.0 (for response rates) or 1.0 (for GMCs).

5.3.6. Secondary Objective 6: persistence of post-primary functional antibody responses

Secondary objective 6 is to evaluate the persistence of post-primary functional serum antibody responses (seroresponse rates and GMTs) to the 10 serotypes in PNEUMOSIL, alone and in comparison to the functional antibody responses to these serotypes induced by Prevenar 13 and Synflorix, at 9 months of age, immediately prior to booster among a subset of 50 subjects per group. For each serotype, the proportion of functional antibody responders (OPA titers ≥ 8) and the GMTs at V5 (just prior to booster) will be reported, together with 95% CIs for the proportions and GMTs. Differences in response rates and GMT ratios (PNEUMOSIL versus each comparison group) will also be reported with 95% CIs. Differences between groups will be considered statistically significant if the 95% CI excludes 0.0 (for response rates) or 1.0 (for GMTs).

5.3.7. Secondary Objective 7: booster responses

Secondary objective 7 is to evaluate booster responses (serum antibody response GMCs and functional response GMTs) to PNEUMOSIL, alone and in comparison to booster responses to Prevenar 13 and Synflorix, from 4 weeks after completion of primary vaccination to 4 weeks after a booster dose (restricted to a subset of 50 subjects per group for functional responses). For each serotype and treatment group, the ratio of within-group GMCs and GMTs (V6 versus V4) will be reported, together with 95% CIs for these booster responses. The totality of the data (responses at V4, V6 and booster responses) will be descriptively compared between groups for clinical relevance.

In addition to tabulations of primary and secondary endpoints, immune response data will be summarized graphically at each of V4, V5, and V6, and over time using bar charts (OPA only) and reverse cumulative distribution (RCD) curves.

Due to the impact of the COVID-19 pandemic on clinic visit schedules, not all subjects selected for the OPA analysis at V4 contributed data at V5 and V6. Per Section 3.5, subjects not contributing V5 and V6 data were replaced with new subjects from the same field site and treatment group. To assess the robustness of Secondary Objective 7 results, the analysis of this objective will be repeated when restricting the sample to subjects who contributed both V4 and V6 data. The results of this sensitivity analysis and any related exploratory analyses will be only used to guide interpretation of the primary analysis results.

5.3.8. Exploratory Analyses of Immunogenicity Data

Due to the impact of the COVID-19 pandemic on clinic visit schedules, a protocol amendment extended the range in which booster vaccinations are given from 9 (+1) months to 9-18 (+1) months of age. The change enables the study to explore the effect of the length of time between completion of the primary series and administration of the booster dose on post-booster responses and booster effects. We will use log-linear models to explore the effect of time between V4 and V5 on post-booster IgG and OPA responses in each treatment group (GMCs and GMTs), and log-linear random effects models to explore the effects of time on booster responses (GMC and GMT ratios). Generalized linear models with logit link will be used to explore the corresponding effects of time on post-booster seroresponse rates (IgG concentrations ≥ 0.35 µg/mL; IgG concentrations ≥ 1 µg/mL; OPA titer ≥ 8). Analyses will be restricted to the Primary Per Protocol Immunogenicity Population. All results will be reported as exploratory in nature using descriptive 95% CIs and p-values.

5.4. Evaluation of Safety and Tolerability

In this document solicited adverse events identified in the 30 (+/-10) minutes after each study vaccination or during field visits in the first 6 days after each study vaccination are referred to as reactogenicity events (REs) to distinguish them from all other (unsolicited) AEs.

5.4.1. Safety Analysis: General Issues

Safety and tolerability of study vaccines will be evaluated using the following endpoints:

- Number and severity of solicited local and systemic REs through Day 6 after each vaccination
- Number, severity and relatedness of all unsolicited AEs until 9 months of age, and from booster vaccination through a 4-week follow-up period
- Number, severity, and relatedness of all serious adverse events (SAEs) through the entire study period

Analysis Population: All analysis of safety and tolerability will be performed using the Safety Population, with analysis of REs conducted within subsets of time contributed to the Safety Population as described below.

Generally, safety evaluations will be descriptive in nature, and observed differences will be evaluated for medical relevance. Any statistical tests of treatment-group differences in safety endpoints, including calculation of 95% CIs around treatment-group differences, are not adjusted for multiple testing and are provided solely as a guide to clinical and scientific judgment.

Clinical assessments (e.g. vital signs) will be summarized separately by baseline and scheduled measurement time point pre-vaccination, post-vaccination and at follow-up visits. Results from unscheduled visits will be included in listings. For ease of review, baseline results may be reported on the same table as post-randomization results.

5.4.2. Adverse events

The onset date will be compared to the date of 1st vaccination (Day 0) to determine if it is a TEAE. Adverse events are considered treatment emergent if (a) onset occurs on or after the date/time of first vaccination, or (b) an event with onset prior to the first vaccination but increases in severity after administration of the vaccination. Only TEAEs with onset on or before V6 (4-weeks post booster) will be included in the formal safety analysis, although listing will be provided of all other AEs that occur in subjects who are not in the Safety Population or are not treatment emergent.

Summary tables of TEAEs (overall and by onset within 28 days of each vaccination) will be presented with numbers of events, and numbers and percentage of subjects, with any: (a) TEAEs; (b) unexpected TEAEs; (c) serious TEAEs; (d) vaccine-related TEAEs; (e) vaccine-related SAEs; (f) TEAEs leading to discontinuation of the vaccination series; and (g) TEAEs leading to death. Treatment-group differences in percent of subjects will be compared for each category (a)-(f) using the Cochran-Mantel-Haenszel (CMH) test stratifying on field site (Fisher's exact tests will be used if the number of events is < 5 for at least one treatment group). The 95% CI around treatment-group differences (PNEUMOSIL versus each comparator) will also be reported using Miettinen-Nurminin Score-type intervals (if the event rate is 0% in each group, then two event records – one for each group – will be included and given a weight of 0.000001 to facilitate computation of the 95% CI).

The process for medical coding will be conducted according to the [redacted] 360 SOP 06006 "Medical Coding of Clinical Study Data using MedDRA". Unsolicited TEAEs will be summarized and grouped by MedDRA System Organ Class (SOC) and AE preferred term using MedDRA™ v22.0 or higher coding terminology, by treatment group and pooled across groups. A similar summary will be provided for non-serious TEAEs (pooling solicited and unsolicited events). Results will be displayed in order of decreasing frequency, both across SOC and within each SOC term. In addition, TEAE summaries will be provided by severity (mild, moderate, severe, or life threatening/death if any), and by relationship to study vaccine (Related, Unrelated), overall and according to onset within 28 days of each vaccination.

A listing of all TEAEs through V6 will be presented by treatment group and will include subject identifier, AE verbatim description, preferred term, SOC, duration, relatedness to product, seriousness, severity, outcome, and action taken with respect to the investigational product.

Because of the number of variables to be reported, TEAE listings may be produced in two parts, sorted in the same order and with the same key identifiers to allow easy cross-reference.

TEAE listings will be repeated for (a) those that were serious, severe (Grade 3 or 4), considered related to vaccine, or leading to discontinuation of the vaccination series, and (b) any events of special clinical interest (including unexpected events) identified in blind review.

The concomitant medication/drug/treatment verbatim text will be coded using a combination of Lexicomp and the on-line Physicians' Desk Reference. Concomitant medications will be tabulated using frequencies and percentages and listed.

Owing to the impact of COVID19 on clinic visit schedules, unsolicited AEs were not routinely collected after 9 months of age but before the booster dose (V5). Any AEs that are recorded in the database that have an onset after 9 months but before V5 will not be excluded from summary tables but will be clearly identified in TEAE listings.

5.4.3. Reactogenicity (Solicited Adverse Events)

Solicited reactogenicity events are assessed at 30 (+/- 10) minutes following each vaccination and at home visits by field workers during the 6 days after each study vaccination. If more than one measurement is obtained on a given day (e.g. due to an unscheduled clinic visit) then the maximum level observed that day will be used in analysis. Note that per protocol, an event with onset on or after Day 7 post-vaccination is an unsolicited AE reported on the AE CRF.

Solicited REs will be tabulated for each assessment period (30 +/- 10 minutes and at each of the following 6 days) after each study vaccination. The percentage of subjects experiencing a grade 1+ or grade 3+ solicited RE in the 6 days following each study vaccination and across all 3 study vaccinations will also be tabulated, separately for local and systemic events.

The percentage of subjects experiencing grade 1+ REs (overall, any local RE, any systemic RE, and each individual event type) will be compared between PNEUMOSIL and the other treatment groups using 95% Miettinen-Nurminin Score-type CIs. If the event rate is 0% in both groups, then two event records – one for each group – will be included and given a weight of 0.000001 to facilitate computation of the 95% CI. Cochran-Mantel-Haenszel tests stratified on field site will be used to assess overall differences across the three groups (or Fisher's Exact tests if fewer than 5 events are observed in one of the treatment groups).

Any subjects with at least one Grade 3+ reactogenicity event post vaccination will be listed separately. For clinical context, the list will include all observations through Day 6 for that subject, reactogenicity endpoint, and vaccination.

5.4.4. Vital signs

Vital signs (temperature, resting respiration rate and resting pulse rate) will be presented in listings and summarized via standard descriptive statistics as well as by protocol severity (toxicity) grades for each treatment group and measurement time point (pre-vaccination, 30

minutes post vaccination, scheduled follow-up visit). Data from subjects with Grade 2+ vital signs at any time, including unscheduled visits, will be listed separately.

6. TABLES, LISTINGS, AND FIGURES

Planned TLFs intended to capture interim and final analyses described in the SAP are reviewed by the Sponsor before going into production. Since numbering and other formatting of the TLFs will change during the analysis, review, and CSR writing process, and because additional TLFs may be created for exploratory analyses not anticipated prior to un-blinding, the TLF shells are maintained separately from the approved version of the SAP.

6.1. Programs and Tables Quality Control

Report production and review will be conducted in accordance with [redacted] BIOS Work Instructions (WI) 03003 (Verification of Analyses and Reports) and 03006 (Preparation and Review of Statistical Reports). In brief, a primary statistician-programmer for a given output will carefully review the program and output, verifying that no error message is highlighted in the "LOG" file and that titles, footers, footnotes, text body, etc. are correct. A second statistician-programmer will independently validate the output by checking the results against separately created SAS programs and checking textual material. Prior to delivery of any statistical output to Sponsor, the lead statistician will review the statistical package for internal inconsistencies or any items where clarifying notes will be helpful to the reviewer. The package is then thoroughly reviewed by the Biostatistics Director or designee before it is distributed.

6.2. Programming Conventions

Reporting conventions will adhere, when possible, to the International Conference on Harmonization Guidance document E3, "Structure and Content of Clinical Study Reports".

All tables and listings will be in landscape format unless otherwise requested.

Each table/figure/listing will have at least three titles:

- The 1st title will have the study/report name
- The 2nd and as needed 3rd titles will be the TLF number and description, and will identify the objective being addressed
- The last title will identify the study population

Each table/figure/listing will also identify:

- Date of data freeze
- Data source (analysis data set)
- Listing source (associated listing, if any, for further details)
- File reference (name of output file)

- Run date

All SAS output for tables and listings will be distributed in PDF files, with RTF files created for inclusion into the CSR or sponsor presentations.

7. LITERATURE AND REFERENCES

Barker N. (2005) A Practical Introduction to the Bootstrap Using the SAS System. Paper PK02, PhUSE conference.

Efron B, Tibshirani R.J. (1993) *An Introduction to the Bootstrap*, Chapman & Hall.

Miettinen OS, Nurminen M. (1985). Comparative analysis of two rates. *Statistics in Medicine*; 4:213–226.

8. APPENDIX

8.1.1. Changes to Analysis Plans after Approval of Protocol Version 1.0

- In the event of any randomization errors, supportive analyses based on the Full Immunogenicity Population will be performed according to randomized treatment assignment, rather than treatment received at enrolment. This change was implemented in Version 1.0 of the SAP, prior to any unblinding of any study team members.

- The SAP was updated throughout to reflect the change in the timing of clinic visits in response to the COVID-19 pandemic and related changes to the definition of safety endpoints (Section 2.2.1), procedures for selecting subjects contributing to OPA analysis (Section 3.5), the use of covariates (Section 3.9) in sensitivity and exploratory analyses of immunogenicity data (Sections 5.3.7 and 5.3.8), and the reporting of unsolicited TEAEs with onset after month 9 of age but before V5 (Section 5.4.2). These modifications to the SAP were made blind to individual patient treatment group assignments.

- The SAP was updated (V3) to provide further details regarding non-random selection of subjects for OPA analysis (Section 3.5) and to provide additional details regarding TEAE summaries (5.4.2). These modifications to the SAP were made blind to individual patient treatment group assignments.

- The SAP was updated (V4) to address a change in reports on timing of AE onset in relation to each vaccination (from 14 days to 28 days). Version 4 also clarified that unblinding of non-immunogenicity analyses may occur before immunogenicity results are available due to laboratory delays arising from the COVID-19 pandemic.

- The SAP was updated (V5) to address issues that arose in blind review of data. The decision was made to compare rates of REs between groups using 95% CIs for differences in proportions (rather that p-values) to be consistent with AE summaries. Also specified in the updated SAP is how to report 95% CIs when the response rate is 0% or 100% in both groups being compared, since SAS PROC FREQ does not report a result in this case.