Statistical Analysis Plan

Study ID: 219651

Official Title of Study: A Phase 2, Randomized, Double-blind, Multi-dose, Dose Finding Study to Assess Safety,Tolerability and Immunogenicity of AFX3772 Compared with PCVs in Healthy Infants.

NCT number: NCT05412030

Date of Document: 13 Aug 2025

Statistical Analysis Plan for Interventional Studies

Text and TFL Shells

SAP Text Version Number: 3.0
SAP Text Date: 11-Aug-2025

Sponsor Name: GSK Biologicals SA.

Protocol Number: AFX3772-003
Protocol Title: A Phase 2, Randomized, Double-blind, Multi-dose, Dose Finding Study to Assess Safety, Tolerability and Immunogenicity of AFX3772 Compared with PCVs in Healthy Infants

Protocol Version and Date: (DD-Mmm-YYYY): Protocol Amendment 5 (27-Jan-2025)

Syneos Health Project Code: 7035898
GSK Abbreviated title (e-Track Number): 24PN-MAPS-PED-002 STG (219651)
Authors: PPD

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	12-Apr-2022	PPD	Initial Release Version
0.2	22-Jun-2022		Updated SAP text and shells to align with final protocol (v1.0, 04-May-2022); Addressed Affinivax feedback from Draft 1 review.
0.3	18-Nov-2022		Additional revision requested for GSK review. Updated SAP text and shells to address GSK comments. Added DMC Analysis Section. Updated definition for Enrolled Set, added Screened Set Added butterfly plots for unsolicited AE visualization.
0.4	27-Mar-2023		Addressed comments from GSK reviewers Updated SAP text and shells to align with protocol amendment 2 (22-March-2023).
0.5	13-Apr-2023		Addressed comments from GSK reviewers. Updated TFLs shells to align with Protocol Amendment 2 (22-Mar-2023) and interim analysis. Added dose response for OPA GMT as an exploratory objective; Added summary of number and percentage of participants by number of serotypes titers >= LLOQ; Updated > LLOQ to >= LLOQ throughout. Removed Screened Set per feedback from Clinical; Updated definition for Enrolled Set.
1.0	27-Apr-2023		Addressed comments from GSK reviewers in SAP review meeting (18Apr2023) and follow-up Stats Meeting (21Apr2023) and made following updates: Updated TFL shell font to Arial and Arial Narrow (for footnotes) throughout. Updated concomitant medication and adverse event start and end date imputation rules. Updated language for data inclusion for Interim Analysis to include all safety and immunogenicity data post study intervention (exclude Standard of Care) – noted as changes from Analysis Planned in Protocol. Up version for finalization.
1.1	14-Aug-2024		Updated SAP text and shells to align with protocol amendment 4 (14-May-2024) Added eCOA compliance section.
1.2	29-Aug-2024		Addressed comments from GSK reviewers.

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.3	18-Sep-2024	PPD	Addressed comments from GSK reviewers about eCOA – removing wording around 36h recall data.
2.0	10-Oct-2024		Addressed comments from GSK reviewer and up-versioned for finalization.
2.1	29-Jul-2025		Updated SAP text and shells to align with protocol amendment 5 (27-Jan-2025)
2.2	07-Aug-2025		Addressed comments from GSK reviewers.
3.0	11-Aug-2025		Up-versioned for finalization

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

PPD Biostatistician II	PPD	11-Aug-2025
Name, Title Developing Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD Sr Biostatistician	PPD	11-Aug-2025
Name, Title Lead Biostatistician, Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)

GSK Biologicals SA. Approval

PPD Project Statistician	PPD	13-Aug-2025
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
PPD Study Statistician	PPD	12-Aug-2025
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
CI	Confidence Interval
CP	Carrier Protein
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
eCOA	Electronic Clinical Outcome Assessment
EOS	End-of-study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
LLOQ	Lower Limit of Quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable

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Abbreviation	Description
NA	Not Applicable
OPA	Opsonophagocytic Activity
PCV13	Prev(e)nar 13®
PCV20	Prev(e)nar 20®
PD	Post Dose
PI	Principal Investigator
PPS	Per Protocol Set
PS	Polysaccharide
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SoC	Standard of Care
SOP	Standard Operating Procedure
TC	Telephone Contact
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure, and Listing
WHODD	World Health Organization Drug Dictionary

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2. Purpose

This statistical analysis plan (SAP) is developed under Protocol Amendment 4 dated 14-May-2024. The purpose of this SAP is to ensure that the data listings, summary tables, and figures which will be produced, and the definition of analysis variables and statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings.

2.2. Timings of Analyses

An independent Data Monitoring Committee (DMC) will review descriptive summaries of accumulating safety, participant disposition, and immunogenicity data if available at the time of the meeting at a frequency outlined in the DMC Charter. Further description of the DMC analyses can also be found in **Section 12.4 DMC Safety Assessment** and the DMC Charter. An unblinded team from Syneos Health Biostatistics will perform the unblinded analyses as described in **Section 4.4.2** and **Section 12.4** of this SAP to maintain the blinding of the study. This analysis will be performed on data as clean as possible.

A total of 4 analyses may be performed in the study:

- In Part 1 participants, 1 primary vaccination series assessment, and a final safety assessment
- In Part 2 participants, affected by the clinical hold on 31 October 2024, an interim analysis of safety, reactogenicity, and immunogenicity may be performed for the purpose of internal decision making primary vaccination series assessments, and a final analyses of all the study objectives will be performed when all the participants have completed the last study visit

For interim analysis, an unblinded team from Syneos Health biostatistics will perform the analyses as described in **Section 4.4.2** of this SAP to maintain the blinding of the study.

In Part 1 participants, the first analysis, an interim analysis of the primary vaccination series will be performed. This will include the analysis of all available safety data for all three cohorts post study intervention and all available immunogenicity data post study intervention and available immunogenicity data for the 1 µg, 2 µg and 5 µg cohorts. A second analysis, i.e., the final assessment will be performed after the last participant in Part 1 completes the study, approximately 6 months after the last participant has received the primary series. The results of this analysis will be unblinded at individual-level.

An interim analysis of the primary vaccination series of Part 2 for the purpose of internal decision making may be performed when the participants, have completed 30 days after the primary series and the immunogenicity results become available.

Since Part 1 and Part 2 participants should receive Standard of Care for the booster vaccination and no safety and immunogenicity assessment is planned for Standard of Care pneumococcal vaccines, no analysis will be performed for booster series.

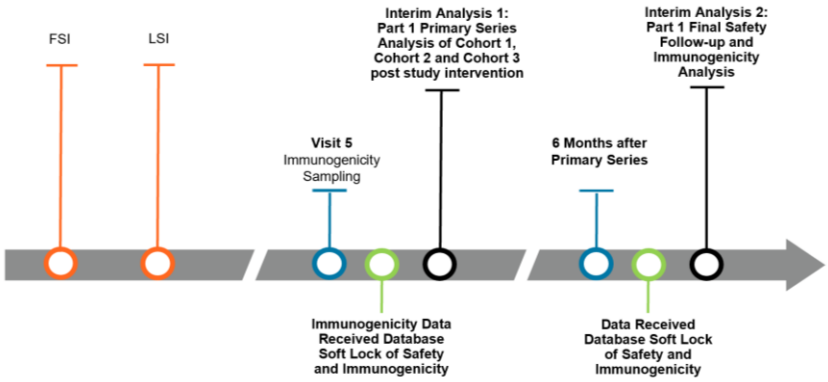
The final analysis will be performed to report all the final safety assessment (SAEs) of Part 2, after the last participant completes the study, approximately 6 months after the vaccination in the last participant. This analysis will include all the data regarding immunogenicity, reactogenicity and safety objectives of the study for Part 2 participants.

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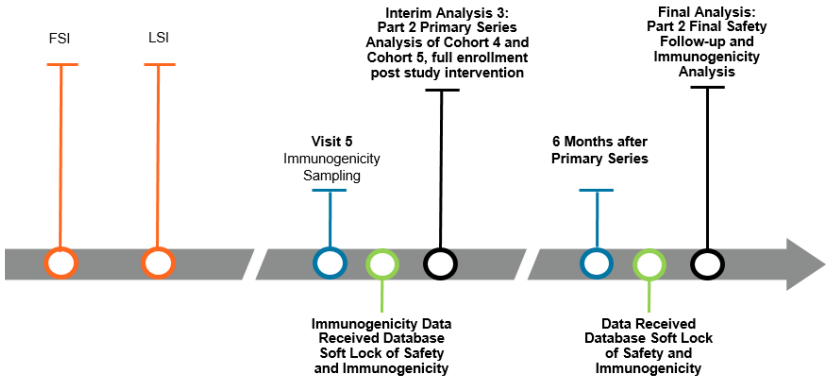
Summary of the various analyses are shown in **Figure 1** below.

Figure 1 Timing of database locks and analyses.

Part 1:



Part 2:



Notes:
FSI: First Subject In; LSI: Last Subject In; LSLV: Last Subject Last Visit

3. Study Objectives

Objectives	Endpoints
Primary	
• To describe the safety and tolerability profiles of 3 different dose levels (1**, 2 and 5 µg) of AFX3772 compared with PCV* with respect to the proportion of participants with AEs	Following any vaccination with AFX3772 or PCV*: • Solicited injection site AEs (tenderness, redness/erythema and swelling) from Day 1 through Day 7 post-vaccination • Solicited systemic AEs (irritability, decrease of appetite and increased sleep, and decrease in sleep) from Day 1 through Day 7 • AEs Day 1 through Day 30 • SAEs through completion of study participation (6 months post last study vaccination)
Secondary	
• To evaluate the immunogenicity of different dose levels of AFX3772 (1**, 2 and 5 µg) compared with PCV*	• The proportion of participants with a pneumococcal serotype-specific IgG concentration ≥0.35 µg/mL or corresponding threshold at 30 days PD2, 30 days PD3, pre-Dose 4 and 30 days PD4 • Serotype-specific IgG GMC at 30 days PD2, 30 days PD3, pre-Dose 4 and 30 days PD4
Exploratory	
CCI [redacted]	

AE: adverse event; GMC: geometric mean concentration; IgG: immunoglobulin G; OPA: opsonophagocytic activity; PCV: Prevnar ; PD: post-dose; SAE: serious adverse event
*:PCV13 [Part 1] and PCV20 [Part 2].
** in Part 1 only

4. Study Details/Design

4.1. Brief Description

This phase 2 study is a randomized, double-blind, multi-dose, dose finding study in infants approximately 2 months of age at the time of first vaccination who are naïve to licensed or investigational pneumococcal vaccines. The safety, tolerability, and immunogenicity of 3 dose levels of AFX3772 will be studied and compared with PCV (active control).

This study will be conducted at approximately 65-75 study sites in the US including Puerto Rico. Up to 480 healthy infants are planned to be enrolled in this study with a subset of 120 initially enrolled (Part 1) followed by 360 participants (Part 2). Sample size calculation is detailed in **Section 4.3**.

On 31 October 2024, GSK was informed of a study hold put in place by the FDA for the ongoing infant study. This study hold has been prompted by potential technical product quality concerns. As a consequence, enrollment and vaccination with investigational pneumococcal vaccine were stopped in the study.

Vaccinations with either AFX3772 (1, 2 or 5 µg, with 1 µg in Part 1 only) or PCV are scheduled at approximately 2, 4, and 6 months of age for the primary series and at 12 months of age for the booster dose. Subsequent immunogenicity assessments are scheduled at 30 days PD2, 30 days PD3, pre-dose 4 and 30 days PD4. In rare cases, if the participant is unable to return to the site, safety data may be collected by telephone and blood collected at a remote location, following study-specific procedures that have been approved by the Sponsor (refer to Protocol Section 10.6 Appendix 6 Clinical Study Continuity for alternative visit procedures in the case of a crisis). The follow-up visit will occur 6 months following the booster dose.

On Day 1 to Day 7 following each vaccination, the participant's LAR will record temperature and solicited local and systemic AEs in an eDiary. Unsolicited AEs will be collected for 30 days following each vaccination. Serious adverse events (SAEs) and deaths, regardless of whether the events are considered to be vaccine-related by the investigator, will be collected from the time consent is signed through an individual's completion of participation in the study.

Immunogenicity data from the primary series (after the third dose of study vaccine) will be used to determine if any participant meets the criteria for rescue vaccination, defined as a serotype-specific IgG concentration below 0.35 µg/mL or corresponding threshold for ≥ 3 of the 13 serotypes contained in PCV13 [Part 1] and 5 out of 20 serotypes in PCV20 [Part 2]. These assessments will be performed by the Sponsor in a timely manner, and the investigator or sub-investigator(s) will be informed of any participants meeting rescue criteria.

Participants will be offered a rescue vaccination with PCV13 (Part 1) or PCV20 (Part 2) within 3 weeks of site notification.

Additional blood volumes will be collected from study participants for the development, validation and maintenance of assays measuring responses to the pneumococcal vaccine needed for the vaccine clinical development program.

Part 1 Dose Escalation

Cohorts 1, 2 and 3 consist of 40 participants per cohort to be randomized 3:1 to receive either AFX3772 (1, 2 or 5 µg) or PCV13 as noted in **Table 1** and **Figure 2**. Following a review of the most recent cohort safety data through Day 7 post-vaccination and any additional safety data from earlier cohorts, the DMC will determine whether to initiate enrollment in the next cohort. The DMC will review all available safety data from Cohorts 1, 2 and 3 to determine if the study will proceed into Part 2 as planned. Following completion of DMC review of safety and tolerability data for the cohorts enrolled in Part 1, approximately 120 participants per dose level (approximately 360 infants if all dose levels are evaluated in Part 2) will be enrolled and randomized equally to receive either PCV13 or AFX3772 at dose levels (1, 2 or 5 µg) approved for Part 2. If the DMC does not recommend evaluating all AFX3772 dose levels in Part 2, an alternative approach, using a reduced number of AFX3772 dose levels, can be used. Study sponsor will take the DMC recommendation into account when deciding how to proceed to Part 2.

Table 1 Number of Participants Enrolled by Treatment Group for Part 1

Cohort	AFX3772	Number of Participants	Comparator	Number of Participants
1	1 µg	30	PCV13	10
2	2 µg	30		10
3	5 µg	30		10

Prior start of enrolment to Part 2, DMC has reviewed the data from Part 1 of the study, and GSK has decided to drop the 1 µg dose level of AFX3772 from Part 2. In addition, the Advisory Committee on Immunization Practices (ACIP) has recommended the use of PCV20 for routine infant immunization. Part 2 will start with target recruitment of a total of 360 healthy infants, i.e., 120 participants in each of treatment arm (AFX3772 2 µg, or AFX3772 5 µg or PCV20).

Part 2a Dose escalation safety lead-in

Part 2a Cohorts 4 and 5 consist of 45 participants per cohort to be randomized 2:1 to receive either AFX3772 (2 or 5 µg) or PCV20 as noted in **Table 2** and **Figure 4**.

Following a review of the tolerability data through Day 7 post-vaccination of 1st dose and cumulative safety data from Cohort 4, the DMC will determine whether to initiate enrollment in the Cohort 5. The DMC will review all available safety data from Cohorts 4 and 5 to determine if the study will proceed into Part 2b as planned.

If the DMC does not recommend evaluating 2 AFX3772 dose levels in Part 2b, an alternative approach, using a reduced number of AFX3772 dose levels, can be used. The Sponsor will take the DMC recommendation into account when deciding how to proceed to Part 2b.

Table 2 Number of Participants by Vaccination Group for Part 2a

Cohort	AFX3772	Number of Participants	Comparator	Number of Participants
4	2 µg	30	PCV20	15
5	5 µg	30		15

Part 2b Full Enrollment

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Following DMC review and agreement to proceed to Part 2b, up to 270 participants (~90 per dose level) will be randomized equally to receive approved AFX3772 dose levels (2, or 5 µg) or PCV20 (**Table 3** and **Figure 5**). The DMC will continue to review safety data as outlined in the DMC charter throughout the study. If the number of dose groups is reduced, the number of participants enrolled in the study overall will be reduced, with the number of participants in each treatment group remaining at approximately 90.

Table 3 Number of Participants by Vaccination Group for Part 2b

AFX3772 2 µg	AFX3772 5 µg	Comparator: PCV20
90	90	90

4.1.1. Dose Escalation and Stopping Criteria

After all vaccinated participants in a dose escalation cohort have completed study safety procedures through Day 7 post-vaccination, the DMC will recommend whether to initiate enrollment in the next cohort based on the review of all available safety data from the current and preceding cohorts. Once the Day 7 safety assessments in the final cohort (Cohort 3) of Part 1 are complete, the DMC will review all available safety data from Cohorts 1, 2 and 3 to recommend if the study should proceed into Part 2 and, if so, which AFX3772 dose level(s) will be recommended for continued evaluation in Part 2.

Once the Day 7 safety assessments in the final cohort (Cohort 5) of Part 2a are complete, the DMC will review all available safety data from the Cohorts 4 and 5 to recommend if the study should proceed into Part 2b and, if so, which AFX3772 dose level(s) will be recommended for continued evaluation in Part 2b.

Depending on the safety data observed in the study, the DMC will recommend whether to proceed with or stop dose escalation. The Sponsor will make the final decision based on all the data available and the DMC's recommendation(s). A stopping rule is met if any of the following rules occur after administration of AFX3772. Reactogenicity eDiary data confirmed by the investigator as being entered by the LAR in error will not contribute to the stopping rule. Dose escalation may proceed unless the following applies to participant(s) receiving AFX3772:

- Two or more participants vaccinated with AFX3772 at any dose level report the same or similar severe (Grade 3) local or systemic AE (see Section 10.2 Appendix 2 Assessment of Intensity) that is possibly related to AFX3772.
- Two or more participants vaccinated with AFX3772 develop fever >104°F (>40°C) for at least 1 daily measurement after vaccination that is assessed as possibly related to AFX3772, or for which there is no alternative, plausible, attributable cause.
- If any participant vaccinated with AFX3772 at any dose level develops a Grade 4 local or systemic AE that is assessed as possibly related to AFX3772 or for which there is no alternative, plausible, attributable cause.
- ≥1 participant(s) experience an SAE, including death, possibly related to AFX3772, or for which there is no alternative, plausible, attributable cause.

  Note: Any events that have been previously reported and deemed related to licensed PCVs or other vaccines administered concomitantly to participants will not be considered to meet the halting criteria.

The DMC will review the event(s) and may decide to unblind the participant(s) treatment assignment. After review of all information, the DMC will recommend whether to resume the study and/or dose escalation. If the DMC does not recommend evaluating all AFX3772 dose levels, an alternative approach,

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using a reduced number of AFX3772 dose levels, can be used. The Sponsor will take the DMC recommendation into account when deciding how to proceed to the next step.

4.1.2. Discontinuation from Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study. A participant may discontinue from study intervention but continue to participate in protocol-specified, AE-monitoring activities. A participant may discontinue study intervention for any of the following reasons:

- The participant's LAR requests to stop vaccination.
- Any clinical AE, laboratory abnormality, medical condition, or intercurrent illness, which, in the opinion of the investigator, indicates continued vaccination is not in the best interest of the participant.
- If rescue vaccination is needed, the participants will be discontinued from study intervention but will be asked to continue to participate in safety follow-up assessments for up to 6 months PD3.

4.1.3. Discontinuation from Study

Individual participant(s) will be withdrawn from the study if the principal investigator deems it clinically appropriate for any of the following reasons:

- Participant is lost to follow-up despite reasonable efforts by the investigator to locate the participant.
- LAR voluntarily withdraws the participant from the study at any time for any reason.

The reason for discontinuation from study must be documented in the participant's medical records and eCRF.

Any participant who has received study vaccine and discontinues treatment early for any reason, including withdrawal of consent, will be asked to participate in the remaining safety assessments.

4.2. Study Population

Healthy male and female infants approximately 2 months of age (42 to 90 days inclusive) will be enrolled in this study.

All screening assessments must be completed and reviewed to confirm the potential participant meets all eligibility criteria. Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

4.2.1. Inclusion Criteria

Participant is eligible for participation in the study only if all of the following apply:

1. Participant has an LAR who understands study procedures, alternative treatments and risks involved in the study and who voluntarily agrees to participate by giving informed consent.
2. Participant is a full-term (≥37 weeks gestation at birth) infant approximately 2 months of age (42 to 90 days, inclusive) at time of obtaining the informed consent.
3. Participant is healthy based on the clinical judgment of the investigator following review of medical history and physical examination.

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4.2.2. Exclusion Criteria

Participant will be excluded from participation in the study if any of the following apply:

1. Participant had prior administration of any pneumococcal vaccine.
2. Participant has a known or suspected hypersensitivity to AFX3772, PCV13, PCV20 or any components of the formulations used.
3. Participant has a known or suspected immunodeficiency (including autoimmune disease) or other conditions associated with immunosuppression that may require immunosuppressive drugs including but not limited to HIV infection, malignancy or organ or bone marrow transplant.
    a. In addition, the participant's biological mother has known HIV infection or known to be hepatitis B surface antigen positive.
4. Participant has any clinically significant allergic condition or history (including anaphylactic reactions, but excluding untreated, asymptomatic, seasonal allergies) prior to the first vaccination for primary immunization series.
5. Participant has functional asplenia.
6. Participant has medical history of epilepsy or febrile convulsion.
7. Participant weighed <2000 g at birth.
8. Participant has known neurological or cognitive behavioral disorders including clinically significant developmental disorder and related disorders.
9. Participant has any active malignancy or history of malignancy.
10. Participant has a history of microbiologically proven invasive disease caused by *S. pneumoniae*.
11. Participant has cochlear implant or cerebrospinal fluid leakage.
12. Has received other licensed non-live vaccines within the 14 days or a licensed live virus vaccine within the 30 days prior to receipt of study vaccine.
13. Participant has received immunoglobulins. **Note:** This does not include monoclonal antibodies, such as palivizumab or nirsevimab.
14. Participant has a bleeding diathesis or condition associated with prolonged bleeding that would contraindicate intramuscular injection.
15. Participant has received systemic corticosteroids (equivalent of >2 mg/kg total daily dose of prednisone or >20 mg/day for persons weighing >10 kg) for a period of more than 14 days and has not completed the treatment for at least 30 days before study vaccine. Topical, ophthalmic and inhaled steroids are allowed.
16. Participant has febrile illness (rectal temperature ≥ 38.1°C [100.5°F] or axillary temperature ≥37.8°C [100.0°F]) in Part 1 and Part 2 prior to the effective date of protocol amendment 4. After protocol amendment 4 becomes effective, febrile illness is defined as rectal temperature ≥38.0°C [100.4°F] or axillary temperature ≥37.5°C (99.1°F) in Part 2. Upon resolution of symptoms, participant can be rescreened.
17. Participant has received any investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to screening.
18. Participant has any condition, which, in the investigator's opinion, makes the participant unsuitable for study participation.
19. LARs that are study personnel or their immediate dependents, family, or household members.

4.2.3. Screen Failures and Rescreening

Screen failures are defined as participants whose LAR provides consent to participate in the clinical study but who are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting to meet the Consolidated Standards of Reporting Trials

(CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and any SAEs meeting reporting requirements as outlined in the data entry guidelines.

For each study participant, a unique subject identifier (Subject ID) is assigned at Screening when the site completes the Enrollment CRF page. The eCRF Completion Guidelines will describe what data points need to be entered on the Enrollment CRF page. If screening criteria are not met, the participant will be considered a screen failure.

Rescreens

The participant can return for a rescreen visit once within 28 days of the initial screening visit, upon which a new informed consent will be obtained, and a new Subject ID assigned. If the participant does not meet all eligibility criteria at the rescreening visit, the participant will be documented as a screen failure.

4.2.4. Criteria for Temporarily Delaying Enrollment and Administration of Study Intervention

Enrollment and study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved:

The following condition(s) are temporary or self-limiting and participant may be vaccinated and/or blood draw at the visit can be performed, once the condition(s) has/have resolved and no other exclusion criteria are met and should other requirements such as appropriate window for study intervention Administration allows.

1. Acute illness or fever at the time of enrollment and/or study intervention administration. Refer to the SoA for definition of fever and preferred location for measuring temperature in this study.

2. Participant with a minor illness (such as mild diarrhea, mild respiratory infection) without fever may be enrolled and/or vaccinated at the discretion of the investigator.

3. Delay is warranted in order to meet the following conditions: Influenza vaccine, SARS-CoV-2 (COVID-19) vaccine should be administered either 7 days prior to or 15 days after the administration of the study vaccine. Non-live vaccines not given concomitantly (i.e., on the same day as study vaccine) should be given at least 7 days prior or at least 15 days after administration of study vaccine. Live vaccines not given concomitantly should be given at least 28 days prior or at least 28 days after study vaccine. Refer also to the Protocol Sections 6.8.1 Permitted Concomitant Therapy and Protocol Section 6.8.2 Prohibited Concomitant Therapy, and Protocol Section 10.4: Appendix 10.4 List of Excluded Concomitant Medications.

4. There is a clinical circumstance that warrants delay of blood collection for immunogenicity assessment. In the event that a participant meets this criterion for delay of blood collection, blood collection can proceed once the window for delay has passed.

5. Participants has been found to have clinically significant hematologic/biochemical values out of normal range (evident in tests performed for any reason outside of study procedures) which are expected to be temporary and warrant re-screening per PI's judgement and dosing within the allowed time interval per protocol.

4.3. Determination of Sample Size

CCI [redacted]

CCI

[redacted]

CCI



4.4. Treatment Assignment and Blinding

4.4.1. Intervention Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. The randomization schedule will be created by Syneos Health Biostatistics and assigned through Randomization and Trial Supply Management (RTSM) in the Syneos Health Randomization Services Group (RSG).

In Part 1, 40 participants per cohort will be enrolled and randomized 3:1 to receive AFX3772 (1, 2 or 5 µg) or PCV13. In part 2a, 45 participants per cohort will be enrolled and randomized 2:1 to receive AFX3772 (2 or 5 µg) or PCV20. If continuation into Part 2b is recommended, approximately 270 additional participants will be randomized 1:1:1 (90 per group) to receive either 2 µg AFX3772, 5 µg AFX3772, or PCV20 as agreed to for evaluation in Part 2b. At Visit 1, after the ICF signature, study site personnel will access the electronic data collection (EDC) system and enter the participant's required information as described in the eCRF Completion Guidelines. Upon completion of the Randomization eCRF page, the EDC system will assign a unique Subject Randomization Number to each randomized participant. Upon completion of the Vaccine Administration eCRF page, the IRT system will assign a unique kit to each randomized participant. An unblinded pharmacist will access the IRT to find out which investigational product kit was assigned to a randomized participant.

If a participant is randomized but does not receive study vaccine, the kit number will not be used again. In this instance, the study vaccine assignment should only be known by the unblinded pharmacist/study site personnel who are responsible for inventory and preparation of study vaccine, or designee.

This document is confidential.

Specific procedures for randomization through the IRT are contained in the IRT/pharmacy manual.

4.4.2. Blinding

A double-blinded technique will be used. The participant's LAR, the investigator, and all site personnel responsible for the clinical evaluation of participants will remain blinded until study completion.

Because AFX3772 and Prevnar 13/Prevnar 20 have different appearances, a member of the study staff (and back-up) will be unblinded for purposes of receiving, maintaining, preparing and administering study vaccines. The syringes will be masked prior to dosing to maintain the blind for the participant's LAR and all other personnel. In order to avoid bias, the unblinded study personnel will not perform any safety assessments after administration of study vaccines. Additionally, blinded site personnel will not be present in the examination room when study vaccines are administered.

The safety and tolerability data for dose escalation by the DMC will be reviewed under blinded conditions. If a participant(s) experiences an AE(s) that meets stopping criteria or that could prohibit dose escalation **(Section 4.1.2 Discontinuation from Study**), the study vaccine assignment for those participants may be unblinded, if requested by the DMC to determine if these events are possibly related to AFX3772 and of clinical concern. In the event there is an AE that is of concern to the DMC, the treatment assignment may be requested for that participant. An independent statistician will provide the treatment assignment, and the unblinding will be documented.

At the planned interim analysis for Part 1 participants, the analysis will be summarized by treatment group. The purpose is to allow proceeding with dose selection for the part 2 of clinical trial.

The Syneos Health blinded team will include a Lead Biostatistician, SDTM programmers, AdaM/TFL programmers, as well as a Senior Reviewing Statistician. A separate unblinded team will work independently of the blinded team to receive, review, and manage the unblinded data. The unblinded team, including an unblinded statistician and unblinded programmers, will not have any day-to-day roles in the conduct of the study. The blinded team will develop and validate the SAS programs necessary for analysis on the blinded data. Once validated, the unblinded programming team members will run the SAS programs on the unblinded study data in a secure, access-restricted area. The unblinded statistician will review the outputs produced by the unblinded team. Unblinded outputs, for interim analysis and DMCs, will be distributed via the project's unblinded sFTP, where only unblinded members have access. Unblinded outputs will be presented in a fully unblinded fashion for treatment groups in summaries, and listings will be presented by treatment group.

Data with the potential to unblind will be available to the blinded team only in a blinded fashion. Any potentially unblinding information would be masked prior to hand-off to the blinded team.

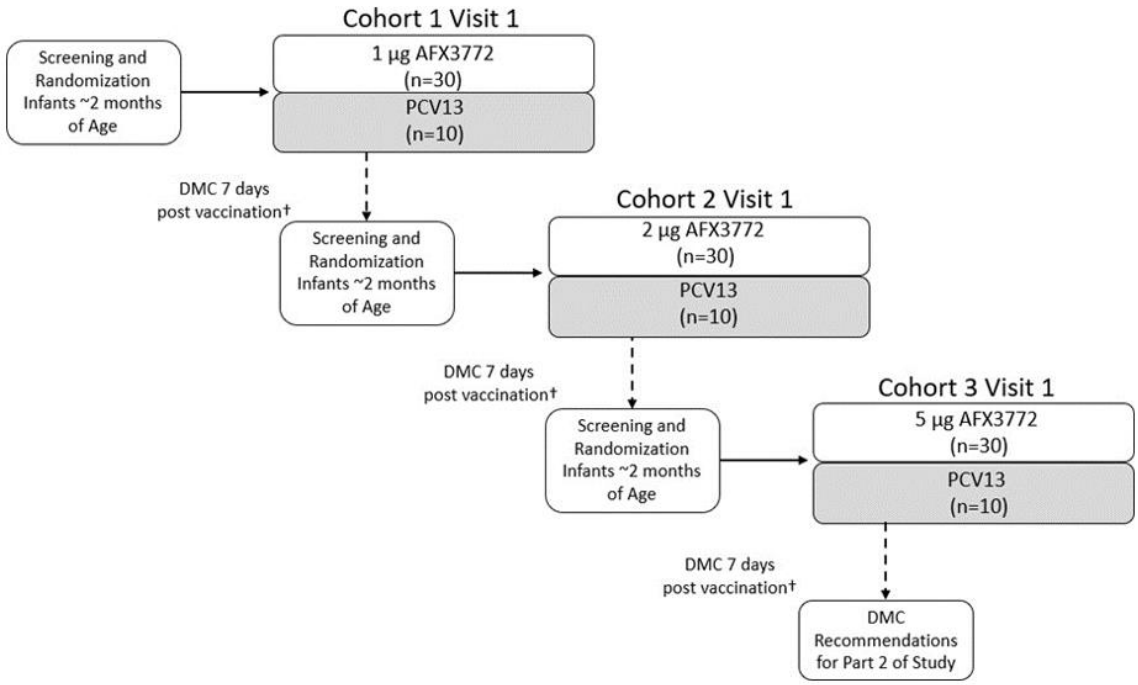
4.5. Administration of Study Medication

AFX3772 and PCV are administered as a 4-dose regimen, with 3-dose series given at 2, 4, and 6 months of age as part of a primary series and a booster dose given at 12 months of age.

4.6. Study Procedure and Flowchart

This study will enroll participants in 2 parts: dose escalation and full enrollment. An overview of the study schema for each portion are presented in **Figure 2 , Figure 3, Figure 4, and Figure 5** respectively.

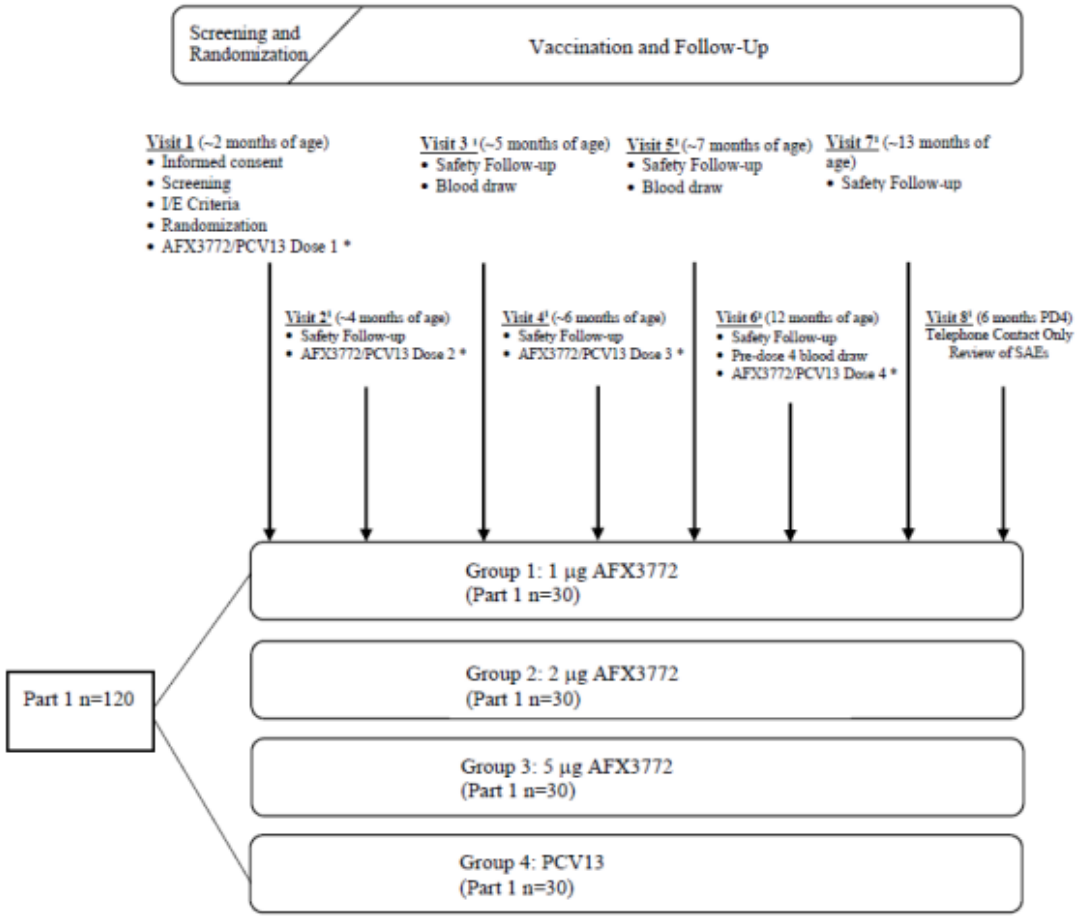
Figure 2 Study Schema Part 1 – Dose Escalation



†DMC reviews safety data through Day 7 for each cohort (approximately 40 participants) after all participants have completed eDiary safety assessments through Day 7 post-vaccination. For Cohorts 2 and 3, DMC will also review all safety data available for prior cohorts.
Subsequent cohorts start after DMC approval to dose escalate.

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Figure 3 Study Schema Part 1



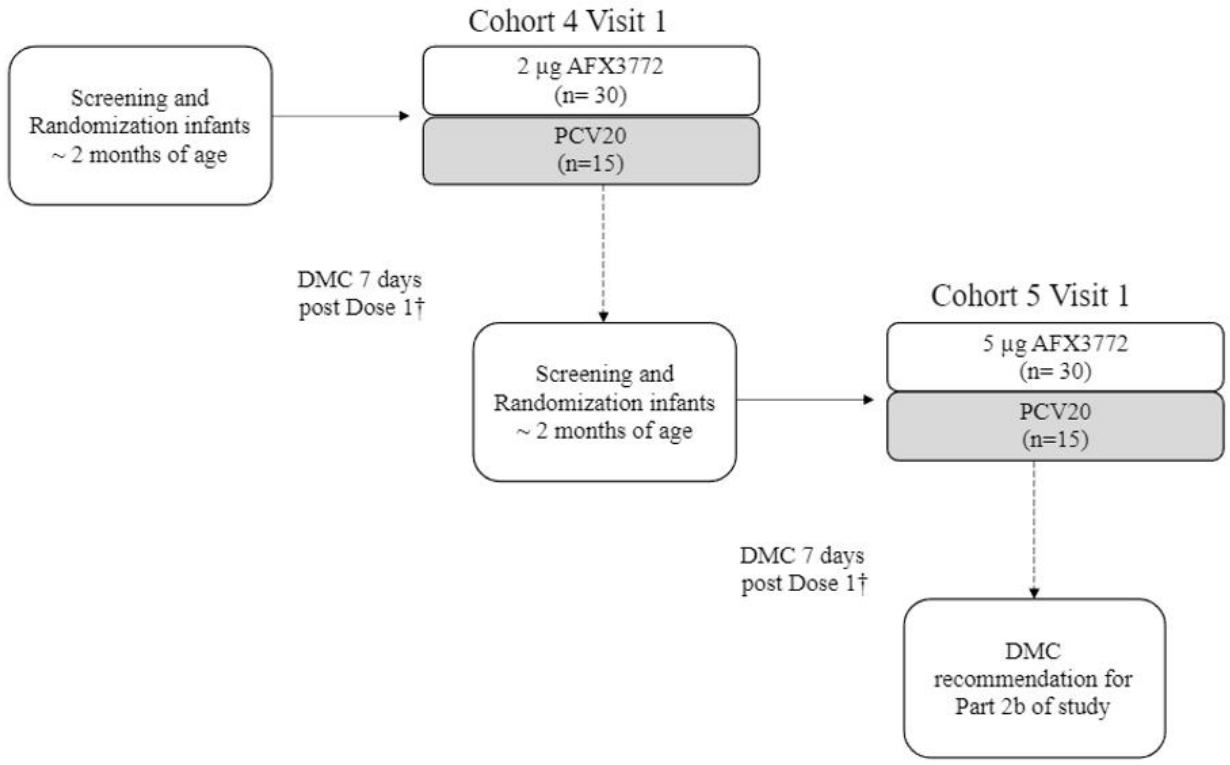
*Telephone contact occurs on Day 8 post-vaccination for safety follow-up and eDiary review
Part 2 starts after DMC review of Cohort 3 safety data through Day 7, plus cumulative safety data from prior cohorts of Part 1 and agreement to proceed to full enrollment.
Concomitant vaccines are permitted as per local requirements.
[1] Applicable only for Part 1 participants affected by Urgent Safety Measure i.e., the replacement of study vaccines with local standard-of-care (SoC) pneumococcal conjugate vaccines following the decision to halt study vaccinations and the Dear-Investigator-Letter (DIL) sent on 24 February 2023:
Timepoints impacted by protocol amendment 2:

- Visit 2 – SoC pneumococcal vaccine to be administered, if not received prior 24 February 2023
- Visit 3 – not applicable for participants who received SoC pneumococcal vaccine as Dose 2.
- Visit 4 – SoC pneumococcal vaccine to be administered, if not received prior 24 February 2023
- Visit 6 –is 6-months post Dose 3 safety follow-up and timepoint for administration of SoC pneumococcal vaccine booster dose for all Part 1 participants (first subject's booster dose expected in April 2023). Visit 6 is to be performed at study site if this option is exercised by participants' LARs or via TC if participants' LARs opt to receive the booster dose at their primary care center.
- Visit 7 and 8 are not applicable for participants who receive SoC pneumococcal vaccine as booster dose, no specific safety and immunogenicity assessment will be performed following the booster dose with SoC

Note: Visit 5 (1-month post Dose 3) includes blood sampling and is maintained for all Part 1 participants (including those who received SoC pneumococcal vaccine) to assess a need for rescue vaccination.
All study-related procedures pertaining to Part 2 remain unchanged.

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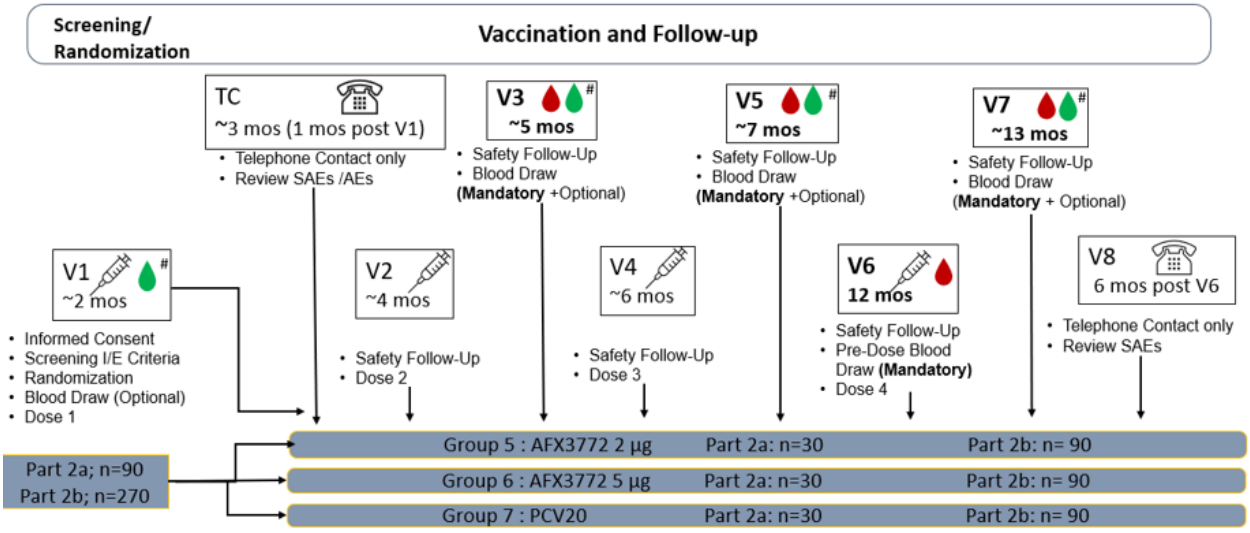
Figure 4 Study Schema Part 2a – Dose escalation



†DMC reviews safety data through Day 7 post-dose 1 for each cohort (approximately 45 participants), after all participants have completed eDiary safety assessments through Day 7 post-vaccination.
Part 2b starts after DMC review of Part 2a Cohort 5 safety data through Day 7 plus cumulative safety data of Part 2a and agreement to proceed to full enrollment.
Subsequent cohort starts after DMC recommendation to dose escalate.

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Figure 5 Study Schema Part 2



TC = Safety follow-up telephone contact at 1-month post-Dose 1,
Part 2b start after DMC review of Part 2a Cohort 2 safety data through Day 7 post-dose 1 and agreement to proceed to full enrollment.
Applicable only for Part 2 participants affected by FDA clinical hold on 31 October 2024, i.e., the replacement of study vaccines with local standard-of-care (SoC) pneumococcal conjugate vaccines following the decision to halt study vaccinations and the Dear Investigator-Letter (DIL) sent on 01 and 04 November 2024:
Timepoints impacted by protocol amendment 5:

- Visit 2 – SoC pneumococcal vaccine to be administered, if not received prior 31 October 2024
- Visit 4 – SoC pneumococcal vaccine to be administered, if not received prior 31 October 2024
- Visit 6 – 6-months post Dose 3 safety follow-up and timepoint for administration of SoC pneumococcal vaccine booster dose for all Part 2 participants. Visit 6 is to be performed at study site if this option is exercised by participants' LARs or via TC if participants' LARs opt to receive the booster dose at their primary care center as per local practice; this will be outside the scope of the study.
- No specific safety and immunogenicity assessment will be performed before or following the booster dose with SoC.
- No collection on solicited AEs on Day 1 to Day 7 following vaccination with SoC vaccine.
- Collection of unsolicited AEs from Day 1 through Day 30 following vaccination with each SoC vaccine.
- Immunogenicity to be done only at Visit 5 to assess need for rescue vaccination.
- SAEs will be collected for 6 months post Dose 3 (primary series).
- Collection of eDiary (solicited) safety data will be halted.
- Collection of optional blood draws will be discontinued.

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An overview of the scheduled visits and measurements to be conducted during the study and their timing is presented in **Table 6** and **Table 7**.

Table 6 Schedule of Assessments for Part 1

Assessments	Intervention										Follow-up		Comments
Visit Number	1	TC1	2[4]	TC2[4]	3[1, 4]	4[4]	TC3[4]	5[1, 4]	6[4]	TC4[4]	7[1, 4]	8[4]	
Scheduled Time	Dose 1 (~2 months of age)	1-week post Dose 1	Dose 2 (~4 months of age)	1 week post Dose 2	1 month post Dose 2 (~5 months of age)	Dose 3 (~6 months of age)	1 week post Dose 3)	1 month post Dose 3 (~7 months of age)	Dose 4 (~12 months of age)	1 week post Dose 4	1 month post Dose 4	6-months post Dose 4	
Visit Window[2]	≥42 to ≤90 Days of age	Day 8 to Day 10 after Dose 1	49 to 70 days after Dose 1	Day 8 to Day 10 after Dose 2	Day 28 to Day 42 after Dose 2	49 to 70 days after Dose 2	Day 8 to Day 10 after Dose 3	Day 28 to Day 42 after Dose 3	365 to 392 days of age	Day 8 to Day 10 after Dose 4	Day 28 to Day 42 after Dose 4	Day 166 to Day 194 after Dose 4	
Informed Consent	X												Informed consent must be obtained prior to the performance of any study-related procedure and before randomization.
Inclusion/ Exclusion Criteria	X†												
Demographics	X†												
Medical History	X†												Clinically significant medical history and vaccination history after birth will be collected at screening prior to vaccination in order to assess inclusion/ exclusion criteria.
Prior/Concomitant Medication	X†	X	X†	X	X	X†	X	X	X†	X	X	X	All concomitant medications or therapies during the eDiary reporting period or

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Assessments	Intervention										Follow-up		Comments
Visit Number	**1**	**TC1**	**2[4]**	**TC2[4]**	**3[1, 4]**	**4[4]**	**TC3[4]**	**5[1, 4]**	**6[4]**	**TC4[4]**	**7[1, 4]**	**8[4]**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
													associated with SAEs through Visit 8 will be collected. This also includes concomitant vaccinations.
Complete Physical Examination	X†												
Targeted Physical Examination			X†			X†			X†				
Body Temperature	X†		X†		X	X†			X†				Rectal or axillary temperature will be taken at the site prior to study vaccination according to the site's standard of care. Participants who have febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring at or within 72 hours of Visits 1, 2, 4 and 6 must be rescheduled.
Blood Sample (4 mL)					X			X[3]	X†		X		

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Assessments	Intervention										Follow-up		Comments
Visit Number	**1**	**TC1**	**2[4]**	**TC2[4]**	**3[1, 4]**	**4[4]**	**TC3[4]**	**5[1, 4]**	**6[4]**	**TC4[4]**	**7[1, 4]**	**8[4]**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
Randomization	X†												
AFX3772 or PCV13 Administration (Blinded)	X		X			X			X				Before vaccine administration, the investigator (or designee) must review medical history to ensure that the participant has no new contraindication to the vaccine. This information must be documented in the participant's chart. Any concomitant vaccinations must not be administered in the same limb as the study vaccine.
Provide eDiary	X												The participant's LAR will be instructed to measure reactogenicity/tolerability and temperature daily from Day 1 through Day 7 following each vaccination, and to record observed events in the eDiary. LAR will also be instructed to contact the study site in case of any

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Assessments	Intervention										Follow-up		Comments
Visit Number	**1**	**TC1**	**2[4]**	**TC2[4]**	**3[1, 4]**	**4[4]**	**TC3[4]**	**5[1, 4]**	**6[4]**	**TC4[4]**	**7[1, 4]**	**8[4]**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
													hospitalization or emergency room visit or if the participant experiences a severe intensity solicited event, as prompted by the eDiary.
30-minute[5] Post-vaccination Observation Period	X		X			X			X				To be performed by blinded study site personnel only.
Review eDiary with participant's LAR		X		X			X			X			On Day 8 post-vaccination, the site will contact the participant's LAR via telephone for safety follow-up, concomitant medications and eDiary review.
Collect eDiary from participant											X		
AE monitoring	←	—	—	—	—	—	—	—	—	—	—	→	AEs (non-serious) are to be reported Day 1 through Day 30 following each vaccination. SAEs and deaths are to be reported within 24 hours of

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Assessments	Intervention										Follow-up		Comments
Visit Number	1	TC1	2[4]	TC2[4]	3[1, 4]	4[4]	TC3[4]	5[1, 4]	6[4]	TC4[4]	7[1, 4]	8[4]	
Scheduled Time	Dose 1 (~2 months of age)	1-week post Dose 1	Dose 2 (~4 months of age)	1 week post Dose 2	1 month post Dose 2 (~5 months of age)	Dose 3 (~6 months of age)	1 week post Dose 3)	1 month post Dose 3 (~7 months of age)	Dose 4 (~12 months of age)	1 week post Dose 4	1 month post Dose 4	6-months post Dose 4	
Visit Window[2]	≥42 to ≤90 Days of age	Day 8 to Day 10 after Dose 1	49 to 70 days after Dose 1	Day 8 to Day 10 after Dose 2	Day 28 to Day 42 after Dose 2	49 to 70 days after Dose 2	Day 8 to Day 10 after Dose 3	Day 28 to Day 42 after Dose 3	365 to 392 days of age	Day 8 to Day 10 after Dose 4	Day 28 to Day 42 after Dose 4	Day 166 to Day 194 after Dose 4	
													awareness throughout the duration of an individual's study participation.

AE: adverse event; CP1: carrier protein 1; IgG: immunoglobulin G; IRT: interactive response technology; LAR: legally acceptable representative; PCV13: Prevnar 13; PD: post-dose: SAE: serious adverse event; TC: telephone contact.

†To be performed prior to administration of study vaccine by the investigator or a medically qualified designee.

1. Refer to Protocol Section 10.6 Appendix 6: Clinical Study Continuity for alternative visit procedures allowed at the noted visits in the case of a crisis.
2. For calculating the visit windows, the day of vaccination is considered Day 1. To calculate visit windows for subsequent vaccinations, confirm participant date of birth and ensure the age of the participant will fall within the appropriate age range for each study visit.
3. Following analysis of PD3 immune responses, investigators will be informed by the Sponsor if participants met rescue criteria (defined as the pneumococcal serotype-specific IgG concentration below 0.35 µg/mL for 3 or more of the 13 serotypes contained in PCV13).
4. Applicable only for Part 1 participants affected by Urgent Safety Measure i.e, the replacement of study vaccines with local standard-of-care (SoC) pneumococcal conjugate vaccines following the decision to halt study vaccinations and the Dear-Investigator-Letter (DIL) sent on 24 February 2023:
   Study timepoints impacted by amendment 2:
   a. Visit 2 – SoC pneumococcal vaccine is administered, if not received prior to 24 February 2023.
   b. Visit 3 – not applicable for participants who receive the SoC pneumococcal vaccine as Dose 2.
   c. Visit 4 – SoC pneumococcal vaccine is administered, if not received prior to 24 February 2023.
   d. TC2, TC3 and TC4 are not applicable for participants who receive the SoC pneumococcal vaccine.
   e. Visit 6 – is 6-months post Dose 3 safety follow-up and timepoint for administration of SoC pneumococcal vaccine booster dose for all Part 1 participants (first subject's booster dose expected in April 2023). Visit 6 is to be performed at study site if this option is exercised by participants' LARs or via TC if participants' LARs opt to receive the booster dose at their primary care center.
   f. Visit 7 and Visit 8 – not applicable for participants who receive SoC pneumococcal vaccine as booster dose. No specific safety and immunogenicity assessment will be performed following the booster dose with SoC

Note: Visit 5 (1-month post Dose 3) includes blood sampling and is maintained for all Part 1 participants (including those who received SoC pneumococcal vaccine) to assess a need for rescue vaccination.

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5. Applicable following administration of SoC pneumococcal conjugate vaccines: Duration of observation period as required by standard medical practice [**Error! Reference source not found.**, 2023].
6. All unscheduled visits and telephone contacts must be reported in the eCRF.

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Table 7 Schedule of Assessments for Part 2

Assessments	Intervention											Follow-up		Comments
Visit Number	**1**	**TC1**	**TC2**	**2**	**TC3**	**3[1]**	**4**	**TC4**	**5[1]**	**6**	**TC5**	**7[1]**	**TC6**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**1 month post Dose 1 (~3 months of age)**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**Day 28 to Day 42 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
Informed Consent	X													Informed consent must be obtained prior to the performance of any study-related procedure and before randomization.
Inclusion/ Exclusion Criteria	X†													
Demographics	X†													
Medical History	X†													Clinically significant medical history and vaccination history after birth will be collected at screening prior to vaccination in order to assess inclusion/ exclusion criteria.

This document is confidential.

Assessments	Intervention											Follow-up		Comments
Visit Number	**1**	**TC1**	**TC2**	**2**	**TC3**	**3[1]**	**4**	**TC4**	**5[1]**	**6**	**TC5**	**7[1]**	**TC6**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**1 month post Dose 1 (~3 months of age)**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**Day 28 to Day 42 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
Prior/ Concomitant Medication	X†	X	X	X†	X	X	X†	X	X	X†	X	X	X	All concomitant medications or therapies during the eDiary reporting period or associated with SAEs through Visit 8 will be collected. This also includes concomitant vaccinations.
Complete Physical Examination	X†													Body weight will be collected at Visit 1.
Targeted Physical Examination				X†			X†			X†				
Body Temperature	X†			X†		X	X†			X†				Rectal or axillary temperature will be taken at the site prior to study vaccination according to the site's standard of care.

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Assessments	Intervention											Follow-up		Comments
Visit Number	**1**	**TC1**	**TC2**	**2**	**TC3**	**3[1]**	**4**	**TC4**	**5[1]**	**6**	**TC5**	**7[1]**	**TC6**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**1 month post Dose 1 (~3 months of age)**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**Day 28 to Day 42 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
														Participants who have febrile illness (rectal temperature ≥38.0°C [≥100.4°F] or axillary temperature ≥37.5°C [≥99.1°F]) occurring at or within 72 hours of Visits 1, 2, 4 and 6 must be rescheduled.
Blood Sample ***(For Part 2) (Mandatory)***						X			X[3]	X†		X		
Blood Sample (For Part 2b) (Optional)	***X***					***X***			***X***			***X***		
Randomization	X†													

Assessments	Intervention											Follow-up		Comments
Visit Number	**1**	**TC1**	**TC2**	**2**	**TC3**	**3[1]**	**4**	**TC4**	**5[1]**	**6**	**TC5**	**7[1]**	**TC6**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**1 month post Dose 1 (~3 months of age)**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**Day 28 to Day 42 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
AFX3772 or PCV20 Administration (Blinded)	X			X			X			X				Before vaccine administration, the investigator (or designee) must review medical history to ensure that the participant has no new contraindication to the vaccine. This information must be documented in the participant's chart. Any concomitant vaccinations must not be administered in the same limb as the study vaccine.
Provide eDiary	X													The participant's LAR will be instructed to measure reactogenicity/tolerability and temperature daily

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Assessments	Intervention											Follow-up		Comments
Visit Number	**1**	**TC1**	**TC2**	**2**	**TC3**	**3[1]**	**4**	**TC4**	**5[1]**	**6**	**TC5**	**7[1]**	**TC6**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**1 month post Dose 1 (~3 months of age)**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**Day 28 to Day 42 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
														from Day 1 through Day 7 following each vaccination, and to record observed events in the eDiary. LAR will also be instructed to contact the study site in case of any hospitalization or emergency room visit or if the participant experiences a severe intensity solicited event, as prompted by the eDiary.
30-minute[5] Post-vaccination Observation Period	X			X			X			X				To be performed by blinded study site personnel only.
Review eDiary with		X	X		X			X			X			On Day 8 post-vaccination, the site will contact the

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Assessments	Intervention											Follow-up		Comments
Visit Number	**1**	**TC1**	**TC2**	**2**	**TC3**	**3[1]**	**4**	**TC4**	**5[1]**	**6**	**TC5**	**7[1]**	**TC6**	
Scheduled Time	**Dose 1 (~2 months of age)**	**1-week post Dose 1**	**1 month post Dose 1 (~3 months of age)**	**Dose 2 (~4 months of age)**	**1 week post Dose 2**	**1 month post Dose 2 (~5 months of age)**	**Dose 3 (~6 months of age)**	**1 week post Dose 3)**	**1 month post Dose 3 (~7 months of age)**	**Dose 4 (~12 months of age)**	**1 week post Dose 4**	**1 month post Dose 4**	**6-months post Dose 4**	
Visit Window[2]	**≥42 to ≤90 Days of age**	**Day 8 to Day 10 after Dose 1**	**Day 28 to Day 42 after Dose 1**	**49 to 70 days after Dose 1**	**Day 8 to Day 10 after Dose 2**	**Day 28 to Day 42 after Dose 2**	**49 to 70 days after Dose 2**	**Day 8 to Day 10 after Dose 3**	**Day 28 to Day 42 after Dose 3**	**365 to 392 days of age**	**Day 8 to Day 10 after Dose 4**	**Day 28 to Day 42 after Dose 4**	**Day 166 to Day 194 after Dose 4**	
participant's LAR[6]														participant's LAR via telephone for safety follow-up, concomitant medications and eDiary review.
Collect eDiary from participant												X		
AE monitoring	←	—	—	—	—	—	—	—	—	—	—	—	→	AEs (non-serious) are to be reported Day 1 through Day 30 following each vaccination. SAEs and deaths are to be reported within 24 hours of awareness throughout the duration of an individual's study participation.

AE: adverse event; CP1: fusion protein 1; IgG: immunoglobulin G; IRT: interactive response technology; LAR: legally acceptable representative; PCV20: Prevnar 20; PD: post-dose: SAE: serious adverse event; TC: telephone contact

†To be performed prior to administration of study vaccine by the investigator or a medically qualified designee.

1. Refer to Protocol Section 10.6 Appendix 6: Clinical Study Continuity for alternative visit procedures allowed at the noted visits in the case of a crisis.
2. For calculating the visit windows, the day of vaccination is considered Day 1. To calculate visit windows for subsequent vaccinations, confirm participant date of birth and ensure the age of the participant will fall within the appropriate age range for each study visit.

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3. Following analysis of PD3 immune responses, investigators will be informed by the Sponsor if participants met rescue criteria (defined as the pneumococcal serotype-specific IgG concentration below 0.35 µg/mL for 5 or more of the 20 serotypes contained in PCV20).
4. All unscheduled visits and telephone contacts must be reported in the eCRF.
5. Applicable following administration of SoC pneumococcal conjugate vaccines: Duration of observation period as required by standard medical practice [CDC., 2023].
6. In-App reminders in the eDiary. There will be a call from the site to the LAR in case of missing data for the day. Also, there will be training for the LAR and sites for eDiary completion.

Note: The optional blood draws will be collected in Part 2b only. The mandatory blood samples are collected in Part 2a and Part 2b throughout the study.

Note: Applicable only for Part 2 participants affected by FDA clinical hold on 31 October 2024, i.e., the replacement of study vaccines with local SoC pneumococcal conjugate vaccines following the decision to halt study vaccinations and the Dear-Investigator-Letter (DIL) sent on 01 and 04 November 2024:

Study timepoints impacted by amendment 5:

- Visit 2 – SoC pneumococcal vaccine to be administered, if not received prior 31 October 2024
- Visit 4 – SoC pneumococcal vaccine to be administered, if not received prior 31 October 2024
- Visit 6 –is 6-months post Dose 3 safety follow-up and timepoint for administration of SoC pneumococcal vaccine booster dose for all Part 2 participants. Visit 6 is to be performed at study site if this option is exercised by participants' LARs or via TC if participants' LARs opt to receive the booster dose at their primary care center as per local practice; this will be outside the scope of the study.
- No specific safety and immunogenicity assessment will be performed before or following the booster dose with SoC.
- No collection on solicited AEs on Day 1 to Day 7 following vaccination with SoC vaccine.
- Collection of unsolicited AEs from Day 1 through Day 30 following vaccination with each SoC vaccine.
- Immunogenicity to be done only at Visit 5 to assess need for rescue vaccination.
- SAEs will be collected for 6 months post Dose 3 (primary series).
- Collection of eDiary (solicited) safety data will be halted.
- Collection of optional blood draws will be discontinued.

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5. Endpoints

The primary, secondary, and exploratory endpoints used to evaluate safety, tolerability, and immunogenicity are described in the following sections.

5.1. Primary Endpoint

The primary endpoint is the following measures of safety and tolerability after each vaccination with AFX3772 or PCV, by treatment group and overall:

- Percentage of participants reporting solicited injection site AEs (tenderness, redness/erythema, and swelling) from Day 1 through Day 7 post-vaccination
- Percentage of participants reporting solicited systemic AEs (irritability, decrease of appetite, increased sleep, and decrease in sleep) from Day 1 through Day 7 post-vaccination

And the following AE measures by treatment group:

- Percentage of participants with AEs Day 1 through Day 30 post-vaccination
- Percentage of participants with SAEs through completion of study participation

5.2. Secondary Endpoints

The secondary endpoints are the following measures of immunogenicity 30 days PD2, 30 days PD3, pre-dose 4, and 30 days PD4, by treatment group:

- Proportion of participants with a pneumococcal serotype-specific IgG concentration ≥0.35 µg/mL or corresponding threshold
- Serotype-specific IgG GMC

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[redacted]

6. Analysis Sets

This section will provide definition of analysis sets to be analyzed.

6.1. Enrolled Set

The Enrolled Set will include all participants whose LAR provided informed consent, regardless of the participant's randomization and treatment group allocation status in the study. Unless specified otherwise, the Enrolled Set will be used for participant listing and for summaries of participant disposition.

6.2. Randomized Set

The Randomized Set will include all participants who are randomized to receive either AFX3772 or PCV. The enrolled and randomized populations are nested, i.e., the randomized population is a subset of the enrolled population. The Randomized Set will be used for participant listing of demographics and baseline characteristics.

6.3. Safety Analysis Set

The Safety Analysis Set (SAF) will include all participants who are randomized and receive at least 1 study vaccination with either AFX3772 or PCV. Participants will be analyzed according to the study vaccine received. The SAF will be used for all primary analyses of safety endpoints and complementary analysis of immunogenicity. Unless specified otherwise, this set will be used for data listings and summaries.

6.4. Per Protocol Set

The Per Protocol Set (PPS) will include all pneumococcal vaccine-naïve health infants approximately 2 months (42 to 90 days) of age who met the inclusion/exclusion criteria for the study and receive at least 2 study vaccinations with either AFX3772 or PCV during this study according to randomization and do not have exclusionary intercurrent events defined in Section 7.

The following participants will have their data excluded from assessments of immunogenicity for the PPS, the primary analysis set for immunogenicity.

1. Participants who have their 30-day blood draw 20 or more days after the 30-day postimmunization scheduled blood collection for that immunogenicity assessment only.
2. Participants who receive systemic corticosteroids at the doses, duration, and timing noted in Section 10.4 Appendix 4 in the protocol, List of Excluded Concomitant Medications and for that immunogenicity assessment only.
3. Participants who have newly diagnosed immunologic abnormalities within the first 2 weeks after receiving the study vaccine will be excluded from all immunogenicity assessments.
4. Participants who receive rescue vaccination (an intercurrent event) will be discontinued from study intervention and not included in subsequent immunogenicity assessments.
5. Participants who have important protocol deviations leading to exclusion from study analysis.

Additional detail regarding protocol deviations can be found in the Protocol Deviation and Non-Compliance Management Plan. Blind Data Review Meeting (BDRM) will be conducted prior to each database lock and unblinding of the treatment group. During the BDRM, a final decision will be taken as to which participants will be excluded from the PPS by the review team.

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6.5. Protocol Deviations

All deviations from the protocol will be tracked in the Clinical Trial Management System. Protocol deviation management is detailed in the Protocol Deviation and Non-Compliance Management Plan. Protocol deviation criteria are graded as not important or important. Protocol deviations considered important will be identified as such before study unblinding.

Important protocol deviations will be summarized by the categories provided in the protocol deviation listing for all participants in the Enrolled Set. All protocol deviations will be listed along with the study day on which it occurred.

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7. Estimands

7.1. Primary Estimand

The primary safety estimand is defined by the following 5 attributes:

Treatment: A total of 4 study vaccinations 0.5 mL each of either AFX3772 (1, 2, or 5 µg) or PCV administered as 4 separate vaccinations with a 3-dose primary series at approximately 2 (no earlier than 6 weeks of age), 4, and 6 months of age + 1 booster vaccination at 12 months of age.

Population: Pneumococcal vaccine-naïve healthy infants approximately 2 months (42 to 90 days) of age at enrollment who meet the eligibility criteria for the study and receive at least 1 vaccination with either AFX3772 or PCV during this study.

Endpoints: See Section 5.1 above.

Intercurrent events and strategies: A treatment policy strategy will be used to address intercurrent events of missed vaccination and taking prohibited medication/vaccine.

Population level summary: The percentage of participants who report each type of AE.

7.2. Secondary Estimands

The secondary estimand is defined by the following 5 attributes:

Treatment: A total of 4 study vaccinations 0.5 mL each of either AFX3772 (1, 2, or 5 µg) or PCV administered as 4 separate vaccinations with a 3-dose primary series at approximately 2 (no earlier than 6 weeks of age), 4, and 6 months of age + 1 booster vaccination at 12 months of age.

Population: Pneumococcal vaccine-naïve healthy infants approximately 2 months (42 to 90 days) of age at enrollment defined by the eligibility criteria for the study.

Endpoints: See Section 5.2 above.

Intercurrent events and their corresponding strategies: The immunogenicity data after the following ICEs are considered not relevant for assessing the vaccine effect and data post ICE will not be considered for the analysis of the outcome measure.

The following intercurrent events will lead to data exclusion from assessments of immunogenicity:

- Immunogenicity data collected after a participant misses a scheduled vaccination will be excluded.
- If the blood draw occurs outside of the allowed visit window, immunogenicity data from that blood draw will be excluded.
- Immunogenicity data collected after a participant receives prohibited systemic corticosteroids at specified doses and duration outlined in the exclusion criteria will be excluded for that assessment only.
- Immunogenicity data collected after a participant has newly diagnosed immunologic abnormality occurring within the first 2 weeks after receiving the study vaccine will be excluded.

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Population level summary: Summaries will be provided after the second vaccination, after the third vaccination, and pre- and post-booster vaccination. By-treatment summaries for each of the endpoints listed above are:

- For each serotype, the percentage of participants with a serotype-specific IgG concentration ≥0.35 µg/mL or corresponding threshold, the 95% confidence interval (CI) and the difference (95% CI) between each AFX3772 dose level and PCV, the GMC (95% CI) for each serotype-specific IgG concentration and the ratio of the GMCs (95% CI) (each AFX3772 dose level/PCV). The GMCs and the corresponding 2-sided 95% CIs will be calculated using logarithmically transformed values and the Student's t distribution for the CIs.

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8. General Aspects for Statistical Analysis

8.1. General Methods

- Unless otherwise specified, summaries will be presented by treatment group and overall.
- Treatment groups will be categorized as:
  - AFX3772 1 µg
  - AFX3772 2 µg
  - AFX3772 5 µg
  - PCV
- Continuous variables will be summarized using the number of participants (n), mean, standard deviation (SD), geometric mean and geometric standard deviation where applicable, median, minimum, and maximum.
- Categorical variables will be summarized using frequency and percentages. The total number of participants in each treatment group with no missing data will be used as the denominator for percentage calculations, unless stated otherwise in the table shell.
- All relevant participant data will be included in listings. All participants entered into the database will be included in participant data listings.
- All statistical analyses and summary outputs will be generated using SAS® version 9.4 or higher.
- For antibody titer and concentration, values above the LLOQ are considered accurate and their quantitated values will be reported. Values below the LLOQ will be set to ½ LLOQ for calculation of geometric means and set to LLOQ for calculation of fold changes.

8.1.1. Geometric Mean

Continuous immunogenicity endpoints will be logarithmically transformed with 10 as base for analysis. Geometric mean titer (GMT) and associated 2-sided 95% CI will be calculated at each available time point for each treatment group. 95% CI will be calculated by back transformation of the 95% CI for the mean of the logarithm10 transformed assay results computed using Student's t distribution.

8.1.2. Geometric Mean Fold Rise (GMFR)

GMFRs will be defined as the latter result divided by the earlier result. The GMFRs and associated CIs will be calculated using the same method as for geometric means but performed on the defined ratios.

GMFR = anti-log10 (mean [log10 Yi/ Bi]) where Yi is the post dose assay result for participant i; and Bi is the baseline assay result for participant i.

8.1.3. Geometric Mean Ratio (GMR)

Ratio of GMT between groups AFX3772 1 µg, AFX3772 2 µg, AFX3772 5 µg, PCV with their standardized asymptotic 95% CIs.

For PD2 and PD3 timepoints, this will be performed using an analysis of variance (ANOVA) model on the logarithm10 transformation of the assay data using the treatment group as fixed effect.

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For PD4 timepoint, this will be performed using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the assay data using the treatment group as fixed effect and pre-booster value as a covariate.

8.2. Key Definitions

Study Day 1 is defined as the date of the first study vaccination. Post Dose 2 (PD2) is defined as the date of the visit 28 to 42 days after Dose 2. Post Dose 3 (PD3) is defined as the date of the visit 28 to 42 days after Dose 3. Pre-dose 4 is defined as the data collected on the date of the fourth vaccination administration (365 to 392 days of age), prior to vaccine administration. Post Dose 4 (PD4) is defined as the date of the visit 28 to 42 days after Dose 4.

8.3. Missing Data

As a general principle, no imputation of missing data will be done, with the exception of start and stop dates of AEs and concomitant medications if they are missing on day of immunization.

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.
• However, where necessary, display macros may impute dates as temporary variables for sorting data in listings. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
If the start date is missing year element, set to null.
If the start date is the same year as at least one of the study vaccinations and the event started before vaccination, start date will be imputed as one day before the first (or only) study vaccination given during that year; otherwise if the event started after vaccination or if it is not known whether event started before or after vaccination, start date will be imputed as the date of the first (or only) study vaccination given during that year.
Otherwise, impute as follows:
<table>
<tr><td>Missing start day</td><td>Imputed as 15th of month</td></tr>
<tr><td>Missing start day and month</td><td>Imputed as June 30</td></tr>
<tr><td>Missing end day</td><td>Imputed as 15th of month</td></tr>
<tr><td>Missing end day and month</td><td>Imputed as June 30</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
If imputed start date is after not imputed end date, then set to end date. If imputed end date is before start date, then set it to start date.</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>Imputed as 15th of month</td></tr>
</table></td></tr>
</table>

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Element	Reporting Detail
	Missing start day and month: Imputed as June 30 Missing end day: Imputed as 15th of month Missing end day and month: Imputed as June 30 Completely missing start/end date: No imputation If imputed start date is after not imputed end date, then set to end date. If imputed end date is before start date, then set it to start date.

The imputed dates will be used to assess if the AEs are within 30 days of vaccine administration or medications are concomitant, respectively. Listings of AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

8.4. Visit Windows

Safety data will be analyzed per study visit. The named visit as recorded in electronic Case Report Form (eCRF) will be displayed. Pre-specified visit windows are given in **Table 6 Schedule of Assessments for Part 1** and **Table 7 Schedule of Assessments for Part 2**.

For calculating the visit windows, the day of vaccination administration is considered Day 1. To calculate visit windows for subsequent vaccinations, participant's date of birth will be confirmed to ensure age of the participant falls within the age range for each study visit.

8.5. Unscheduled Visits

Data collected at unscheduled visits will be included in listings but not included in summaries.

8.6. Pooling of Centers

No by-center analyses are planned.

8.7. Subgroups

No subgroup analyses are planned.

9. Demographic, Other Baseline Characteristics and Medication

9.1. Participant Disposition and Withdrawals

Participant disposition will be presented for the Enrolled Set, including the following:

- The number of participants screened;
- The number of participants resulting in screen failure;
- The number of participants enrolled;
- The number of participants randomized;
- The number of participants in each study population (Randomized Set, SAF, and PPS).

Among the SAF, the following will be summarized by treatment group for AFX3772 (1 µg, 2 µg, or 5 µg), immunization group (AFX3772 or PCV 13), and overall:

- The number and percentage of participants who completed the treatment;
- The number and percentage of participants who prematurely discontinued from the treatment and the reasons for treatment discontinuation;
- The number and percentage of participants who completed the study;
- The number and percentage of participants who discontinued from the study and the reasons for study discontinuation.

All disposition details, dates of first and last evaluations for each participant, and protocol deviations will also be listed.

9.2. Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Randomized Set, SAF, and PPS by treatment group for AFX3772 (1 µg, 2 µg, or 5 µg), immunization group (AFX3772 or PCV), and overall.

Demographics and baseline characteristics are age, sex, ethnicity, race, and weight at screening.

Age will be calculated for at time of randomization, where:

age at randomization (in months) = (randomization date - date of birth + 1) / 12; and
age at randomization (in days) = randomization date – date of birth + 1.

Weight conversion from lb to kg will follow weight (in kg) = weight (in lbs) * 0.4536.

9.3. Medical History and Concomitant Diseases

Medical history will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT). The number and percentage of participants will be displayed for each SOC and PT for the SAF by treatment group and overall. Summaries will be ordered by descending frequency of SOC, and then within a SOC, by descending frequency of PT in the total column. If a participant has one or more history events more than once, the participant is counted only once under any given SOC or PT.

All prior and concomitant medical history data of participants will be listed for the SAF.

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9.4. Prior and Concomitant Medications

All medications will be coded using the most recent version of the World Health Organization Drug Dictionary (WHODD). Missing medication dates will be handled as described in Section 8.3.

Prior medications are defined as medications that discontinued prior to Study Day 1. Concomitant medications are defined as any medications with start date or stop date on or after Study Day 1. Start Date and Stop Date for medications, in conjunction with the Ongoing indicator, from the eCRF will be used to determine whether medication is prior or concomitant. If the medication is Ongoing on Study Day 1, it is considered to be concomitant. If the medication is not Ongoing but the Start Date to End Date overlaps with the start of vaccination, then it is also considered concomitant.

Medications will be summarized by Anatomical Therapeutic Chemical (ATC) Level 4 and PT. If ATC Level 4 is missing, the next higher non-missing ATC Level will be used. For each medication, the number and percentage of participants will be displayed for the SAF by treatment group and overall. The tables will be sorted by descending frequency of ATC Level 4 and then, within an ATC Level, by descending frequency of PT in the total column. Participants will be counted only once for each ATC and PT if they have multiple records of the same ATC or PT. Prior and concomitant medications will also be listed.

9.5. Concomitant Vaccinations

All non-study vaccines that were received during the study will be summarized by vaccine names (Influenza, Td (Tetanus, Diphtheria), Tdap (Tetanus, Diphtheria, Pertussis), and Other). The number of percentage of participants will be displayed for each vaccine name for the SAF by treatment group and overall. The table will be sorted by descending frequency of vaccine name in the total column. Concomitant vaccinations will also be listed.

9.6. Extent of Exposure

The frequency and percentage of dosage administered (full dose or partial at 0.1 mL increment) will be listed and summarized for SAF by treatment group and overall.

9.7. Electronic Clinical Outcome Assessment (eCOA) Compliance

Solicited AE's

The study protocol defines a 7-day solicited AE follow-up period. The single datapoint for the compliance calculation is the completion of each eDiary symptom by the LAR or reported by LAR through recall, in each day of the reporting period.

eDiary data

The number and proportion of completed eDiary symptoms on each day of the follow-up period will be summarized by treatment group using frequency table:

- for each day of the 7-day follow-up period
- overall across the 7-day follow-up period
- overall across days beyond Day 7

For the 7-day follow-up period, the denominator will be the number of expected eDiary symptoms to be completed for the corresponding summary level. The numerator will be the number of completed eDiary symptom entries.

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For days beyond Day 7, the denominator will be the expected eDiary symptoms to be completed. A symptom is expected to be completed when the same was reported on the previous day. For example, if irritability was reported on Day 7, it will be an expected symptom to be completed on Day 8 and onwards until it resolves. The numerator will be the number of eDiary symptom entries completed among the expected entries contributing to the denominator.

Day 8 recall data

The number and proportion of events recorded based on recall data and not otherwise reported in eDiary by the LAR will be summarized by treatment group using frequency table:

- for each day of the 7-day follow-up period
- overall across the 7-day follow-up period

In these summaries, the denominator will be the number of entries reported by LAR using eDiary or through recall. The numerator will be the number of entries reported by LAR through recall.

Compliance summary

Compliance will be summarized 1) eDiary data only; and 2) eDiary data combined with Day 8 recall data. Summaries will be provided both *by each solicited symptom* and *overall across all symptoms*. Additionally, these summaries will be provided both *by dose* and *overall across doses*. The denominator and numerator will be calculated for the corresponding summary level.

The below example shows the calculation for the overall study eDiary compliance for the 7-day follow-up period (across all symptoms/participants/doses):

$$\frac{total\ number\ of\ completed\ eDiary\ entries\ across\ all\ participants, doses, and\ days\ (Day\ 1\ to\ 7)}{total\ number\ of\ expected\ eDiary\ entries\ across\ all\ participants, doses, and\ days\ (Day\ 1\ to\ 7)} =$$

$$= \frac{\Sigma_{k=1}^{n}\ \Sigma_{J=1}^{m_k}\ \Sigma_{d=1}^{7}\ c_{k,j,d}}{\Sigma_{k=1}^{n}\ \Sigma_{J=1}^{m_k}\ d_j^k \times 8}$$

n = total number of vaccinated participants
m_k = number of doses received by participant k
$c_{k,j,d}$ = number of completed eDiary entries for participant k on dose j on day d, where d $\in$ {1, 2, 3, 4, 5, 6, 7}
d_j^k = expected number of reporting days per participant k on dose j
8 = number of eDiary solicited symptoms

The target compliance for the study is at least 80% based on overall eDiary compliance (across symptoms for the 7-day follow-up period), without inclusion of recall data from Day 8.

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10. Immunogenicity

The immunogenicity analyses will be performed on the PPS, unless otherwise stated. The immunogenicity analysis on PPS will be complemented by the analysis on SAF. All data will be listed.

Immunogenicity data will be summarized by treatment group and will include participants from both the dose-escalation cohorts and the full enrollment cohort. Common serotypes with PCV13 are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, and unique serotypes are 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20B, 22F, 33F. Common serotypes with PCV20 are 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F, and unique serotypes are 2, 9N, 17F, 20B. Results will be summarized separately for common serotypes and unique serotypes.

10.1. Immunogenicity Endpoints and Analyses

The immunogenicity endpoints are evaluated by treatment group at 4 time points: 1) 30 days PD2; 2) 30 days PD3; 3) pre-dose 4; and 4) 30 days PD4. The endpoints are defined as:

- Proportion of participants with a pneumococcal serotype-specific IgG concentration ≥0.35 µg/mL or corresponding threshold
- Serotype-specific IgG GMC

10.1.1. IgG concentration ≥0.35 µg/mL or corresponding threshold

For each serotype, the proportion measure of IgG concentration ≥0.35 µg/mL or corresponding threshold and the 95% CI (Clopper-Pearson, exact method) will be calculated for each treatment group. The difference between each AFX3772 dose level and PCV (AFX3772–PCV) at each timepoint and associated 95% CI will be calculated for each serotype (Miettinen and Nurminen, 1985).

Number and percentage of participants will also be summarized by the number of serotypes concentrations ≥0.35 µg/mL or corresponding threshold.

10.1.2. Geometric mean for IgG concentration (GMC)

For each serotype, IgG GMC will be calculated for each dose level of AFX3772 and PCV after each concentration has been logarithmically transformed. Two-sided 95% CIs for GMC will be constructed after back transforming the CIs for the mean of the logarithmically transformed assays computed using Student's t distribution.

The ratio of the IgG GMC for each AFX3772 dose level and PCV (AFX3772/PCV) at each time point and associated 95% CI will be calculated for each serotype. The ratio of IgG GMC is calculated after each concentration has been logarithmically transformed and finding difference between treatment means (i.e., AFX3772 – PCV), and then back transformed. Two-sided 95% CIs for the ratio of IgG GMC is calculated by finding 95% CI for difference of treatment means (i.e., AFX37372 – PCV) in log scale, and then back transformed.

Boxplots of serotype specific IgG concentration by visit will be displayed using geometric mean by vaccination group.



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11. Safety

11.1. Adverse Events / Adverse Drug Reactions

The population used for safety analyses will be the Safety Analysis Set (SAF).

An adverse event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

An unsolicited AE is an AE that was not solicited using a participant eDiary and that is communicated by a participant's LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their eDiary.

Solicited local reactions and systemic AEs within 7 days after each vaccination, solicited AEs ongoing after Day 7 post-vaccination, unsolicited AEs within 30 days after each vaccination, and serious AEs (SAEs) are primary safety endpoints.

An overall summary of the number and percentage of participants reporting the following will be provided:

- Solicited AEs Day 1 through Day 7 after each vaccination
  - Any solicited local AE
  - Any solicited systemic AE
  - Any solicited local AE by grade
  - Any solicited systemic AE by grade
  - Any solicited local AE related to study intervention
  - Any solicited systemic AE related to study intervention
  - Any solicited local AE related to study intervention and grade ≥3
  - Any solicited systemic AE related to study intervention and grade ≥3

- Solicited AEs ongoing after Day 7 post-vaccination
  - Any solicited AE ongoing after Day 7
  - Any vaccine-related solicited AE ongoing after Day 7
  - Any solicited AE ongoing after Day 7 and grade ≥3
  - Any vaccine-related solicited AE ongoing after Day 7 and grade ≥3

- Unsolicited AEs
  - Any Unsolicited AE
  - Any vaccine-related AE
  - Any severe AE
  - Any severe vaccine-related AE
  - Any serious AE (SAE)
  - Any vaccine-related SAE

- Any AE leading to treatment discontinuation
- Any life-threatening AE
- Any AE leading to death

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Summaries on solicited AEs by grade will be done for LAR grading from eDiary, principal investigator (PI) grading, and worst-case scenario grading using the worse grade of the two.

Listings will be provided for solicited AEs, AEs, and serious AEs. Unless otherwise stated, the listings will display study day, which is calculated as (event date – first vaccination date + 1). All AEs reported from the time of consent will be listed.

AEs entered into the CRF will be classified by SOC and PT using the most recent version of MedDRA.

11.1.1. Solicited Adverse Events / Reactogenicity within 7 Days of Study Vaccine Administration

The occurrence of solicited AEs or reactogenicity will be collected in the eDiary by the participant's LAR for 7 consecutive days following administration of each vaccine dose (including the day of administration).

In this study, solicited local AEs include tenderness, redness/erythema, and swelling. The participant's LAR will observe reactogenicity and tolerability from Day 1 through Day 7 and record observed events daily in the eDiary. Injection site redness and swelling will be evaluated by maximum size and then categorized during analysis as mild, moderate, or severe based on the grading scale in **Table 8** below. Reactogenicity will not be applicable for participants in Part 2 receiving SoC. Grade 3 and Grade 4 events after SoC will follow spontaneous reporting on AE page.

Table 8 Local Reactogenicity Grading Scale

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Pain/Tenderness	Hurts if gently touched (e.g., whimpers, winces, protests, or withdraws)	Hurts if gently touched, with crying	Interferes with limb movement	Emergency room visit or hospitalization for severe pain (tenderness) at injection site
Induration/Swelling	0.5 to 2.0 cm	>2.0 to 7.0 cm	>7 cm[b]	Necrosis
Erythema/Redness	0.5 to 2.0 cm	>2.0 to 7.0 cm	>7 cm[b]	Necrosis

Note: If the size of the redness and/or swelling falls between 2 measuring device units, the higher measuring device unit number will be recorded in the eDiary.
a. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the eDiary but as an AE on the eCRF. The severity of the local reaction should be graded using the AE severity scale.
b. Legally acceptable representatives of the participants experiencing local reactions >7.0 cm are to be contacted by the study site. An unscheduled visit may be required.

Solicited systemic AEs include irritability, appetite lost, increased sleep, and decrease in sleep from the day of vaccination to day 7 post-vaccination. The symptoms will be assessed by the participant's LAR as mild, moderate, or severe according to the grading scale in **Table 9** below. Only an investigator is able to classify a participant's systemic event as Grade 4, after physical examination of the participant or documentation from another medically qualified source (e.g., emergency room or hospital record) or telephone contact with the participant's LAR.

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Table 9 Systemic Reactogenicity Grading Scale

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Decreased appetite	Decreased interest in eating	Decreased oral intake	Refusal to feed	Emergency room visit or hospitalization for severe decreased appetite
Increased sleep	Increased or prolonged sleeping bouts	Slightly subdued, interfering with daily activity	Disabling, not interested in usual daily activity	Emergency room visit or hospitalization for severe increased sleep
Irritability	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted	Emergency room visit or hospitalization for severe irritability
Decrease in sleep	Needing more time to fall asleep	Interfering with daily activity	Disabling, not interested in daily activity	Emergency room visit or hospitalization for severe decreased sleep

a. Grade 4 assessment should be made by the investigator. Grade 4 will not be collected in the eDiary but as an AE on the eCRF. The severity of the local reaction should be graded using the AE severity scale.

Solicited local and systemic AEs will be summarized as below by treatment group and overall for each vaccination, for the primary series, and overall for all vaccinations:

- The number and percentage of participants who reported each type of solicited event within 7 days after the vaccine administration by day
- The number and percentage of participants who reported each type of solicited event with grade ≥3 within 7 days after vaccine administration by day
- The number and percentage of participants who reported each type of vaccine-related solicited event within 7 days after the vaccine administration by day
- The number and percentage of participants who reported each type of vaccine-related solicited event with grade ≥3 within 7 days after vaccine administration
- The number and percentage of participants who reported each type of solicited event within 7 days after the vaccine administration by maximum toxicity grade

Stacked bar charts of solicited local and systemic AEs will be presented by maximum toxicity grade.

11.1.2. Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited using a participant eDiary and that is communicated by a participant's LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Unsolicited AEs will be collected from after the first study immunization and up to 30 days following each dose, at the time points specified in the schedule of assessments and reported on the eCRF.

The severity of AEs is determined by the investigator as Mild, Moderate, and Severe

The relationship (causality) of AE to the vaccine will be assessed by the investigator as 'Yes' or 'No' to whether there is a reasonable possibility that the event may have been caused by the vaccine.

Unsolicited AEs will be summarized as below by treatment group and overall:

- The number and percentage of participants reporting unsolicited AEs by SOC and PT

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- The number and percentage of participants reporting unsolicited AEs by SOC, PT and maximum severity
- The number and percentage of participants reporting vaccine-related unsolicited AEs by SOC and PT
- The number and percentage of participants reporting severe unsolicited AEs by SOC and PT
- The number and percentage of participants reporting severe and vaccine-related unsolicited AEs by SOC and PT
- The number and percentage of participants reporting unsolicited AEs by PT
- The number and percentage of participants reporting vaccine-related unsolicited AEs by PT
- The number and percentage of participants reporting severe unsolicited AEs by PT
- The number and percentage of participants reporting severe and vaccine-related unsolicited AEs by PT

Summaries will be ordered by descending frequency of SOC, and then within each SOC, descending frequency of PT in the total column. If a participant has one or more unsolicited AEs more than once, the participant is counted only once under any given SOC or PT.

Butterfly plots of unsolicited AEs by preferred term will be presented for each AFX3772 vaccination group compared to the PCV group.

11.1.3. Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence, at any dose:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Other situations, based on medical or scientific judgment, may jeopardize the patient or may require medical or surgical interventions to prevent one of the other outcomes listed in the above definition.
- If an event is not an AE, then it cannot be an SAE even if serious conditions are met.

SAEs will be summarized as below by treatment group and overall:

- The number and percentage of participants reporting SAEs by SOC and PT.
- The number and percentage of participants reporting vaccine-related SAEs by SOC and PT.
- The number and percentage of participants reporting death.

All SAEs through 6 months after the last vaccination will be listed.

11.1.4. Immediate Adverse Reactions

All immediate adverse reactions that occurred within 30 minutes after vaccination will be listed.

11.2. Body Temperature

At the dosing visits, a rectal or axillary temperature will be taken prior to administration of study vaccine. The method used by the site will be based on their standard of care for temperature measurement. The participant's LAR will measure body temperature and record it to 1 decimal place in the eDiary. Axillary temperature is the preferred method for the LAR to obtain the participant's temperature. All summaries on

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the temperature values will be done in both Fahrenheit and Celsius where Temperature (in °F) = Temperature (in °C) x 1.8 + 32. Body temperature data will be listed in both Fahrenheit and Celsius.

Body temperature will be grouped into ranges based on **Table 10 Error! Reference source not found.**below. Maximum body temperature grade will be summarized as n and percentage by treatment group and vaccination.

Table 10 Fever Ranges for Grouped Analysis

Temperature Range
<100.4°F (<38.0°C)
100.4°F to 101.1°F (38.0°C to 38.4°C)
101.2°F to 102.0°F (38.5°C to 38.9°C)
102.1°F to 104.0°F (39.0°C to 40.0°C)
>104.0°F (>40.0°C)

11.3. Laboratory Evaluations

No laboratory tests will be collected in this study other than immunogenicity testing (Section 10).

11.4. Vital Signs and Physical Examination

Vital sign measurements include weight as collected at each clinic visit.

Whether a physical examination was performed is recorded for each visit, findings of the physical examination is not recorded.

Weight and physical examination data will be listed.

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12. Interim Analyses

Periodic DMC safety assessments will be performed for Dose escalation in part 1 and during part 2.

A total of 4 analyses may be performed in the study related to the study objectives:

- In Part 1 participants, 1 primary vaccination series assessment, and a final assessment
- In Part 2 participants affected by the clinical hold on 31 October 2024, an interim analysis of safety, reactogenicity, and immunogenicity may be performed for the purpose of internal decision making primary vaccination series assessments, and a final analyses of all the study objectives will be performed when all the participants have completed the last study visit

12.1. Primary Series Analysis

In Part 1 participants, the first analysis, an interim analysis of the primary vaccination series will be performed. This will include the analysis of all available safety data for all three cohorts post study intervention and all available immunogenicity data post study intervention (excluding Standard of Care). A second analysis, i.e., the final assessment will be performed after the last participant in Part 1 completes the study, approximately 6 months after the last participant has received the primary series (including Standard of Care). The results of this analysis will be unblinded at individual-level.

An interim analysis of the primary vaccination series of Part 2 for the purpose of internal decision making may be performed when the participants, have completed 30 days after the primary series and the immunogenicity results become available.

12.2. Booster Vaccination Analysis

Since Part 1 and Part 2 participants should receive SoC for the booster vaccination and no safety and immunogenicity assessment is planned for SoC pneumococcal vaccines, no analysis will be performed for booster series.

12.3. Final Safety Analysis

The final analysis will be performed to report all the final safety assessment (SAEs) of Part 2, after the last participant completes the study, approximately 6 months after the vaccination in the last participant. This analysis will include all the data regarding immunogenicity, reactogenicity and safety objectives of the study for Part 2.

12.4. DMC Safety Assessment

Part 1 Dose Escalation

The DMC will review the most recent cohort safety data through Day 7 post-vaccination (including Visit Day 8 – Phone Call data) and any additional safety data from earlier cohorts.

For the first dose escalation DMC meeting, summaries of subject disposition will be summarized at cohort level for the Enrolled Set. Solicited AEs will be summarized by vaccination number and overall at cohort level.

For the second and third dose escalation DMC meetings, summaries of subject disposition will be summarized at cohort level for the Enrolled Set. Solicited AEs and unsolicited AEs will be summarized by vaccination number and overall at cohort level for the Safety Analysis Set. AEs, SAEs, and AEs leading to discontinuation of study vaccine will be listed. Concomitant medications and vaccinations, immediate

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adverse reactions, medical history, reactogenicity events, and study vaccine administration data will also be listed.

For all dose escalation meetings, eDiary vendor data on post-vaccination solicited AEs and body temperature log will be listed with subject disposition status.

The DMC safety assessments will be performed for data as clean as possible at the database lock.

Part 2a Dose escalation safety lead-in

Following a review of the tolerability data through Day 7 post-vaccination of 1st dose and cumulative safety data from Cohort 4, the DMC will determine whether to initiate enrollment in the Cohort 5. The DMC will review all available safety data from Cohorts 4 and 5 to determine if the study will proceed into Part 2b as planned.

Part 2b Full Enrollment

Following DMC review and agreement to proceed to Part 2b, the DMC will continue to review safety data from the Primary Series Analysis and Booster Vaccination Analysis. In addition, the DMC will review all available safety data at 6-month intervals to ensure the benefit/risk profile continues to support the continued dosing of AFX3772 in infants.

Full enrollment data reviews will include the following:

Enrollment, Disposition, Demographic and Baseline Characteristics

1. Summary of Participant Disposition
2. Summary of Important Protocol Deviations
3. Demographics and Baseline Characteristics
4. Summary of Medical History
5. Summary of Concomitant Medications
6. Summary of Concomitant Vaccinations

Study Vaccine Administration

7. Summary of Vaccine Administration

Adverse Events

8. Proportion of Participants with Solicited Adverse Events by PI Toxicity Grading
9. Proportion of Participants with Solicited Adverse Events by LAR Toxicity Grading
10. Proportion of Participants with Solicited Local Adverse Events within 7 Days of Vaccination by Maximum PI Toxicity Grade
11. Proportion of Participants with Solicited Local Adverse Events within 7 Days of Vaccination by Maximum LAR Toxicity Grade
12. Proportion of Participants with Vaccine-Related Solicited Local Adverse Events within 7 Days of Vaccination by Maximum PI Toxicity Grade
13. Proportion of Participants with Vaccine-Related Solicited Local Adverse Events within 7 Days of Vaccination by Maximum LAR Toxicity Grade
14. Proportion of Participants with Solicited Systemic Adverse Events within 7 Days of Vaccination by Maximum PI Toxicity Grade
15. Proportion of Participants with Solicited Systemic Adverse Events within 7 Days of Vaccination by Maximum LAR Toxicity Grade

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16. Proportion of Participants with Vaccine-Related Solicited Systemic Adverse Events within 7 Days of Vaccination by Maximum PI Toxicity Grade
17. Proportion of Participants with Vaccine-Related Solicited Systemic Adverse Events within 7 Days of Vaccination by Maximum LAR Toxicity Grade
18. Proportion of Participants with Unsolicited Adverse Events Overall and by Dose
19. Proportion of Participants with Unsolicited Adverse Events by System Organ Class and Preferred Term
20. Proportion of Participants with Unsolicited Adverse Events by System Organ Class and Preferred Term and Maximum Severity
21. Proportion of Participants with Vaccine-Related Unsolicited Adverse Events by System Organ Class and Preferred Term
22. Proportion of Participants with Severe Unsolicited Adverse Events by System Organ Class and Preferred Term
23. Proportion of Participants with Severe and Vaccine-Related Unsolicited Adverse Events by System Organ Class and Preferred Term
24. Proportion of Participants with Unsolicited Adverse Events by Preferred Term
25. Proportion of Participants with Solicited Adverse Events Ongoing after Day 7 Post-Vaccination
26. Proportion of Participants with Serious Adverse Events by System Organ Class and Preferred Term
27. Proportion of Participants with Vaccine-Related Serious Adverse Events by System Organ Class and Preferred Term
28. Proportion of Participants with Serious Adverse Events Lead to Death by System Organ Class and Preferred Term
29. Listing of All Deaths
30. Listing of Serious Adverse Events
31. Listing of Adverse Events Leading to Discontinuation of Study Vaccine
32. Summary of Maximum Body Temperature within 7 Days of Vaccination by Dose
33. Listing of Solicited Adverse Events
34. Listing of Reactogenicity Events
35. Listing of Immediate Adverse Reactions
36. Listing of Adverse Events
37. Stacked Bar Chart of Solicited Local Adverse Events within 7 Days of Vaccination by Maximum PI Toxicity Grade
38. Stacked Bar Chart of Solicited Local Adverse Events within 7 Days of Vaccination by Maximum LAR Toxicity Grade
39. Stacked Bar Chart of Solicited Systemic Adverse Events within 7 Days of Vaccination by Maximum PI Toxicity Grade
40. Stacked Bar Chart of Solicited Systemic Adverse Events within 7 Days of Vaccination by Maximum LAR Toxicity Grade
41. Butterfly Plot of Unsolicited Adverse Events by Preferred Term.
42. Butterfly Plot of Vaccine-Related Unsolicited Adverse Events by Preferred Term.
43. Butterfly Plot of Severe Unsolicited Adverse Events by Preferred Term.
44. Butterfly Plot of Severe and Vaccine-Related Unsolicited Adverse Events by Preferred Term

The DMC safety assessments will be performed for data as clean as possible at the database lock.

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13. Changes from Analysis Planned in Protocol

Additional analyses are included in this SAP that are not in the protocol. Details are listed as below (note some are clarifications of the analysis noted in the protocol).

13.1. Logarithm Base

The protocol refers to log transformations but did not define the base to be used. This is clarified in this SAP and all values to be log transformed take a log base 10.

13.2. Analysis Sets

Enrolled Set is not defined in the Protocol, but added in this SAP to include all participants whose LAR provided informed consent.

Definition of the PPS in the SAP include an additional criterion for exclusion from the PPS:

5. Participants who have important protocol deviations leading to exclusion from study analysis.

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13.4. Body Temperature

SAP is defining a no fever category “<100.4°F (<38.0°C)” which is not specified in the Protocol.

14. Reference List

Marcy SM, Kohl KS, Dagan R, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004; 22(5-6): 551-6.

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15. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated TFL output will adhere to the following specifications.

15.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output
- One output file can contain several outputs, or each output will be stored in a separate file
- Output files will be delivered in Word format or portable document format pdf
- Numbering of TFLs will follow ICH E3 guidance

15.2. Table, Figure, and Listing Format

15.2.1. General

- All TFLs will be produced in landscape format on American letter size, unless otherwise specified
- All TFLs will be produced using the Arial font, size 10 which is the smallest acceptable point size for the Regulatory Authorities
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides
- Titles and headers will be Arial font, size 11. And footers will be in Arial Narrow font, size 10 which is the smallest acceptable point size for the Regulatory Authorities
- Legends will be used for all figures with more than one variable, group, or item displayed
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below)
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate

15.2.2. Headers

- All output will have the following header at the top left of each page:

  Sponsor: GSK Biologicals SA.

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Protocol No.: AFX3772-003 (219651)

- And the following header at the top right of each page:

  Draft/Final Run (DDMMMYYYY)

  Data Cutoff Date (DDMMMYYYY)

  Page n of N

- All output will have Page n of N at the top right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)

- The date the output was generated and date the analysis dataset was created will appear along with the program name as a footer on each page

15.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (e.g., Table 14.1.1). ICH E3 numbering is strongly recommended. A decimal system (x.y and x.y.z) is used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parentheses. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last line of the title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

15.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment

- For numeric variables, include ‘unit’ in column or row heading when appropriate

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of participants in the analysis set

- The order of treatments in the tables and listings will be AFX3772 (by increasing dose level) first, AFX3772 combining across all dose levels (if applicable), PCV, followed by a total column

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15.2.5. Body of the Data Display

15.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal point aligned.

15.2.5.2. *Table Conventions*

- Units will be included where available.
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
mild	0
moderate	8
severe	3

Where percentages are presented in these tables, zero percentages will be presented and so counts of 0 will be presented as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more participants.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value is less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999.

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- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). For values that round down to 0.0, a common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of participants in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the total column in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC4 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'

- The percentage of participants will normally be calculated as a proportion of the number of participants assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of participants exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of participants) where a participant can be included in more than one category, a footnote or programming note will be added describing whether the participant is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

15.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, participant number, visit/collection day, and visit/collection time

- Missing data will be represented on participant listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DDMMMYYYY': 01JUL2000). Missing portions of dates will be represented on participant listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the participant will be output as 'N/A', unless otherwise specified

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26, and midnight as 00:00:00, or 00:00). Time will only be reported if it was measured as part of the study

- Units will be included where available

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15.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis

15.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible
- Participant specific footnotes are avoided, where possible
- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z')
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

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16. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907).

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

This document is confidential.

17. Index of Tables/Listings/Figures

Separate mock shell file(s) will provide all details.

18. Appendices

There are no appendices applicable for this SAP.

This document is confidential.

afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean

Final Audit Report 2025-08-13

Created:	2025-08-11
By:	PPD
Status:	Signed
Transaction ID:	PPD
Documents:	afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx (72 pages)
Number of Documents:	1
Document page count:	72
Number of supporting files:	0
Supporting files page count:	0

"afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean" History

Document created by PPD
Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx
2025-08-11 - 7:34:22 PM GMT- PPD

Document emailed to PPD for signature
2025-08-11 - 7:36:31 PM GMT

Document emailed to PPD for signature
2025-08-11 - 7:36:31 PM GMT

Document emailed to PPD for signature
2025-08-11 - 7:36:32 PM GMT

Agreement viewed by PPD
Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx
2025-08-11 - 7:36:32 PM GMT- PPD

Document emailed to PPD for signature
2025-08-11 - 7:36:32 PM GMT

Document e-signed by PPD
Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx
Signing reason: I am the author

Syneos Health
Powered by Adobe Acrobat Sign

Signature Date: 2025-08-11 - 7:37:02 PM GMT - Time Source: server- PPD

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-08-11 - 7:37:02 PM GMT

Email viewed by PPD

2025-08-11 - 8:00:06 PM GMT- PPD

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2025-08-11 - 8:00:54 PM GMT

Agreement viewed by PPD

Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx

2025-08-11 - 8:00:55 PM GMT- PPD

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-08-11 - 8:01:29 PM GMT

Document e-signed by PPD

Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx

Signing reason: I am the reviewer

Signature Date: 2025-08-11 - 8:01:32 PM GMT - Time Source: server- PPD

Email viewed by PPD

2025-08-12 - 9:23:04 AM GMT- PPD

Agreement viewed by PPD

Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx

2025-08-12 - 9:23:15 AM GMT- PPD

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-08-12 - 9:26:57 AM GMT

Document e-signed by PPD

Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx

Signing reason: I am the approver

Signature Date: 2025-08-12 - 9:26:59 AM GMT - Time Source: server- PPD

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2025-08-12 - 9:27:55 AM GMT

Email viewed by PPD

2025-08-13 - 3:17:11 PM GMT- PPD

Agreement viewed by PPD

Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx

2025-08-13 - 3:17:42 PM GMT- PPD

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-08-13 - 3:18:39 PM GMT

Document e-signed by PPD

Documents: afx3772-003_statistical analysis plan_text_v3.0_11Aug2025_clean.docx

Signing reason: I am the approver

Signature Date: 2025-08-13 - 3:18:40 PM GMT - Time Source: server- PPD

Agreement completed.

2025-08-13 - 3:18:40 PM GMT