Statistical Analysis Plan

A Phase 1/2, Randomized, Placebo-Controlled, Observer-Blind Study to Assess the Safety, Tolerability, and Immunogenicity of *Streptococcus pneumoniae* Whole Cell Vaccine, Inactivated and Adsorbed to Aluminum Hydroxide (PATH-wSP) in Healthy Kenyan Young Adults (18 to 40 years) and Toddlers (12 to 21 months)

Protocol: VAC-040, IND No. 14904

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

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The Statistical Analysis Plan has been completed and reviewed and the contents are approved for use for the analysis.

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ABBREVIATIONS AND DEFINITIONS:

AC	Adult Cohort
AE	adverse event (in SAP typically refers to unsolicited events)
BLQ	below limit of quantification
BIOS	Biostatistics
CI	confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
ELISA	enzyme-linked immunosorbent assay
GMC	geometric mean concentration
GMFR	geometric mean fold rise
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IMM	Immunogenicity Population
IND	Investigational New Drug
ITT	Intent to Treat
IST	Internal Safety Team
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PATH	Program for Appropriate Technology in Health
PCV	pneumococcal conjugate vaccine
PDV	Protocol Deviation/Violation CRF
PE	physical examination
PI	Principal Investigator
PP	Per Protocol
PP_IMM	Per Protocol Immunogenicity Population
PT	Preferred Term
PVS	PATH Vaccine Solutions
Q-Q	Quantile-to-quantile
RE	reactogenicity event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	MedDRA System Organ Class
SOP	standard operating procedure
SPWCA	*Streptococcus pneumoniae* Whole Cell Vaccine
SS	Safety Analysis Set

TC	Toddler Cohort
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

REVISION HISTORY

Document Version	Changes Made	Document Date
Version 0.1	First Draft based on Final protocol VAC-040 IND No. 14904, dated 25APR2016, and final CRF, dated 17JUN2016.	27SEP2016
Version 0.2	2nd draft	02DEC2016
Version 0.3	3rd draft based on internal review comments	13FEB2017
Version 0.4	4th draft for sponsor to review	15FEB2017
Version 0.5	5th draft	01MAR2017
Version 0.6	6th draft based on protocol amendment	03NOV2017
Version 0.7	7th draft based on sponsor's comments	29NOV2017
Version 0.8	8th draft for final review	05JAN2018
Version 1.0	Final Version (same as V0.8)	11JAN2018

1. INTRODUCTION

Each year the bacterium *Streptococcus pneumoniae* (pneumococcus) kills hundreds of thousands of children before their fifth birthday, mostly in low-resource areas of the world. Parenteral immunization with killed whole cell bacteria is one of the oldest and most successful approaches to vaccine-induced protection against several bacterial infections. PATH Vaccine Solutions (PVS) is developing a whole cell candidate vaccine made from unencapsulated pneumococcal cells called *Streptococcus pneumoniae* Whole Cell Vaccine (SPWCV) inactivated and adsorbed to aluminum hydroxide adjuvant, or PATH-wSP. PATH-wSP has been tested in Phase 1/2 studies in healthy US adults (VAC-002), and in healthy Kenyan adults and toddlers (VAC-010). A single-vial formulation of PATH-wSP, an adsorbed suspension of SPWCV and Alum, has now been manufactured by PT Bio Farma, Indonesia. The purpose of this study (VAC-040) is to assess the safety and tolerability of this new formulation.

This statistical analysis plan (SAP) describes the statistical analyses to be performed for the study described in Protocol VAC-040 IND No. 14904, dated NOV2017 and titled:

A Phase 1/2, Randomized, Placebo-Controlled, Observer-Blind Study to Assess the Safety, Tolerability, and Immunogenicity of Streptococcus pneumoniae Whole Cell Vaccine, Inactivated and Adsorbed to Aluminum Hydroxide (PATH-wSP) in Healthy Kenyan Young Adults (18 to 40 years) and Toddlers (12 to 21 months)

The purpose of this SAP is to outline the planned analyses of safety and immunogenicity data to be performed to support the completion of the Clinical Study Report (CSR) for protocol VAC-040 INC No. 14904. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. The statistical plan for interim analysis for the Data and Safety Monitoring Board (DSMB) will be described in a separate document.

The reader of this SAP is encouraged to also read the clinical protocol and annotated case report forms (CRFs) for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- To evaluate the safety and tolerability of 2 dose levels (0.6 mg and 1 mg) of PATH-wSP vaccine, administered in a 2-series schedule 4 weeks apart, in healthy adults.

- To evaluate the safety and tolerability of 2 dose levels (0.6 mg and 1 mg) of PATH-wSP vaccine, administered in a 2-series schedule 8 weeks apart, in healthy toddlers when co-administered with a booster dose of licensed pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, *Haemophilus influenzae* type b, and hepatitis B combined vaccine) at the second vaccination.

2.1.2. Secondary Objective

- To assess immunogenicity of PATH-wSP vaccine when given as a 2-vaccination series to adults and toddlers.

2.1.3. Exploratory objectives

- To evaluate the potential for sera from PATH-wSP-immunized subjects to afford passive protection in an animal challenge model (subset of subjects).
- To identify novel antibody targets for future vaccine candidates using PBMCs (i.e. plasmablasts) stimulated *in vitro* (adults only). [1]

2.2. Study Endpoints

2.2.1. Safety and Tolerability Endpoints

The following safety and reactogenicity endpoints will be evaluated to address the primary objectives of the study when 2 doses of PATH-wSP vaccine are given alone in healthy young adults or given alone at the first vaccination or concomitantly with pentavalent booster at the second vaccination visit in healthy toddlers:

- Occurrence and severity of solicited local and systemic AEs (reactogenicity) and clinical laboratory abnormalities through one week post vaccination.
- Occurrence, severity, and relatedness to vaccination of unsolicited AE and SAEs through 4 weeks (in adults) or 8 weeks (in toddlers) after each study vaccination and from Day 0 (1st vaccination) through the last study contact.

2.2.2. Secondary Endpoints

The Immunoglobulin G (IgG) response to pneumococcal-specific proteins (Ply and PspA Fam 1)

[1] This objective will be evaluated via scientific and clinical review of the analysis package as a whole; no specific analysis is conducted. Thus, it is not addressed further in this SAP.

measured by ELISA, and the IgG response to nine pre-selected pneumococcal proteins measured on the MSD platform, will be evaluated based on the following analyses:

- Geometric mean concentration (GMC) and geometric mean fold rise (GMFR) (from baseline) 4 weeks after the second vaccination.
- Percentage of subjects with IgG concentration of a predefined threshold level (responders), measured 4 weeks after the second vaccination.

2.2.3. Exploratory Endpoints

- Assessment of protection of mice against IV *S. pneumoniae* challenge after passive transfer of serum obtained from a subset of subjects pre-vaccination and 4 weeks post second vaccination.

3. STUDY DESIGN

3.1. General design and plan

This Phase 1/2, randomized, placebo-controlled, observer-blind trial is designed to sequentially evaluate PATH-wSP at two escalating doses (0.6 mg and 1 mg) in both adults and toddlers. The study population will consist of healthy Kenyan adults (18-40 years old) and toddlers (12-21 months old) residing in the vicinity of the study site, who have provided consent for participation—or, in the case of toddlers, whose parents or legal guardians have provided consent—after being fully informed about the study.
The following 2 adult and 2 toddler cohorts will be sequentially evaluated in this study:

Adult Cohorts

In each adult cohort, approximately 24 eligible healthy adult Kenyan subjects (18-40 years old inclusive) will be randomized in a 1:1 ratio to receive two doses of either PATH-wSP (at the 0.6 mg or 1 mg dose level for Cohort 1 and 2 respectively) or saline placebo at an interval of 28 (+7) days between injections.

- Cohort 1: Two 0.6 mg doses of PATH-wSP (12 subjects) **or** saline (12 subjects) with a 28-day interval between doses.
- Cohort 2: Two 1 mg doses of PATH-wSP (12 subjects) **or** saline (12 subjects) with a 28-day interval between doses.

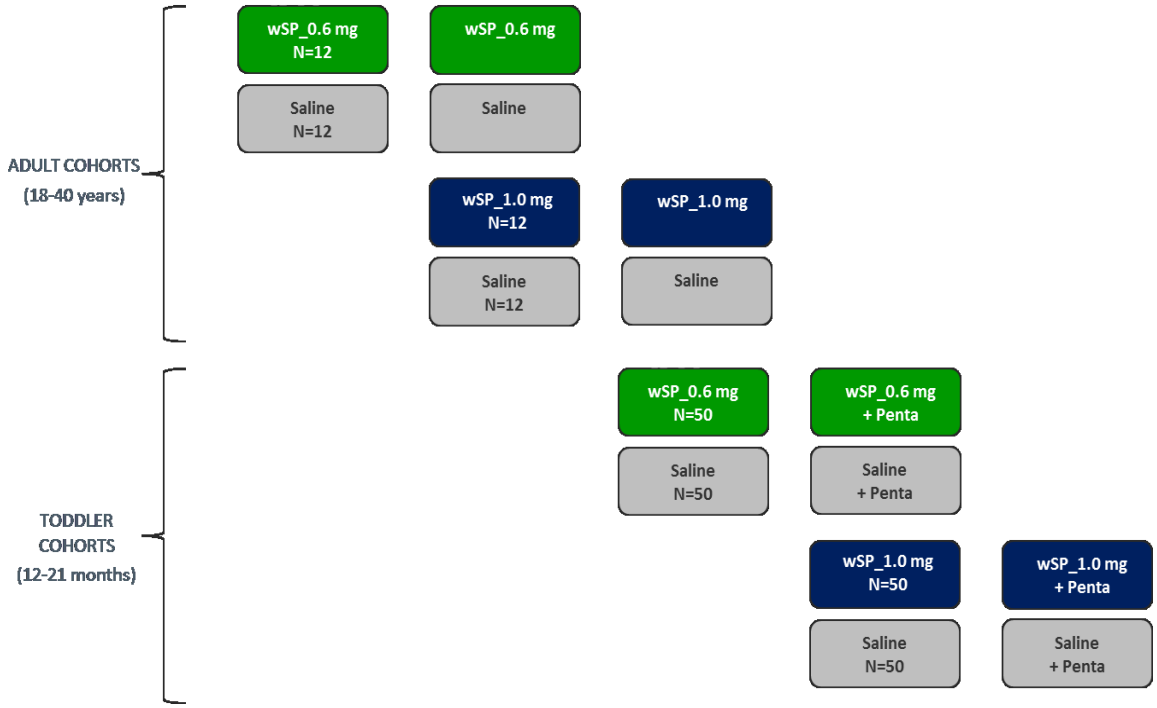
Toddler Cohorts

In each toddler cohort, approximately 100 eligible healthy Kenyan toddlers (12-21 months old inclusive) will be randomized in a 1:1 ratio to receive two doses of either PATH-wSP (at the 0.6 mg or 1 mg dose level for Cohort 1 and 2 respectively) or saline placebo at an interval of 56 (+7) days between injections.

Cohort 1: Two 0.6 mg doses of PATH-wSP (50 subjects) **or** saline (50 subjects) with a 56-day interval between doses, and pentavalent vaccine co-administered with the second dose.

Cohort 2: Two 1 mg doses of PATH-wSP (50 subjects) **or** saline (50 subjects) with a 56-day interval between doses, and pentavalent vaccine co-administered with the second dose.

Figure 1: Study Cohorts



All cohorts will be enrolled sequentially; each subsequent cohort will only be triggered after a favorable review of the post Dose 1 safety and reactogenicity data of the previous cohort by the Internal Safety Team (IST) (Adult Cohort 2, Toddler Cohort 1) or the Data Safety Monitoring Board (DSMB) (Toddler Cohort 2).

3.2. Visit Schedule and Visit Windows

Each adult subject will undergo a total of 6 scheduled visits (V), including at least one screening visit (V0) no more than 28 days prior to randomization and first vaccination (V1, Day 0); two vaccination visits (V1 and V3) scheduled 28 (+7) days apart; two safety visits (V2 and V4) occurring 7 (+3) days post vaccination visits; and a final visit (V5) occurring 28 (+14) days after the final vaccination.

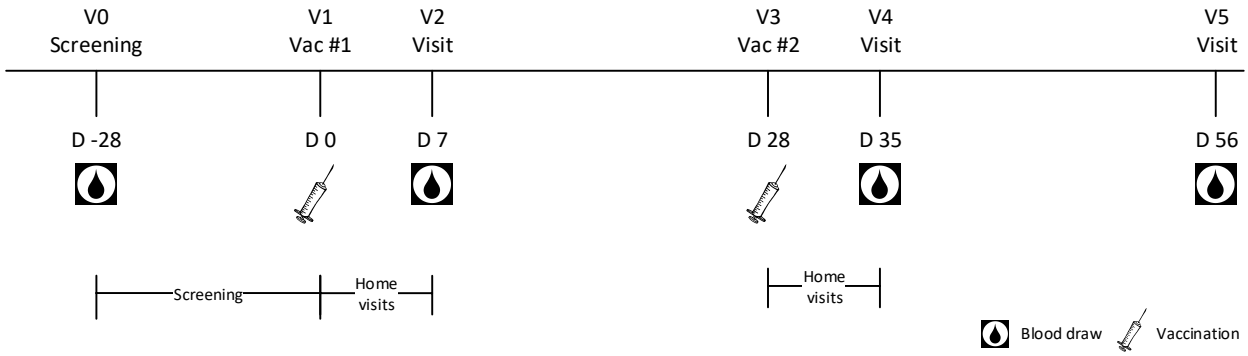
Each toddler subject will undergo a total of 8 scheduled visits, including at least one screening visit no more than 28 days prior to vaccination (V0), two vaccination visits (V1 and V4, scheduled 56 days apart), two safety visits at 7 and 28 days after the first vaccination (V2 and V3, respectively) and three safety visits at 7, 28 and 56 days after the second dose (V5, V6 and V7, respectively).

Toddlers will receive two vaccinations (wSP co-administered with pentavalent vaccine) at the second vaccination visit (V4), whereas adults will only receive one (see Figures 2 and 3).

Daily reactogenicity assessments during 6 calendar days post vaccination will be completed in all subjects by fieldworkers using a standard home visit diary and solicited reactogenicity will also be assessed at a scheduled clinic visit at Day 7 post each vaccination.

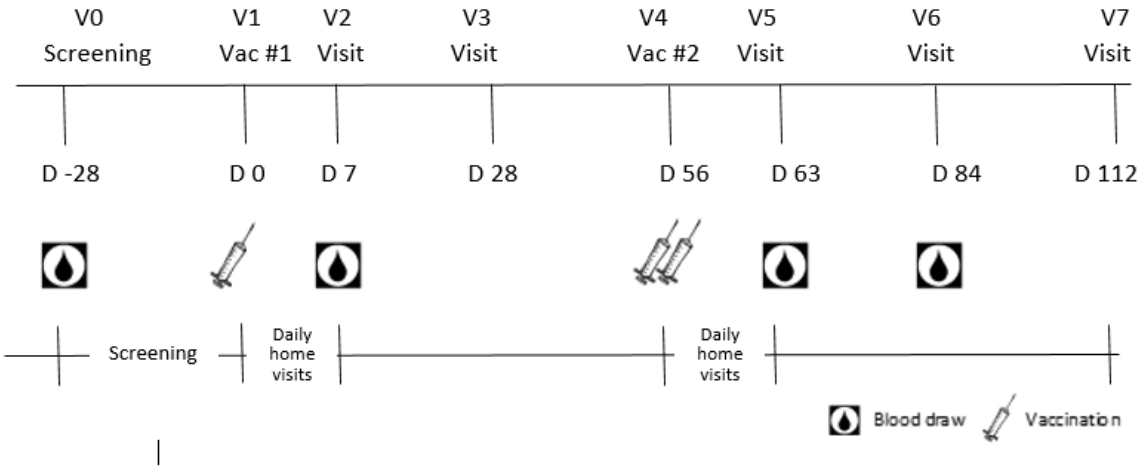
For all subjects, blood draws for safety laboratory tests and/or PATH-wSP-induced immune responses will be performed at screening (baseline safety and immunogenicity), 7 days after each study vaccination (safety only) and 28 days after the second vaccination (immunogenicity only).

Figure 2. Study Schematic for Adult Cohorts



Abbreviations: D = day; V = visit
Notes: Screening must occur not more than 28 days before the Day 0 (V1) vaccination visit. Home visits by fieldworkers occur on Days 1 through 6 and Days 29 to 34 following vaccinations.

Figure 3. Study Schematic for Toddler Cohorts



Abbreviations: D = day; V = visit
Notes: Screening must occur not more than 28 days before the Day 0 (V1) vaccination visit. Home visits by fieldworkers occur on Days 1 through 6 and Days 57 to 62 following vaccinations.

The following scheduled visits[2] are included in the study with the following windows for study subjects.

Table 1. Study Visit Windows[3]

Visit	Description	Relative Day	
		Min	Max
Adult Cohorts			
V0 (Screening)	Screening Period	-28	-1
V1 (Day 0)	1st Vaccination Visit: Day 0	0	0
V2 (Day 7)	1st Safety Visit: Day 7	7	10
V3 (Day 28)	2nd Vaccination Visit: Day 28	28	35
V4 (Day 35)	2nd Safety Visit: Day 35	35	45
V5 (Day 56)	Final Visit: Day 56	56	77
Toddler Cohorts			
V0 (Screening)	Screening Period	-28	0

[2] See protocol for a description of test schedule at each study visit.

[3] Minimum day is relative to randomization/1st vaccination. Maximum day is relative to most recent vaccination. For example, the 2nd vaccination for adults may take place from Day 28 through Day 35. If the 2nd vaccination occurred on Day 35, the 7-day post vaccination 2 safety visit ("2nd safety visit: Day 35") would take place on Day 35+7=Day 42 with 3-day window allowing up to Day 45 and the 5th safety visit window would be Day 35 + 28 + 14 = 77.

V1 (Day 0)	1st Vaccination Visit: Day 0	0	0
V2 (Day 7)	1st Safety Visit: Day 7	7	10
V3 (Day 28)	2nd Safety Visit: Day 28	28	35
V4 (Day 56)	2nd Vaccination Visit: Day 56	56	63
V5 (Day 63)	3rd Safety Visit: Day 63	63	73
V6 (Day 84)	4th Safety Visit: Day 84	84	105
V7 (Day 112)	5th Safety Visit: Day 112	112	133

3.3. Sample size justification

Sample sizes were selected to provide adequate data to assess whether the safety and immunogenicity of PATH-wSP measured in adults and toddlers in this trial support advancing into an infant population. All vaccinated subjects are expected to provide data for safety analyses. It is estimated that with a 10% attrition rate approximately 90% of subjects will be evaluable for immunogenicity analyses.

Safety: A sample size of 12 subjects per treatment group for the adult cohorts will provide a 90% chance of observing at least one occurrence of an AE that has an approximately 17.5% rate of occurrence. The 50 subjects per treatment group for toddler cohorts will provide 90% chance of observing at least one occurrence of an AE that has an approximately 4.5% rate of occurrence. If no AEs/SAEs are observed among 12 and 50 subjects receiving PATH-wSP, the upper limits of exact 2-sided 95% confidence intervals for the rate of AE/SAE occurrence will be 26.5% and 7.1%, respectively.

Immunogenicity: In the first Phase 1 study in adults (VAC-002), the standard deviations (SD's) of log10 of the GMFR for ELISA PspA and Ply concentrations were estimated to be ≤ 0.55. Assuming SD = 0.55 for each adult cohort, 11 evaluable subjects in each study group will provide approximately 68.5% power to detect a 4.0-fold increase in GMFR for PATH-wSP recipients compared to recipients of the saline control based on a two-sided, 0.05 significance level test. For the toddler cohorts, 45 evaluable subjects per study group will provide > 99% power to detect a 4.0-fold increase in PATH-wSP recipients. Power for analysis of GMFR was estimated based on a 2-sample t-test and a 1-sided 0.025 significance level and calculated using PASS 12 (Number Cruncher Statistical Systems, Kaysville, Utah). Thus it is planned to enrol approximately 48 healthy adults and 200 healthy toddlers.

3.4. Randomization and blinding

After a subject meets all study eligibility requirements at screening and confirmed again at day of randomization, the subject will be randomized to 1 of 2 treatment groups (in each cohort) using a 1:1 randomization ratio. Randomization will occur at V1, the day of vaccination.

Except as noted below, the PI, clinic staff, the Sponsor, and the contract research organization (CRO) will remain blinded to subject treatment assignment until scheduled end-of-trial unblinding, unless unblinding is warranted due to subject safety concerns or for related SAEs. Site personnel responsible for preparation and administration of study vaccine, CRO personnel who are monitoring procedures related to vaccine

preparation and administration, and the independent statistician providing unblinded statistical reports to the DSMB will remain unblinded and will not participate in other activities of the clinical trial. All monitoring reports from the unblinded monitor will be written such that the blind will be maintained during trial conduct.

Details on interim analysis blinding/unblinding will be described in a separate SAP for the DSMB.

3.5. Blinded data review

Prior to scheduled study unblinding, the data will be reviewed by the PATH Study Director or designee for analysis decisions. The lead statistician will be responsible for developing specific listings for this review and will document the PATH Study Director's decisions prior to unblinding. These reviews will include (but not necessarily be restricted to) protocol violations for inclusion/exclusion of subjects and/or data points, particularly with respect to the PP_IMM Population (see section 4.2); distribution of time points of data collection that are out-of-window according to protocol for possible reclassification (e.g. allowable windows for analysis); and incorrect allocation of treatment at either Vaccination 1 and/or Vaccination 2. Protocol violations will include those documented on a PDV CRF as well as selected deviations that can be detected directly from the data base. Blinded data review may also include clinical evaluation of safety data for reasonableness or to issue clinical queries to the site if needed. Any decisions affecting analysis will be described in the clinical study report.

4. STATISTICAL ANALYSIS

4.1. General Issues

A final database lock for the 2 age groups – adults and toddlers– is planned for this study. No separate database lock is planned for each cohort. However, a soft database lock might be conducted after all data collected at the clinical site are finalized and data discrepancies are resolved. This data base lock will serve as the basis for all final analyses except those using external lab data sets. Scheduled study unblinding will be based on completion of this CRF data base. Following receipt of immunogenicity, mouse challenge, and any other data received from external labs, a final database lock comprising both CRF and external data sets will be conducted.

All tabular summaries will be presented by treatment group. For both age groups, all summaries will be provided for each treatment group and its respective control group. Treatment comparisons will be made within age cohorts only. Adult and toddler data will not be reported together. Thus, except for differences in objectives or study design across cohorts or otherwise noted below, all analyses described below are produced separately by age group.

General descriptive statistics for numeric variables include the n (number of observed values), the mean, standard deviation, median, minimum, and maximum values. For categorical variables, the number and percentage of subjects with a specific level of the variable will be presented. The percentage will be

calculated using the subjects with a reported value. Descriptive statistics will be presented by treatment group and by visit/time point, as relevant.

General reporting conventions will include the following:

- The baseline value for any measurement is the last value obtained prior to receiving 1st vaccination on Day 0 or, for selected measurements (e.g. vital signs and physical examinations), immediately prior to 2nd vaccination on Day 56 for Toddlers or Day 28 for Adults. To avoid confusion, measurements obtained immediately before Vaccination 2, which serve as a baseline for post-Vaccination 2 safety endpoints (i.e. vital signs and physical examination), will be identified as "Pre-vac #2" or similar terminology.
- All nominal time points will be used for analysis; actual assessment times will not be used to reclassify the time point at which a measure was taken unless reclassification was decided during blinded data review.
- Study day: Study day will be calculated relative to the date of 1st vaccination (Day 0) as: Date of event – Date of 1st vaccination administration. This formula will be used when calculating days to a specific event (i.e., concomitant medication and/or AE start date). A negative study day indicates an event prior to 1st vaccination.
- Other than log-transformations as described below for the immunogenicity data, no data transformations are planned.
- Unless otherwise noted, all percentages will be presented to one decimal place.
- All data listings will be sorted by Cohort, treatment group, and subject screening ID.
- Post-dose data from unscheduled visits will be excluded from the summary tables but included in the data listings.
- This study is considered to be hypothesis generating in the sense that treatment comparisons will be carried out for the purposes of identifying safety or immunogenicity concerns for future research. No formal hypothesis testing will be performed. P-values and 95% confidence intervals are intended to serve as an aid to clinical and scientific judgment. Conclusions based on inclusion or exclusion of "no-difference" values (e.g. 0 or 1, depending on the analysis) within the confidence interval should be made cautiously, in light of no adjustment for multiple comparisons and the potentially low statistical power for some analyses.
- All P-values will be assessed at two-sided 0.05 significance level and p-values will be rounded to three decimal places. Statistical significance will be declared if the p-value is less than or equal to 0.05.

All AE diagnosis will be coded with the MedDRA™ v 21.0 coding terminology. The process for medical coding is managed by FHI 360's Data Management division and will be conducted according to the FHI 360 SOP 06006 "Medical Coding of Clinical Study Data using MedDRA". The concomitant

medication/drug/treatment field text will be coded using a combination of Lexi-comp and the on-line PDR.

4.2. Analysis Sets

Except ITT, subjects will be analyzed according to the treatment they actually received. The following analysis sets will be used in the study:

- **Intent-to-Treat (ITT)**: The ITT Population includes all randomized subjects. Treatment group will be assigned according to the initial randomization, regardless of whether subjects receive any investigational product or receive an investigational product different from that to which they were randomized. Unless specified otherwise, this population will be used for summaries of subject disposition.
- **Safety Analysis Set (SS):** includes all subjects who receive any study vaccine and have post-vaccination safety data available. Treatment groups for safety analysis will be assigned according to the actual treatment received at Dose 1.
- **Immunogenicity Per-Protocol Population (PP_IMM):** includes all subjects who receive investigational product and had post-dose immunogenicity measurement(s) with no major protocol violations that are determined to potentially interfere with immune responses to the study vaccine. Treatment groups for immunogenicity analysis will be assigned according to the actual treatment received at 1st vaccination.
- **Mouse Challenge Set (MCS):** includes a subset of randomly selected subjects (N=28) for the mouse challenge (passive transfer) test. 7 subjects in each treatment group (PATH-wSP vs Saline) from both adult and toddler high-dose (1.0 mg) cohorts will be randomly selected.

The criteria for exclusion of subjects from various populations will be established based on the blinded review of protocol violations. Subjects who do not receive VAC #2, but remain in study (e.g. being followed for safety) will be excluded from immunogenicity analysis if they provided post vac #2 immunogenicity data. Screen failures will be included in subject population accounting but otherwise will not be included in the analysis.

Primary analysis populations and conditions for supportive analysis are summarized in Table 2.

Table 2. Summary of Planned Analyses, by Population

ANALYSIS	ITT[1]	SS	PP_IMM	MCS
Disposition	√	√[2]		
Baseline	√	√[3]		
Safety		√		
Immunogenicity			√	
Exploratory (mouse challenge)				√

[1] If Intent-to-Treat Population is the same as Safety Analysis Set, analyses will be identified as Safety Analysis Set
[2] Only if ≥ 10% of ITT differs from SS.
[3]Only if ≥ 10% of ITT differs from SS.

4.3. Covariates

No covariates will be utilized in any statistical analyses of treatment effects, safety, or tolerability.

4.4. Pooling of Sites

This is a single-center study; no pooling for multiple sites is required.

4.5. Multiple Comparisons

Due to the hypothesis-generating nature of this analysis no multiplicity adjustment is planned for this early phase study.

4.6. Interim Analyses

Three DSMB reviews of unblinded data in toddlers are planned for this study.

- The first safety evaluation will be organized when safety data up to 6 weeks after the first vaccination are available for subjects enrolled during the first week of recruitment into the 0.6 mg toddler cohort (e.g. first 15 subjects). DSMB will review all reported cases of suspected pneumonia and other respiratory events and make a recommendation regarding administration of the second vaccination in the 0.6 mg toddler cohort. *Note: the assessment will only be performed if at least 6 suspected pneumonia cases are reported prior to this time point.*
- The second safety assessment will be performed when safety data at approximately 6 weeks post-Dose 1 are available for all subjects in the 0.6 mg toddler cohort. All available post-Dose 2 information will also be evaluated at this stage. The DSMB will make a recommendation regarding initiation of enrollment into the 1.0 mg toddler cohort.
- The third assessment will be organized when all 0.6 mg cohort safety data through Day 7 post-vaccination #2 are available, and the DSMB will make a recommendation regarding continuation of vaccination in the 1.0 mg toddler cohort.

At each time point, the DSMB will conduct an unblinded review of the available reactogenicity and safety data to make recommendations for study continuation and design. A separate DSMB Charter will identify the membership and define the specific procedures of the committee.

4.7. Data Review Meetings

In addition to the three DSMB reviews, two blinded safety data reviews by the Internal Safety Team (IST) are planned for this study. The first blinded safety data review will be conducted when all subjects in the 0.6 mg adult cohort complete Day 7 after the first dose, and will be the basis for the IST assessing whether to initiate the 1.0 mg adult cohort. The second blinded safety data review will take place when all subjects in the 1.0 mg adult Cohort complete Day 7 after the first dose, and will be the basis for the IST assessing whether to initiate the 0.6 mg toddler cohort. These reviews are carried out in the context of the IST's routine weekly blinded safety reviews of data summaries prepared by the Data Management division.

4.8. Handling missing and incomplete data

4.8.1. 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 analyses. Per protocol, subjects who are discontinued from the study after vaccination (regardless of reason) will not be replaced, but a subject who is discontinued after randomization but prior to 1st vaccination will be replaced using a new randomization ID for the replacing subject.

Unless otherwise specified, e.g. from blinded data review, each event will be analyzed using all available data. Data are assumed to be missing at random and therefore missingness is ignorable. Except where otherwise noted (see Section 4.8.2.), missing data will not be estimated or imputed. Similarly, other than documented exclusions, subjects with missing data will be excluded only from analyses for which data are not available.

4.8.2. Imputed Data

In the event that 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 15th will be used for any calculations of relative time (e.g., UNMAY2012 will become 15MAY2012).
- If only the year is known, but the month and date are missing, June 15th of the known year will substitute for any calculations of relative time (e.g., UNUNK2011 will become 15JUN2011).
- 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).
- Other imputation rules may be required on a case-by-case basis, determined in blinded review.

Generally, no imputation will be made for missing values in safety and immunogenicity analysis, except for the following:

All immunogenicity assays reported as being below the limit of quantification ("BLQ") or below a threshold (e.g. "<.15") will be assigned a value of one-half the lower limit of quantification (LLOQ) or threshold value (e.g. .075 for the given example), using values of LLOQ or other information provided by the responsible laboratory.

4.9. Software Package

Version 9.4 or higher of the SAS ®Statistical software package will be used to provide all summaries and data listings.

5. EVALUATION OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

5.1. Subject enrolment and disposition

Disposition information will be provided overall and separately for each treatment group.

The number of subjects screened, numbers in the ITT, Safety Analysis Set, PP_IMM, and MCS, and amount of observation time (person/days) will be provided in the population flowchart ("population trees") tables.

As a measure of the quality of study conduct, the number of home visits that were missed and clinic visits missed or outside of protocol window will be summarized. Highest Visit number completed, number of subjects discontinued and reason for early discontinuation will be summarized as well.

Early discontinued subjects and the reasons for withdrawal/termination will be listed individually.

5.2. Protocol violations and unscheduled unblinding

As described above, protocol violations will be reviewed during blinded data review, and analysis decisions due to these violations, if any, will be documented prior to unblinding. Protocol deviations will be listed. Any cases of unscheduled unblinding, whether for safety reasons or inadvertently, will be described in the clinical study report.

5.3. Treatment Compliance

Treatment compliance for adults and toddlers is defined as having received both investigational vaccines. Subjects with less than full compliance, other than those who discontinued early or were lost to follow-up, will be listed.

5.4. Demographics and baseline characteristics

Demographic characteristics (including age, sex, race, ethnicity, marital status, education, and occupation), and socioeconomic status will be summarized using descriptive statistics. No statistical comparisons of differences in demographics/baseline data will be performed.

5.5. Medical History and Baseline Assessment

Medical history, contraception method, disease screening for HIV, Hepatitis B and C, and baseline height, weight, BMI (where BMI = Weight (kg)/Height $(m)^2$) will be summarized.

5.6. Concomitant medications

A summary of all concomitant medications taken during the course of the study will be listed. Drug name, dose, route, frequency, indication, and start and end dates will be included.

5.7. Pregnancies

The protocol requires women of child-bearing potential to use an adequate method of contraception prior to and during participation in the study. Pregnancies are therefore not anticipated. Data from any pregnancies reported on the Pregnancy Outcome CRF will be listed.

5.8. Evaluation of safety

All analysis of safety will be performed using the Safety Analysis Set. Results of all safety assessments, including AE monitoring, post vaccination reactogenicity events (RE[4]) assessment, clinical laboratory evaluations, vital sign determinations, and physical examinations, will be summarized with descriptive statistics by treatment group and overall, and/or presented in data listings.

Generally, safety evaluations will be descriptive in nature, and observed differences will be evaluated for medical relevance. For both age groups, all of the safety tabular summaries will be provided for each treatment group and respective control. Safety data will be summarized separately by baseline and scheduled measurement time points and when relevant by vaccination number (Vaccination 1 and Vaccination 2). 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.

5.8.1. Adverse events

The onset date of an adverse event will be compared to the date of 1st vaccination (Day 0) to determine if the adverse event is treatment emergent or not. Unsolicited adverse events are considered treatment

[4] For clarity, solicited adverse events will be referred to in this SAP as "reactogenicity events" to distinguish them from unsolicited AEs which are analyzed differently.

emergent (TEAEs) if onset occurs on or after first vaccination. Only treatment-emergent unsolicited AEs will be included in the analysis. Adverse events in the data base for subjects in the Safety Analysis Set that are not TEAE will be listed.

TEAEs will be summarized and grouped by MedDRA System Organ Class (SOC) and specific adverse event type (Preferred Term [PT]) using MedDRA™ v 21.0 or higher coding terminology. Results will be displayed in order of decreasing frequency, both across SOC and within each SOC term. Listings will include the AE verbatim description.

TEAE will be summarized in a table that presents the number and percent of subjects with any TEAE, with any serious TEAE, with any vaccine-related TEAE, and with any TEAE leading to discontinuation by treatment group. It will also include the total number of adverse events in each of these categories. An overview summary of the number and percentage of subjects with any AE, and the total number of AE episodes (defined as the number of AE records in the data base with the same PT) will be provided by treatment group. The denominator for percentages will be the number of subjects in the treatment group with an opportunity to report an AE if s/he had one. (Since AEs are assessed at the one-hour post-vaccination assessment, it is anticipated that all subjects in the Safety Analysis Set will contribute to the AE analysis.)

Listings of all adverse events (including non-treatment-emergent events) will be provided. This listing will be presented by Cohort and treatment group and will include subject identifier, adverse event (verbatim AE description, PT and SOC), duration, relatedness to product, seriousness, severity, outcome, and action taken with respect to the investigational product. In addition to this full listing of all TEAEs, a separate listing will be created isolated to TEAEs of special interest, specifically: those that were serious (SAE), severe (Grade 3 or 4), considered related to vaccine, or led to product discontinuation. A summary table of these selected TEAEs may be produced if the number of events is sufficient that a summary table would be useful.

Suspected pneumonia cases will be listed. The listing will include days from 1st and, as relevant, 2nd vaccination, laboratory assessment, chest radiography outcome, respiratory symptoms, and final clinical diagnosis.

5.8.2. Reactogenicity Events (REs)

REs will be ssessed separately for each vaccination, at 1 hour (h) post vaccination and then daily through Day 7. If more than one measurement is obtained on a given day (e.g. from unscheduled clinic visits for RE follow-up) the maximum level observed that day will be used in analysis. Note that by protocol, a RE with onset on or after Day 8 is considered to be an unsolicited AE and is reported on the Adverse Event (AE) CRF.

Reactogenicity events will be described separately each day of the 7-day post vaccination interval as well as overall (e.g. highest severity of each reaction type experienced during that 7-day interval). Reactogenicity results will be summarized separately for (a) all reactions, and (b) systemic reactions considered vaccine related, per the investigator's assessment.

To characterize subject-level reactogenicity, the highest severity of reactogenicity will be determined for each subject and type of solicited reaction within 7 days of vaccination, separately for each vaccination. Subjects' most severe reaction will be summarized separately for (a) all reactions and (b) vaccine-related systemic reactions. The determination of highest severity will be based on observed data; thus, in accordance with the principle of ignorable missingness (see section 4.8.1) missing reactogenicity assessments, if any, will be assumed to not be consistently higher or lower in severity than those observed. If the proportion of missing assessments of a given reactogenicity category exceeds 20% of the expected data for subjects still in the study at the time the assessments would have been made, a sensitivity analysis, e.g. assuming the missing assessment is higher in severity than those observed, may be conducted.

For each type of reaction, 2-sided 90% exact confidence intervals (CIs) around treatment group proportions will also be provided for summary groupings based on the following comparisons of severity level; that is, proportions (a) with any reactogenicity event (Grade 1+ vs. Grade 0); (b) those with moderate or severe events (Grade 2+ vs. Grade 0-1); and (c) those with severe events (Grade 3+ vs. Grade 0-2), per protocol categories. These comparisons will be based on subjects' highest level of reaction within 7 days post vaccination separately for the 2 vaccinations. In addition, *P*-values for the proportion differences between treatment groups on the overall distribution of reactogenicity grade will be computed using the unconditional exact method proposed by Newcombe (1998). Some modification of the approach (for example, pooling categories or statistically comparing treatment groups across the distribution of grades 0 to 3+) may be implemented by the lead statistician, with input as needed from the Study Director, if doing so will lead to more interpretable results.

Any subjects with at least one Grade 3+ reaction post vaccination will be listed. The list will include all observations in the 7-day interval of that reactogenicity reaction for that subject for clinical context.

5.8.3. Clinical laboratory evaluation

Scheduled hematology, blood chemistry, and organ function tests will be obtained at baseline and 7-day post vaccination visits (Visit 2 and Visit 4 in adults or Visit 5 in toddlers). The results of scheduled tests will be summarized by descriptive statistics of the actual measurements as well as frequencies and proportions of abnormal measurements based on protocol-defined toxicity grades (Appendix II & III).

For both vaccinations, summary descriptive statistics on change from baseline will also be provided. Clinical evaluation of change from baseline will take into account the possibility of regression-to-the-

mean artefact.[5] Test results from post-randomization unscheduled visits will be included in listings, and tests performed as a retest will be identified as such in the listing.

A listing will be provided for subjects who experienced a markedly abnormal post-vaccination lab value, defined as a value meeting the criteria of (a) toxicity grade 3 or 4 or (b) toxicity grade 1 or 2 but considered clinically significant by the site clinician. This listing will select subjects/analytes where at least one markedly abnormal value was observed, then list all observed values of the analyte for that subject (including those obtained at unscheduled visits) for clinical context.

5.8.4. Vital signs

Temperature (fever) is considered a systemic reactogenicity measurement and will be reported on reactogenicity tables. Respiration rate, pulse rate and (for adults) systolic/diastolic blood pressure will be summarized via standard descriptive statistics (mean, standard deviation, etc.) as well as by protocol severity (toxicity) grades for each treatment group and measurement time point pre-vaccination, at 1H and on Day 7 and Day 28, separately for Vaccination 1 and Vaccination 2. Data from subjects with abnormal vital signs will be listed.

5.8.5. Physical examination

The results of physical examinations at scheduled visits will be summarized by body system and visit/time-point. Data from subjects with any abnormality detected after Vaccination 1 will be listed. For context the list will include examination findings at all visits for that subject and body system.

6. EVALUATION OF IMMUNOGENICITY

The immunogenicity analyses will be conducted on the PP_IMM Population. Immunogenicity assessment is pre-specified as being secondary and exploratory. Reverse Cumulative Distribution (RCD) curves will be generated for the IgG responses to the pneumococcal-specific proteins (Ply and PspA Fam 1) measured by ELISA, and the IgG responses to nine pre-selected pneumococcal proteins measured on the MSD platform, by visit (baseline, post vac #2) and treatment group.

[5] By protocol, randomized subjects are pre-selected to have acceptable clinical lab results. Thus, changes from normal baseline to more adverse result post-vaccination can be observed but the reverse (adverse baseline to normal post-vaccination results) cannot.

6.1. Analysis of primary immunogenicity endpoints

No immunogenicity analysis is pre-specified as being primary.

6.2. Analysis of secondary immunogenicity endpoints

Immune response will be evaluated for each assay and protein component using (a) geometric mean concentration (GMC) and Geometric Mean Fold Rise (from baseline) 4 weeks after the second vaccination, and (b) Percentage of subjects with IgG concentration of a predefined threshold level (responders), measured 4 weeks after the second vaccination.

6.2.1. GMC/GMFR

The IgG immune response will be summarized by treatment group and by visit with corresponding 2-sided 95% CIs based on the t-distribution to provide population estimates.

The geometric mean will be calculated as:

Geometric mean = antilog (mean [$\log_e$ x])

The GMFR will be calculated as the geometric mean of the ratios of post-vaccination to baseline measure:

$$\text{GMFR} = \text{antilog}\{\text{mean}[\log_e (\frac{\text{x at 4 weeks after 2nd vaccination}}{\text{x at baseline}})]\}$$

Where x is the assay result and e is the natural logarithm.

Treatment group differences will be based on the ratio of treatment group GMFRs (active PATH-wSP vs. saline) assuming log-normal distribution. The 95% CI around the mean ratio will be calculated on the log scale using t-distribution for the mean difference between the 2 treatment groups, then exponentiated to obtain the treatment group GMFR ratio and corresponding CI in the original scale. The lead statistician will evaluate the appropriateness of this assumption to the given data via visual inspection of data distributions, for example, Q-Q plots or evaluating coverage inconsistency.

If the assumption of log-normality is not supported, the following method will be used: Point estimates (i.e., group-specific GMCs, GMFRs, and treatment-group ratios) of these endpoints will be calculated directly from the data. Confidence intervals around these point estimates will be calculated using the bias-corrected and accelerated (BCa) method (Efron and Tibshairani [1993]; Barker [2005]), which addresses discrepancies (bias) between point estimates obtained from bootstrap samples and the original

calculation from the raw data as well as possible variation in the standard error as a function of the value of the estimate. Each bootstrap estimate will be based on 10,000 randomly selected replicates. The use of an alternative method, if any, will be documented in the clinical study report.

6.2.2. Seroresponse/seroconversion

Seroresponse/seroconversion for each measure is defined as ≥ n-fold increase from baseline for presence of pneumococcal-specific proteins at 4 weeks after second vaccination. The threshold for seroresponse for each measure will be predefined and documented prior to scheduled unblinding.

The frequency, proportion and 2-sided exact (Clopper-Pearson) 95% CIs around the proportion of sero-responders will be computed for each treatment group.

Treatment group differences will be estimated by the difference in proportion of sero-responders, with a 2-sided exact 95% confidence interval around the difference calculated using the unconditional exact method of Newcombe (1998). Although inference regarding seroresponse is not of primary concern in this study, a 2-sided 95% CI that excludes 0 would be indicative of statistically significant difference.

6.3. Analysis of exploratory immunogenicity endpoint

Mouse challenge is an exploratory analysis related to efficacy.

6.3.1. Mouse Challenge

The mouse challenge test is conducted to evaluate the effect of passive transfer of protection against *S. pneumoniae* for mice who have been inoculated with serum from subjects who receive PATH-wSP. Mouse challenge testing will be done on a subset of subjects (7 in each treatment group from each high dose cohort) selected by PATH.

For each subject and time point (i.e. pre-vaccination or post-vaccination), a group of mice[6] will be inoculated with a subject's serum, then given IV administration of *S. pneumoniae* and followed for 337 hours. Protection will be operationally defined by (a) time to moribund state as defined by laboratory test protocol and (b) overall mortality rates.

All analysis will be conducted on a per-subject basis; that is, survival among the mice receiving a subject's pre-vaccination serum will be compared to that among the mice receiving that subject's post-vaccination serum.

[6] Number of mice will be pre-specified.

For descriptive purposes, per-subject/time point measurements will be summarized for the inoculated mice as (a) median time to moribund state, censoring time at 337 hours (337h) and (b) proportion alive at 337h. Kaplan-Meier (KM) curves will be graphed for time to moribund state for pre- vs. post vaccination mouse groups, separately by subject.
KM curves will be statistically compared using the log-rank test, and the proportions of mice surviving to 337h pre- vs. post vaccination will be statistically compared separately by subject using Fisher's Exact Probability Test. These methods assume that any correlation between pre- and post-vaccination data from the same subject may be ignored.

7. TABLES AND LISTINGS

7.1. Programs and Tables Quality Control

The statistician-programmer of the tables, listings, and figures will carefully review the programs and will verify that no error message is highlighted in the "LOG" file. Moreover, a second statistician-programmer will verify the internal consistency of each table, listing, and figure by checking the results using different SAS programs. Prior to delivery of any statistical output to the Sponsor, the lead statistician will review the statistical package as a whole for internal inconsistencies or any items where clarifying notes will be helpful to the reviewer. The package will then be thoroughly reviewed by an independent senior statistician before it is distributed.

7.2. Programming Conventions

Reporting conventions will adhere, when possible, to the International Conference on Harmonization (ICH) Guidance document E3, "Structure and Content of Clinical Study Reports". Modifications may be made during stat report production. Some specific conventions are outlined below:

1. All tables and listings will be in landscape format unless otherwise requested.
2. Each table /figure/listing will have three titles:

- The 1st title will have the study/report name;
- The 2nd title will be the table/figure/listing number with the description of the table/figure/listing;
- The 3nd title will be a description of the study population presented in the table/figure/listing.

3. All SAS output for tables and listings will be distributed in PDF files, though RTF files will be made available for inclusion into the Clinical Study Report (CSR) or Sponsor presentations.

7.3. Lists of tables and listings

Table Number	Title
14.1-1	POPULATION FLOW CHART
14.1-2	STUDY DISPOSITION / ITT POPULATION
14.1-3	STUDY COMPLETION STATUS / SAFETY ANALYSIS SET
14.1-4.1	DEMOGRAPHIC AND SOCIOECONOMIC STATUS/ SAFETY ANALYSIS SET
14.1-4.2	BASELINE ASSESSMENT AND MEDICAL HISTORY / SAFETY ANALYSIS SET
14.1-4.3	BASELINE CLINICAL LABORATORY VALUES / SAFETY ANALYSIS SET
14.3.1-1	Overall SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS / SAFETY ANALYSIS SET
14.3.1-2	TREATMENT-EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM / SAFETY ANALYSIS SET
14.3.2-1.1	POST VACCINATION REACTOGENICITY ASSESSMENT THROUGH DAY 7, BY DAY AND VACCINATION NUMBER: ALL REACTIONS / SAFETY ANALYSIS SET/0.6 MG PATH-WSP
14.3.2-1.2	POST VACCINATION REACTOGENICITY ASSESSMENT THROUGH DAY 7, BY DAY AND VACCINATION NUMBER: ALL REACTIONS / SAFETY ANALYSIS SET/1.0 MG PATH-WSP
14.3.2-1.3	POST VACCINATION REACTOGENICITY ASSESSMENT THROUGH DAY 7, BY DAY AND VACCINATION NUMBER: ALL REACTIONS / SAFETY ANALYSIS SET/SALINE
14.3.2-2.1	POST VACCINATION REACTOGENICITY ASSESSMENT THROUGH DAY 7, BY DAY AND VACCINATION NUMBER: VACCINE-RELATED SYSTEMIC REACTIONS / SAFETY ANALYSIS SET/0.6 MG PATH-WSP
14.3.2-2.2	POST VACCINATION REACTOGENICITY ASSESSMENT THROUGH DAY 7, BY DAY AND VACCINATION NUMBER: VACCINE-RELATED SYSTEMIC REACTIONS / SAFETY ANALYSIS SET/1.0 MG PATH-WSP
14.3.2-2.3	POST VACCINATION REACTOGENICITY ASSESSMENT THROUGH DAY 7, BY DAY AND VACCINATION NUMBER: VACCINE-RELATED SYSTEMIC REACTIONS / SAFETY ANALYSIS SET/ SALINE
14.3.2-3.1	SUBJECTS' HIGHEST GRADE OF REACTOGENICITY WITHIN 7 DAYS POST VACCINATION, BY VACCINATION NUMBER /ALL REACTIONS / SAFETY ANALYSIS SET
14.3.2-3.2	PROPORTIONS AND 90% CONFIDENCE INTERVAL FOR THE HIGHEST GRADE OF REACTOGENICITY POST VACCINATION, BY VACCINATION NUMBER /ALL REACTIONS / SAFETY ANALYSIS SET

14.3.2-3.3	SUBJECTS' HIGHEST GRADE OF REACTOGENICITY POST VACCINATION / VACCINE-RELATED SYSTEMIC REACTIONS ONLY, BY VACCINATION NUMBER / SAFETY ANALYSIS SET
14.3.2-3.4	PROPORTIONS AND 90% CONFIDENCE INTERVAL FOR THE HIGHEST GRADE OF REACTOGENICITY POST VACCINATION / VACCINE-RELATED SYSTEMIC REACTIONS ONLY, BY VACCINATION NUMBER / SAFETY ANALYSIS SET
14.3.3-1	VITAL SIGNS BY VISIT / SAFETY ANALYSIS SET/0.6 MG PATH-WSP
14.3.3-2	VITAL SIGNS BY VISIT / SAFETY ANALYSIS SET/1.0 MG PATH-WSP
14.3.3-3	VITAL SIGNS BY VISIT / SAFETY ANALYSIS SET/SALINE
14.3.4	SUMMARY OF CLINICAL LABORATORY VALUES / SAFETY ANALYSIS SET
14.3.5-1	PHYSICAL EXAMINATION BY VISIT / SAFETY ANALYSIS SET/0.6 MG PATH-WSP
14.3.5-2	PHYSICAL EXAMINATION BY VISIT / SAFETY ANALYSIS SET/1.0 MG PATH-WSP
14.3.5-3	PHYSICAL EXAMINATION BY VISIT / SAFETY ANALYSIS SET/ SALINE
14.4.1-1	IMMUNOGLOBULIN RESPONSE TO PNEUMOCOCCAL PROTEINS: GMC/ PP_IMM POPULATION
14.4.1-2	IMMUNOGLOBULIN RESPONSE TO PNEUMOCOCCAL PROTEINS: GMFR AT 28 DAYS AFTER THE 2ND VACCINATION / PP_IMM POPULATION
14.4.2	IMMUNOGLOBULIN RESPONSE TO PNEUMOCOCCAL PROTEINS: SERO-RESPONDER: FOLD-RISE>=DEFINED THRESHOLD AT 28 DAYS AFTER THE 2ND VACCINATION / PP_IMM POPULATION
14.4.3-1	MOUSE CHALLENGE TEST MEDIAN SURIVIVAL TIME AND LOG-RANK TEST OF DIFFERENCE IN SURVIVAL PRE- VS. POST VACCINATION/ MOUSE CHALLENGE SET
14.4.4-2	MOUSE CHALLENGE TEST, SURIVIVAL STATUS THROUGH 337 HOURS/ MOUSE CHALLENGE SET

Listing Number	Title
16.2.1	PATIENT DISCONTINUATIONS / ALL SUBJECTS
16.2.2	PROTOCOL DEVIATIONS / SAFETY ANALYSIS SET
16.2.4-1	DEMOGRAPHICS / SAFETY ANALYSIS SET
16.2.4-2	ABNORMAL MEDICAL HISTORY / SAFETY ANALYSIS SET
16.2.5	CONCOMITANT DRUGS AND TREATMENTS / SAFETY ANALYSIS SET
16.2.7-1.1.1	ALL TREATMENT-EMERGENT ADVERSE EVENTS/SAFETY ANALYSIS SET
16.2.7-1.1.2	ALL TREATMENT-EMERGENT ADVERSE EVENTS/SAFETY ANALYSIS SET

16.2.7-1.2.1	TREATMENT-EMERGENT AES MEETING ANY OF THESE CRITERIA: SERIOUS, GRADE 3+, LED TO DISCONTINUATION, RELATED TO VACCINE OR STUDY PROCEDURE/ SAFETY ANALYSIS SET
16.2.7-1.2.2	TREATMENT-EMERGENT AES MEETING ANY OF THESE CRITERIA: SERIOUS, GRADE 3+, LED TO DISCONTINUATION, RELATED TO VACCINE OR STUDY PROCEDURE/ SAFETY ANALYSIS SET
16.2.7-1.3.1	TREATMENT-EMERGENT PNEUMONIA CASES / SAFETY ANALYSIS SET
16.2.7-1.3.2	TREATMENT-EMERGENT PNEUMONIA CASES / SAFETY ANALYSIS SET
16.2.7-2	REACTOGENICITY DATA FOR ANY SUBJECT WITH AT LEAST ONE GRADE 3+ REACTION POST VACCINATION/ SAFETY ANALYSIS SET
16.2.8	CLINICAL LABORATORY VALUES LABORATORY RESULTS FOR ANY SUBJECT WITH (A) GRADE 3+ TOXICITY, OR (B) CLINICALLY SIGNIFICANT AND AT LEAST GRADE 1 TOXICITY PAST VACCINATION / SAFETY ANALYSIS SET
16.4.1	VITAL SIGNS FOR ANY SUBJECT WITH AT LEAST ONE CLINICALLY SIGNIFICANT OR GRADE 3+ SIGN POST VACCINATION / SAFETY ANALYSIS SET
16.4.2	ABNORMAL PHYSICAL EXAMINATIONS RESULTS POST-VACCINATION/ SAFETY ANALYSIS SET
16.4.3-1	SUSPECTED PNEUMONIA CASES / SAFETY ANALYSIS SET
16.4.3-2	SUSPECTED PNEUMONIA CASES / SAFETY ANALYSIS SET
16.4.5-1	POST RANDOMIZATION IMMUNOGLOBULIN(IGG) DATA / PP_IMM POPULATION
16.4.5-2	INDIVIDUAL SUBJECTS' IGG FOLD-RISE /PP_IMMPOPUATION

7.4. Table shells

Table shells are provided in a separate document (Appendix I).

8. 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. New York: Chapman & Hall.

Newcombe, R. G. "Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods," *Statistics in Medicine*, 1998; **17:** 873–890.

9. APPENDICES

Appendix I: MOCK-UPS OF TABLES AND LISTINGS (V0.4)

Appendix II: VAC040 Adult Protocol Toxicity Grading Tool (V3.0)

Appendix III: VAC040 Toddler Protocol Toxicity Grading Tool (V1.7)