VAX24-101

CLINICAL STUDY PROTOCOL: A Phase 1/2a, Randomized, Observer-Blind, Dose-Finding, Controlled, Parallel-Group, Two-Stage Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 24-Valent Pneumococcal Conjugate Vaccine (VAX-24) in Healthy Adults Aged 18 to 64 Years

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CLINICAL STUDY PROTOCOL

PROTOCOL TITLE:	A Phase 1/2a, Randomized, Observer-Blind, Dose-Finding, Controlled, Parallel-Group, Two-Stage Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 24-Valent Pneumococcal Conjugate Vaccine (VAX-24) in Healthy Adults Aged 18 to 64 Years
PROTOCOL NUMBER:	VAX24-101
INVESTIGATIONAL PRODUCT:	VAX-24 (24-valent Pneumococcal Conjugate Vaccine)
SPONSOR:	Vaxcyte, Inc. 825 Industrial Road Suite 300 San Carlos, CA 94070 USA Tel: 650 837 0111
VERSION:	4.0
DATE:	31 May 2022

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PROTOCOL SIGNATURE PAGE

Protocol Number VAX24-101

(Version 4.0)

This Clinical Study Protocol document and all information provided to you, the Principal Investigator, related to this protocol are the confidential and proprietary information of Vaxcyte, Inc. ("Sponsor") and are subject to the terms of the Confidential Disclosure Agreement between you and Vaxcyte, Inc.

By signing below, I hereby confirm the following:

I agree to abide by the terms of the Vaxcyte, Inc. Confidential Disclosure Agreement.

I have read this protocol entitled, "A Phase 1/2a, Randomized, Observer-Blind, Dose-Finding, Controlled, Parallel-Group, Two-Stage Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 24-Valent Pneumococcal Conjugate Vaccine (VAX-24) in Healthy Adults Aged 18 to 64 Years" in its entirety and I agree to conduct the study according to this protocol. Any changes in procedure will only be made if necessary to protect the safety, rights, or welfare of subjects.

I agree to comply with the current International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice in addition to the appropriate FDA Code of Federal Regulations (CFRs) and applicable state and local regulations.

I agree to conduct the study in person or to supervise the study.

I agree to ensure that all who assist me in the conduct of the study have access to the study protocol, including any amendments thereto, and are also made aware of their responsibilities in meeting the foregoing obligations.

Principal Investigator
(Print Name)

Title

Signature **Date**

Site to send signed copy to Vaxcyte, Inc. and to keep original for files.

TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL 1
VAXCYTE APPROVALS 2
PROTOCOL SIGNATURE PAGE 3
TABLE OF CONTENTS 4
LIST OF TABLES 8
LIST OF FIGURES 8
LIST OF ABBREVIATIONS 9
PROTOCOL SYNOPSIS 11
1 INTRODUCTION 14
1.1 Background and Rationale 14
1.2 Name and Description of Investigational Vaccine 16
[redacted]
1.2.2 Rationale for Dosage and Route of Administration 19
2 OBJECTIVES AND ENDPOINTS 20
2.1 Primary 20
2.2 Secondary 20
[redacted]
3 STUDY PLAN 22
3.1 Study Design 22
3.2 Number of Study Participants 23
3.3 Estimated Study Duration 23
3.4 Study Population 24
3.4.1 Inclusion Criteria 24
3.4.2 Exclusion Criteria 25
4 STUDY VACCINE 27
4.1 Investigational Vaccine (VAX-24) 27
4.1.1 Active Comparator 27
4.1.2 Other Supplies 28

4.2 Dose Preparation of Study Vaccines 28
4.3 Accountability Procedures for Study Vaccines 29
5 STUDY PROCEDURES 30
5.1 Informed Consent 30
5.2 Screening 30
5.3 Medical History 31
5.4 Physical Examination 31
5.5 Vital Signs 32
5.6 Laboratory Tests 32
5.6.1 Blood Volume 32
5.6.2 Safety Laboratory Assessments 34
5.6.3 Immune Response Assessments 35
5.7 Pregnancy Testing and Contraception 35
5.8 Randomization 36
5.9 Study Vaccine Administration 37
5.10 Acute Observation 37
5.11 Solicited Adverse Events 37
5.12 Unsolicited Adverse Events 38
5.13 Prior and Concomitant Medications and Procedures 38
5.14 Prohibited Medications and Therapies 38
5.15 Emergency Unblinding 39
5.16 Protocol Deviations 39
5.17 Dosing Errors 39
5.18 Study Completion: For Individual Subjects 39
5.19 Early Discontinuation 39
5.20 Subject Replacement 40
5.21 Study Completion: Overall 40
6 STUDY PROCEDURES BY VISIT 41
6.1 Scheduled Study Visits 41
6.1.1 Screening (-30 days to Day 1) 41
6.1.2 Day 1 41
6.1.3 Day 8 (+3 days) 42
6.1.4 Day 15 (+3 days) 42

6.1.5 Day 29 (± 3 days) 42
6.1.6 Months 3, 4, 5, 6 (90 to 180 days after Day 1 (± 5 days)) 43
6.2 Early Discontinuation Visit 43
6.3 Unscheduled Visits 44
7 SAFETY 45
7.1 Definitions 45
7.1.1 Adverse Event 45
7.1.2 Solicited Adverse Event 46
7.1.3 Unsolicited Adverse Event 46
7.1.4 Serious Adverse Event 46
7.2 Severity Grading 47
7.3 Causality Assessment 47
7.4 Follow-up of Adverse Events 48
7.5 Reporting of Adverse Events 48
7.5.1 Reporting Periods 48
7.5.2 Documentation 49
7.6 SAE Reporting 49
7.7 Other Events Requiring Immediate Reporting 51
7.7.1 Pregnancy 51
7.8 Medical Monitor 51
7.9 Data Monitoring Committee 51
7.10 Study Stopping Rules 52
8 DATA HANDLING 54
8.1 Source Documentation 54
8.2 Retention of Study Documentation 54
8.3 Data Monitoring 54
8.4 Electronic Patient Reported Outcome Data 54
8.5 Laboratory Data 55
8.6 Audit Compliance 55
9 STATISTICAL ANALYSIS 56
9.1 Sample Size Calculation 56
9.2 Treatment Period 56
9.3 Treatment Groups 57

9.4 Populations for Analysis 57
9.5 Demographic and Baseline Characteristics Analysis 58
9.6 Safety Analysis 58
9.6.1 Analysis of Extent of Exposure 58
9.6.2 Solicited AEs 58
9.6.3 Unsolicited AEs 59
9.6.4 Combined Solicited and Unsolicited AEs 60
9.6.5 Analysis of Other Safety Data 60
9.7 Immunogenicity Analysis (50 to 64 years) 60
9.7.1 GMT/GMR 60
9.7.2 Threshold analyses 61
9.8 Defined Safety Evaluation 61
10 ADDITIONAL INFORMATION 62
10.1 Ethical Conduct of the Study 62
10.2 IRB Oversight 62
10.3 Informed Consent 62
10.4 Subject Confidentiality 63
10.5 Compensation for Injury 63
10.6 Clinicaltrials.gov 63
10.7 Public Disclosure and Publication Policy 63
10.8 Amendments 63
11 REFERENCES 64
[redacted]

LIST OF TABLES

[redacted] [redacted]
Table 3 Blood Collections 33
Table 4 Treatment Groups 57

LIST OF FIGURES

Figure 1 Study Schema for Subjects 18 to 49 Years of Age 22
Figure 2 Study Schema for Subjects 50 to 64 Years of Age 23
Figure 3 Safety Events Reporting Periods 49

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
ALPO	Aluminum phosphate
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CBC	Complete Blood Count
CI	Confidence Interval
CRF	Case report form
CRO	Contract research organization
CRP	C reactive protein
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DP	Drug Product
eCRF	Electronic Case Report Form
eCRM	Proprietary non-toxic diphtheria toxin carrier protein used in VAX-24
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
eSD	Electronic Source Document
FDA	US 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
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HIV EIA	Human Immunodeficiency Virus, Enzyme Immunoassay
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEP	Immunogenicity Evaluable Population

Abbreviation	Definition
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
LLOQ	Lower Limit of Quantitation
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary of Regulatory Activities
MSD	Meso Scale Discovery
NOCI	New Onset of Chronic Illness
NZW	New Zealand White (species of rabbits)
OPA	Opsonophagocytic assay
pAMF	Para-azidomethyl-L-phenylalanine
[redacted]	[redacted]
PCV	Pneumococcal Conjugate Vaccine
PCV13	Prevnar® 13
PCV20	Prevnar 20™
PD	Pneumococcal Disease
PFS	Pre-filled Syringe
PPV23	Pneumovax® 23
PS	Polysaccharide
S. pneumoniae	*Streptococcus pneumoniae*
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMMP	Safety Medical Management Plan
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
VAX-24	24-valent investigational pneumococcal conjugate vaccine
US	United States
WHO	World Health Organization

PROTOCOL SYNOPSIS

Sponsor
Vaxcyte, Inc.

Name of Investigational Product
VAX-24 (24-valent Pneumococcal Conjugate Vaccine)

Names of Comparator Products
Prevnar 20™ (20-valent Pneumococcal Conjugate Vaccine; PCV20)

Study Title
A Phase 1/2a, Randomized, Observer-Blind, Dose-Finding, Controlled, Parallel-Group, Two-Stage Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 24-Valent Pneumococcal Conjugate Vaccine (VAX-24) in Healthy Adults Aged 18 to 64 Years

Study Number VAX24-101

Study Phase 1/2a

Study Sites
Approximately 10 investigative sites in the US

Study Objectives and Endpoints

Primary:

The primary objectives are:

- To evaluate the safety and tolerability of a single injection of VAX-24 at three dose levels administered to healthy adults 18 to 64 years of age.
- To compare the safety of VAX-24 to that of PCV20 administered to two control groups: 1) subjects 18 to 49 years of age receiving PCV20, and 2) subjects 50 to 64 years of age receiving PCV20.

Primary endpoints are:

- Percentage of subjects reporting solicited local reactions within 7 days after vaccination (redness, swelling, and pain at injection site) in each age group.
- Percentage of subjects reporting solicited systemic events within 7 days after vaccination (fever, headache, fatigue, muscle pain, and joint pain) in each age group.
- Percentage of subjects reporting unsolicited AEs within 1 month after vaccination in each age group.
- Percentage of subjects reporting Serious Adverse Event (SAE) and new onset of chronic illness (NOCI) within 6 months after vaccination.
- Percentage of subjects reporting AEs with a new onset or a worsening of a condition that prompts the subject to seek unplanned medical advice at a physician's office, urgent care center, or Emergency Department (medically attended adverse event [MAAE]).

Secondary:

The secondary objectives are:

- Safety: To assess laboratory value abnormalities and/or potentially clinically significant laboratory values following VAX-24 at 3 dose levels compared to control groups receiving PCV20 for subjects aged 50 to 64 years.
- Immunogenicity: To assess the induction of antibody responses by VAX-24 dose levels compared to control groups receiving PCV20 for subjects aged 50 to 64 years.

The secondary endpoints include the following:

- Safety: Percentage of participants with laboratory value abnormalities and/or potentially clinically significant laboratory values at 1 month after vaccination.

- Immunogenicity: 24 VAX-24 Pneumococcal serotype-specific opsonophagocytic assay (OPA) geometric mean titer (GMTs) at 1 month after vaccination (Day 29).
- Immunogenicity: 24 VAX-24 Pneumococcal serotype-specific IgG geometric mean concentration (GMCs) at 1 month after vaccination (Day 29).

[redacted]

Study Design

This Phase 1/2a parallel-group, randomized, observer-blind study is to be conducted in two populations of healthy adults, 18 to 49 years of age and 50 to 64 years of age. Subjects will be randomly assigned in a 1:1:1:1 ratio to receive either VAX-24 at one of three dose levels or the active comparator.

A Phase 1 cohort of 64 subjects (16 for each VAX-24 dose group and 16 for the comparator group) aged 18 to 49 years will be enrolled initially. Subjects will receive VAX-24 or PCV20 on Day 1. All subjects will have safety labs analyzed at Baseline and one month post-vaccination (Day 29). Solicited AEs will be collected for 7 days post-vaccination and unsolicited safety information for 28 days post-vaccination, with SAEs, NOCIs, and MAAEs collected up to 6 months post-vaccination. A defined safety review of data (solicited and unsolicited AEs, and SAEs) through 7 days post-vaccination will occur by an independent Data Monitoring Committee (DMC) before proceeding with enrollment of the remaining subjects, adults 50 to 64 years of age.

Subjects in the 50-to-64-year-old group will receive VAX-24 or PCV20. Solicited AEs will be collected for 7 days post-vaccination and unsolicited safety information for 28 days post-vaccination, with safety data (limited to SAEs, NOCIs, and MAAEs) collected up to 6 months post-vaccination. All subjects in this age group will have blood samples drawn for immunogenicity analysis (OPA and IgG) at Days 1, 29.

[redacted]

Study Population

The study population will be composed of at least 864 healthy US adults: approximately 64 eligible subjects aged 18 to 49, up to 700 subjects aged 50 to 59, minimum of 100 subjects aged 60 to 64.

Main Criteria for Inclusion

Healthy adult volunteers aged 18 to 64 years, without previous history of pneumococcal disease or previous receipt of a licensed or investigational pneumococcal vaccine.

Test Product; Dose; and Mode of Administration

VAX-24 will be administered once, by intramuscular (IM) injection, at one of 3 dose levels: 1.1, 2.2, or 2.2/4.4 mcg/dose, where mcg is the measured amount of total polysaccharide per conjugate.

Reference Therapy; Dose; and Mode of Administration

PCV20 will be administered once, by IM injection, at a dose of 0.5 mL, as packaged by the manufacturer.
Treatment and Duration of Treatment Treatment consists of a single IM injection of VAX-24 or a single IM injection of PCV20.
Safety Assessments Subjects will be evaluated for solicited and unsolicited adverse events (AEs), including injection site reactions following vaccine administration. Additionally, changes in laboratory values (complete blood count [CBC] and differential, chemistry; tests for HIV EIA, HBsAg, HCV Ab, urinalysis), NOCI, physical examinations, and vital signs following administration of study vaccines will be evaluated.
Statistical Methods Various standard statistical methods will be employed to analyze the data, including descriptive statistics, linear models, and graphical displays. Summary statistics will consist of frequencies and percentages of responses in each category for discrete measures and of counts, means, medians, standard deviations, 95% confidence intervals, and minimum and maximum values for continuous measures, and will be presented by study treatment. All calculated fields will be listed in various data listings for review. Additional analyses may be performed by the Sponsor to supplement these results. Version 9.4M6 (TS1M6) or higher of the SAS® statistical software package will be used to provide all statistical analyses.

1 INTRODUCTION

1.1 Background and Rationale

Streptococcus pneumoniae (*S. pneumoniae*) is the pathogen that causes pneumococcal disease (PD), classified as either non-invasive (otitis media, sinusitis, pneumonia) or invasive (bacteremia, meningitis). A persistent global incidence of PD, driven by emerging serotypes not covered by currently available vaccines, has resulted in high morbidity and mortality worldwide. Pneumococci cause over 50% of all cases of bacterial meningitis in the US (Gierke 2015). Mortality rates for invasive pneumococcal disease in the United States range from 11% to 30% in adults (Centers for Disease Control and Prevention 2018). The overall case-fatality rate for pneumococcal bacteremia is approximately 20% overall, increasing to 60% in the elderly (Centers for Disease Control and Prevention 2021). Pneumococcal pneumonia case fatality rates are also quite significant, estimated to be 5% to 7% overall with much higher rates also among elderly persons (Gierke 2015). In a prospective population-based cohort study of adult residents in Louisville, Kentucky, from 1 June 2014 to 31 May 2016, mortality during hospitalization was 6.5%, corresponding to an estimated 102,821 annual deaths in the United States (Ramirez 2017).

Despite substantial reductions in PD with the availability of pneumococcal conjugate vaccines (PCVs), due to the diversity of serotypes and the phenomenon of serotype replacement, a significant burden of PD remains which is currently not covered by Prevnar 13® (PCV13). In fact, just 28.6% of invasive PD cases in individuals ≥5 years old in the US in 2017 are due to serotypes included in PCV13, while non-PCV13 serotypes accounted for 71.4% (Varghese 2020). In the United States, a PCV vaccine covering all the serotypes in PCV13 and Pneumovax® 23 (PPV23) would increase serotype coverage from 28.6% in individuals (>5 years old) for PCV13 to 69.6% for VAX-24, respectively, as calculated from the data in Table 1 (Varghese 2020).

In August 2014, the Advisory Committee on Immunization Practices (ACIP) recommended use of PCV13 followed by PPV23 for adults aged ≥ 65 years of age to protect against pneumococcal disease in the US. At the time, the recommendation was warranted because PCV13-type disease among adults was assessed to be an important public problem. However, in the long-term, ACIP recognized that continued reductions in PCV13-type disease due to indirect effects from pediatric PCV13 use might limit the utility of this recommendation (Matanock 2019).

With the recent FDA approval of Prevnar20™ (PCV20), a 20-valent pneumococcal conjugate vaccine, the ACIP reconvened in October 2021 to revise their recommendation to use PCV20 without a subsequent dose of PPV23 or use Vaxneuvance™ (PCV15) followed by PPV23.

Even with the approval of PCV20, due to the diversity of serotypes and the phenomenon of serotype replacement, a significant burden of PD remains which is currently not covered by PCV20. For example, currently PCV20 is estimated to cover just over half the serotypes causing invasive PD in those ≥65 years of age. The estimated incremental coverage a 24-valent

pneumococcal conjugate vaccine could contribute above PCV20 varies between 8 to 15% in adults (Gierke 2021). However, adding valency to existing PCVs using conventional technologies has proven difficult, for several reasons. First, data show that as more carrier protein/polysaccharide (PS) conjugates are added to existing PCVs, immune responses to the PSs often decrease due to the cumulative amount of carrier protein, which immunologically competes with the PS antigens (Dagan 2010), as most recently seen with PCV20 (Prevnar 20 Package Insert 2021). Second, conjugating additional PSs to a carrier protein molecule may mask existing T-cell epitopes that are critically important in eliciting an immune response. In the PCV13 carrier protein CRM197, approximately 20% of the 39 lysine residues border relevant T-cell epitopes (Choe 1992; Diethelm-Okita 2000; Raju 1995). Since conventional conjugation chemistry heterogeneously conjugates PSs to lysine residues independent of their proximity to T-cell epitopes, a bound PS may block the presentation of a T-cell epitope to the immune system, thus preventing the induction of a T-cell response. Meanwhile, the B-cell epitopes of both the carrier protein and the antigen are presented to the immune system, increasing B-cell competition for any available T-cell help. The masking of these critical epitopes prevents the conversion to a T-cell dependent immune response and negates the benefit of the carrier protein. This competition for T-cell help diminishes the immune response to the PS antigen and is believed to result in the phenomenon known as carrier suppression (Dagan 2010).

To address this issue, Vaxcyte is developing its PCV product, VAX-24, using a novel process that combines site-specific conjugation to the carrier protein and a highly efficient conjugation chemistry. Vaxcyte employs a cell-free protein synthesis platform to insert the non-native amino acid para-azidomethyl-L-phenylalanine (pAMF) into eCRM, a recombinant version of CRM197. These pAMF residues serve as PS conjugation sites, and are inserted in place of purposefully selected lysines, such that critical T-cell epitopes remain consistently exposed upon conjugation to maximize the T-cell-dependent immune response.

This first-in-human trial VAX24-101 is a dose-finding Phase 1/2a that will examine the safety, tolerability, and immunogenicity of the VAX-24 Drug Product (DP) vaccine at three different strengths, and the results will be compared to those for the currently recommended regimen of PCV20. The study will be conducted in healthy adult populations: aged 18 to 49 years and 50 to 64 years. The trial will be enrolled in two sequential stages: a Phase 1 cohort of 64 subjects aged 18 to 49 years will be enrolled for safety evaluation prior to enrolling the Phase 2 cohort of 800 subjects aged 50 to 64 years, giving a total of 864 subjects. Subsequent studies will include individuals 65 years and older where the disease burden is the greatest.

1.2 Name and Description of Investigational Vaccine

VAX-24 consists of capsular polysaccharide antigens of *Streptococcus pneumoniae (S. pneumoniae)* serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23F, and 33F, with each of the 24 polysaccharides (one from each serotype) individually conjugated in a site-specific manner to a novel and proprietary recombinant diphtheria carrier protein referred to as eCRM, and mixed with aluminum phosphate (ALPO).

VAX-24 is described further in Section 4.

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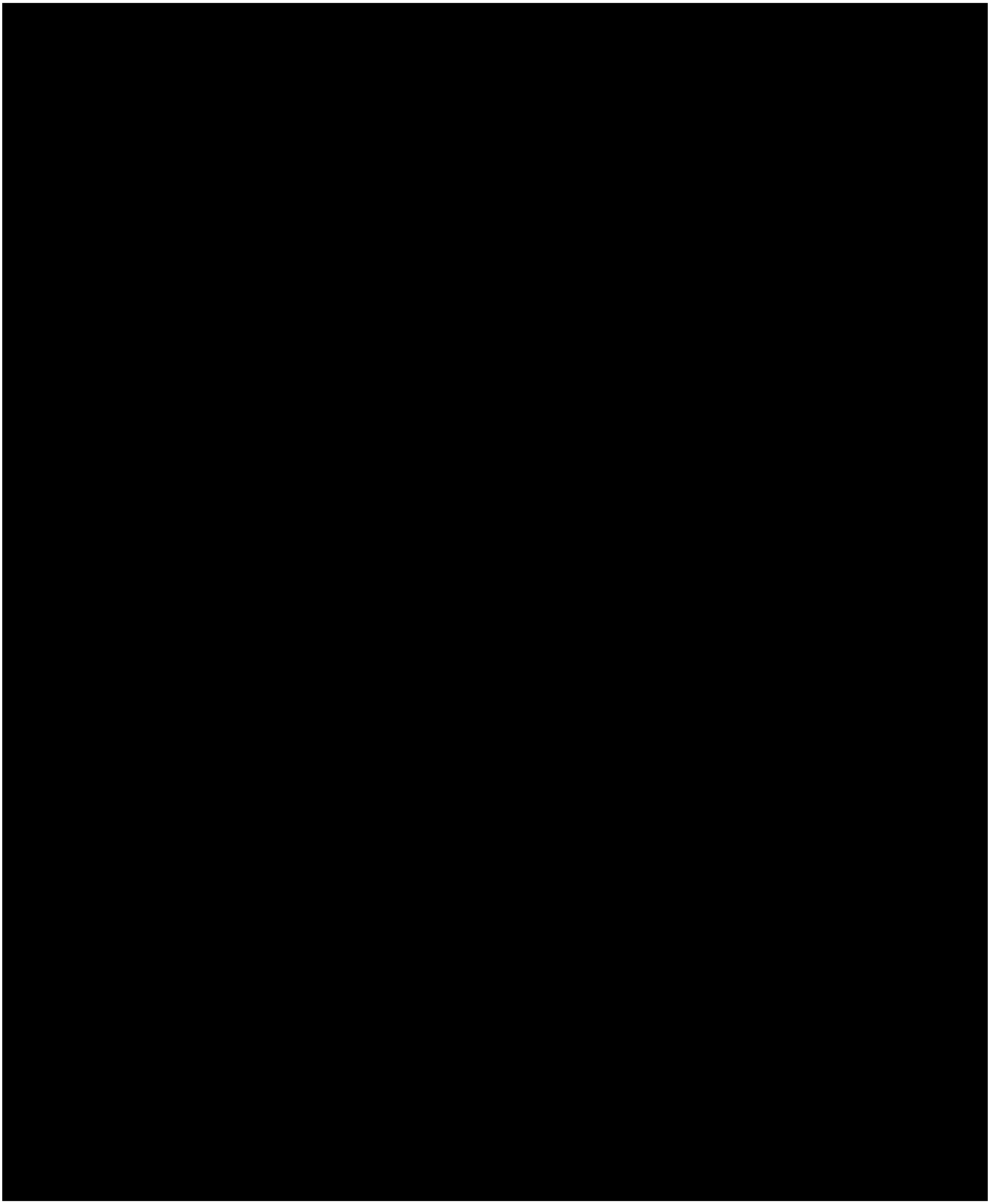

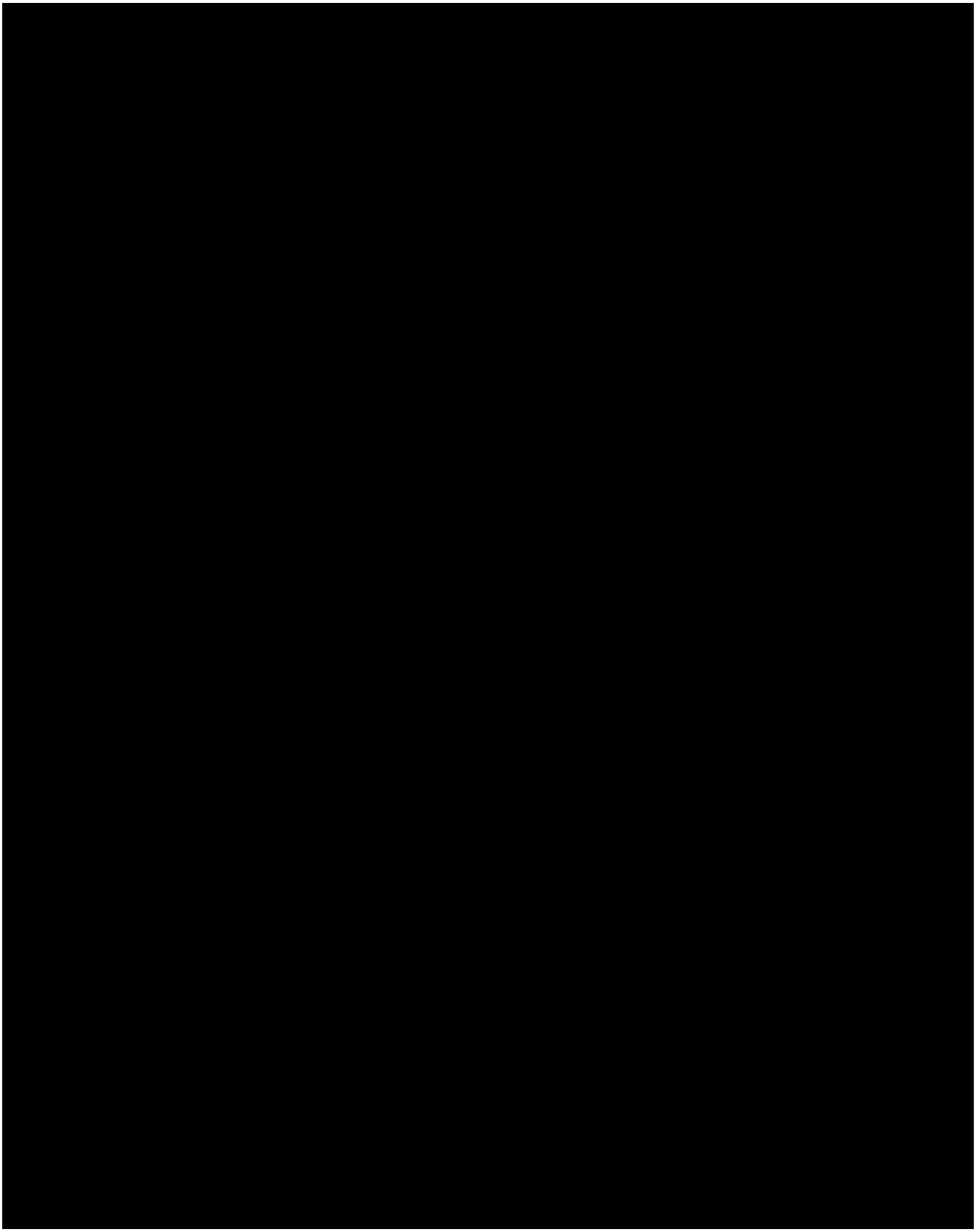

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1.2.2 Rationale for Dosage and Route of Administration

The dosages of VAX-24 are 1.1 mcg/dose (low), 2.2 mcg/dose (mid), or 2.2/4.4 mcg/dose (mixed), where potency of the formulated vaccine is determined by quantification of each of the saccharide antigens in the individual glycoconjugates. Based on the body of literature available on conjugated pneumococcal vaccines, the closest comparison to VAX-24 to establish a dose range was PCV20. Each 'Mid' dose is formulated to contain a similar quantity of *Streptococcus pneumoniae* polysaccharides as that of PCV20, the current standard of care. The 'Mixed' dose includes a similar quantity as the 'Mid' with the exception of inclusion of a higher amount for seven serotypes: two important epidemiologically relevant serotypes (3, 19A), and five shown to exhibit a dose-dependent response during the development of PCV13 (Varghese 2020, Jackson 2007). By utilizing site-specific conjugation to the CRM protein carrier thereby increasing the PS-to-eCRM ratio and enhancing overall T-cell epitope exposure, VAX-24 may be more potent than PCV13 and so a dose roughly half that of PCV13 has also been included in this study.

These doses are below or approximately equivalent to those used in the nonclinical toxicology studies. [redacted]

2 OBJECTIVES AND ENDPOINTS

2.1 Primary

The primary objectives are:

- To evaluate the safety and tolerability of a single injection of VAX-24 at three dose levels administered to healthy adults 18 to 64 years of age.
- To compare the safety of VAX-24 to that of PCV20 administered to two control groups: 1) subjects 18 to 49 years of age; and 2) subjects 50 to 64 years of age.

Safety and tolerability will be assessed by measuring the incidence of solicited local and systemic adverse events (AEs), unsolicited AEs, serious adverse events (SAEs), new onset of chronic illness (NOCI), and medically attended adverse events (MAAEs):

- Percentage of subjects reporting solicited local reactions within 7 days after vaccination (redness, swelling, and pain at injection site) in each age group
- Percentage of subjects reporting solicited systemic events within 7 days after vaccination (fever, headache, fatigue, muscle pain, and joint pain) in each age group
- Percentage of subjects reporting unsolicited AEs within 1 month after vaccination in each age group
- Percentage of subjects reporting SAEs and NOCI within 6 months after the vaccination
- Percentage of subjects reporting AEs with a new onset or a worsening of a condition that prompts the subject to seek unplanned medical advice at a physician's office, urgent care center, or Emergency Department (MAAE).

2.2 Secondary

The secondary objectives are:

- Safety: To assess laboratory value abnormalities and/or potentially clinically significant laboratory values following VAX-24 at 3 dose levels compared to control groups receiving PCV20 for subjects aged 50 to 64 years.
- Immunogenicity: To assess the induction of antibody responses by VAX-24 dose levels compared to control groups receiving PCV20 for subjects aged 50 to 64 years.

The secondary endpoints include the following:

- Safety: Percentage of participants with laboratory value abnormalities and/or potentially clinically significant laboratory values at 1 month after vaccination.
- Immunogenicity: 24 VAX-24 Pneumococcal serotype-specific OPA geometric mean titer (GMTs) at 1 month after vaccination (Day 29).

- Immunogenicity: 24 VAX-24 Pneumococcal serotype-specific IgG geometric mean concentration (GMCs) at 1 month after vaccination (Day 29).

[redacted]

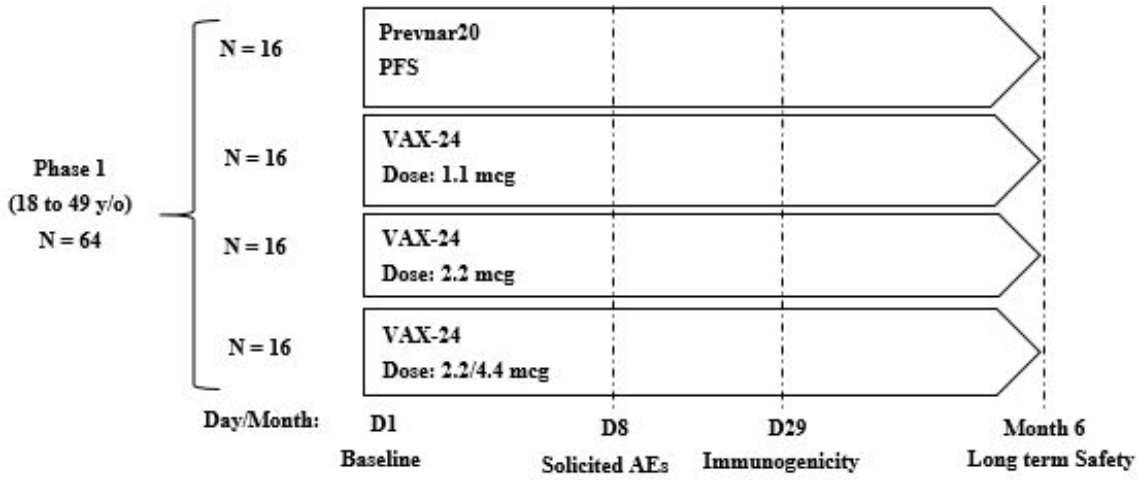
3 STUDY PLAN

3.1 Study Design

This Phase 1/2a parallel-group, randomized, observer-blind study is to be conducted in two populations of healthy adults, 18 to 49 years of age and 50 to 64 years of age. Subjects will be randomly assigned in a 1:1:1:1 ratio to receive either VAX-24 at one of three dose levels (1.1 mcg, 2.2 mcg, or 2.2/4.4 mcg) or the comparator (PCV20).

A Phase 1 cohort of 64 subjects (16 from each VAX-24 dose group and 16 from the comparator group) aged 18 to 49 years will be enrolled initially (Figure 1). Safety labs will be evaluated at screening for eligibility including pregnancy test for females of childbearing potential and safety labs will be repeated 28 days post-vaccination. Subjects will receive VAX-24 or PCV20 on Day 1. Solicited AEs will be collected for 7 days post-vaccination and unsolicited safety information for 28 days post-vaccination, with safety data (limited to SAEs, NOCIs, and MAAEs) collected up to 6 months post-vaccination. All the subjects in this age group will have blood samples drawn for safety labs at Screening and Day 29 (refer to Section 5.6). A defined safety review of data (AEs) through 7 days post-vaccination will occur by an independent data monitoring committee (DMC) before proceeding with enrollment of the Phase 2 subjects.

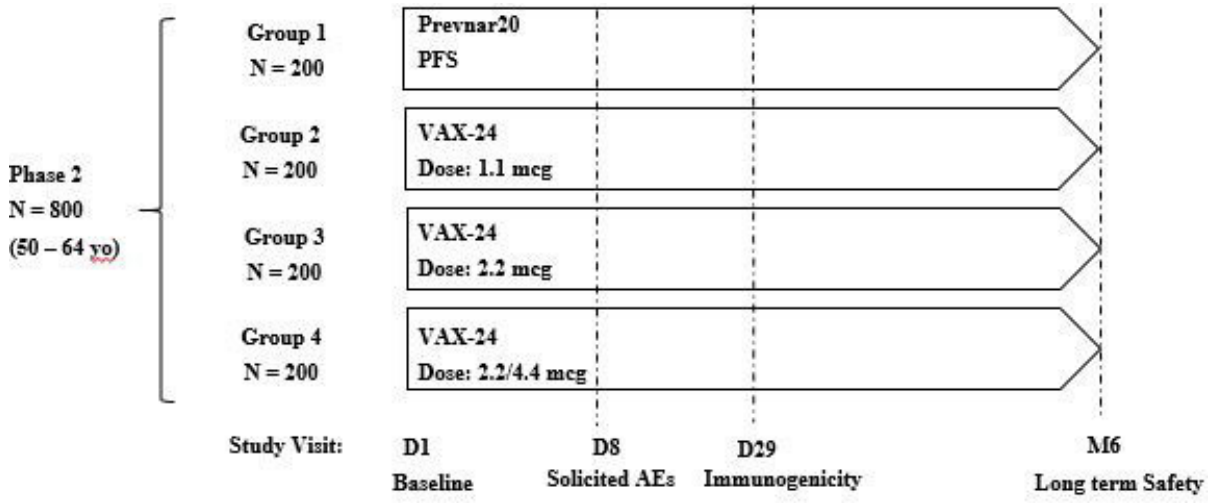
Figure 1 Study Schema for Subjects 18 to 49 Years of Age



A Phase 2 cohort of 800 subjects in the 50-to-64-year-old age range (200 in each arm) will be split into 4 groups (Figure 2). A minimum of 100 of the 800 subjects will be aged 60 to 64 years. Solicited AEs will be collected for 7 days post-vaccination and unsolicited safety information for 28 days post-vaccination, with SAEs, NOCIs, and MAAEs collected up to 6 months post-

vaccination. All the subjects in this age group will have blood samples drawn for safety labs and immunogenicity analysis (OPA and IgG) at Screening and Day 29 (refer to Section 5.6).

Figure 2 Study Schema for Subjects 50 to 64 Years of Age



Approximately 100 subjects aged 50 to 64 years will be consented for additional blood collection, by a limited number of clinical sites. These subjects will have an additional 32 mL of blood collected per blood draw to be processed for peripheral blood mononuclear cells (PBMCs) to further characterize the immune response to VAX-24. Additional serum samples collected from all subjects aged 50 to 64 years may also be used for further characterization and validation of clinical assays.

3.2 Number of Study Participants

The study population will be composed of at least 864 healthy US adults who meet the eligibility criteria listed in Section 3.4.

Approximately 64 eligible subjects aged 18 to 49 and 800 subjects aged 50 to 64 years will be enrolled.

3.3 Estimated Study Duration

The Screening period is 30 days, treatment and observation period is from Day 1 to Day 29, and the follow-up period is through Day 180 (6 months from study vaccination). The maximum possible study duration for an individual is 210 days.

3.4 Study Population

3.4.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be enrolled:

1. Male or female age 18 to 49 years (inclusive) for the Phase 1 group, or 50 to 64 years (inclusive) for the Phase 2 group at the time of enrollment into the study.
2. Able and willing to complete the informed consent process.
3. Available for clinical follow-up through the last study visit at 6 months after the study vaccination.
4. In good general health as determined by medical history, vital signs, physical examination, and clinical judgment of the investigator.
5. Screening laboratory values must be within the central laboratory normal limits[1] prior to study enrollment. Minor abnormalities are considered acceptable if not clinically significant.

   Note: Laboratory values lower than the normal range may be acceptable if the Principal Investigator or a designated licensed clinician determines that these laboratory findings are not clinically significant. The HIV 1/2 antibody/antigen test, Hepatitis B surface antigen (HBsAg), and Hepatitis C virus (HCV) antibody must be non-reactive.
6. Willing to have blood samples collected, stored indefinitely, and used for research purposes.
7. Able to provide proof of identity to the satisfaction of the study staff completing the enrollment process.
8. Negative pregnancy test (urine and serum) for women of childbearing potential. Non-pregnant, non-lactating females must also meet one of the following criteria: (a) no reproductive potential because of menopause (one year without menses) or because of a hysterectomy, bilateral oophorectomy, or tubal ligation; (b) subject agrees to be heterosexually inactive at least 14 days prior to vaccination and throughout the duration of the study; or (c) agrees to consistently practice contraception at least 7 days prior to enrollment and throughout the duration of the study by one of the following methods: condoms, male or female, with or without a spermicide, diaphragm or cervical cap with spermicide, intrauterine device, contraceptive pills or patch, Norplant, Depo-Provera, or other FDA approved contraceptive method, or a female with a male partner that has previously undergone a vasectomy.

[1] See Central Laboratory Manual for normal values.

3.4.2 Exclusion Criteria

Subjects who meet any of the following criteria cannot be enrolled:

1. Previous pneumococcal disease (either confirmed or by self-reporting).
2. Previous receipt of a licensed or investigational pneumococcal vaccine.
3. Receipt of any investigational study product within 30 days prior to enrollment into the study, currently participating in another interventional investigational study, or having plans to receive another investigational product(s) while on study.
4. Planned or actual administration of any licensed vaccine during the period starting 30 days before enrollment into the study through Day 29.
5. Physical examination indicating any clinically significant medical condition.
6. Body Temperature > 38.0°C (> 100.4°F) or acute illness within 3 days prior to study vaccination (subject may be rescheduled).
7. Seropositive to HIV, HCV, or HBsAg.
8. History of severe allergic reaction with generalized urticaria, angioedema, or anaphylaxis.
9. Female who is breast-feeding or planning to become pregnant during study participation.
10. Bleeding disorder diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or bleeding difficulties with IM injections or blood draws.
11. Any other chronic or clinically significant medical condition that, in the opinion of the investigator, would jeopardize the safety or rights of the subject or confound evaluation of the study vaccine, including but not limited to: diabetes mellitus type I, untreated hypertension, chronic hepatitis; or clinically significant forms of: drug or alcohol abuse, asthma, autoimmune disease, psychiatric disorders, heart disease, pulmonary disease, neurologic disease, cancer, or any known or suspected impairment immune function.
12. Any medical, psychiatric, or social condition that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a subject's ability to give informed consent.
13. Received blood or blood product (including Immune Globulin IV) within 90 days prior to enrollment into the study.
14. Received systemic corticosteroids for ≥ 14 consecutive days and has not completed treatment ≤30 days prior to enrollment into the study.

15. Receiving immunosuppressive therapy, including chemotherapeutic agents used to treat cancer or other conditions, immunostimulants, and treatments associated with organ or bone marrow transplantation, or autoimmune disease.
16. History of malignancy ≤5 years before enrollment, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

4 STUDY VACCINE

4.1 Investigational Vaccine (VAX-24)

VAX-24 is the Sponsor's research name for a Pneumococcal Conjugate Vaccine. VAX-24 consists of capsular polysaccharide antigens of *Streptococcus pneumoniae (S. pneumoniae)* serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23F, and 33F, with each of the 24 polysaccharides (one from each serotype) individually conjugated in a site-specific manner to a proprietary non-toxic diphtheria carrier protein referred to as eCRM, and mixed with ALPO.

[redacted]

Each vial is filled to deliver a single 0.5 mL (extractable volume) dose of VAX-24 vaccine for IM administration, with no preservative.VAX-24 is manufactured by Laboratoire Baccinex (Switzerland) and will be supplied at three strengths in single-use 2 mL glass vials. The vial is sealed with a 13 mm gray bromo butyl rubber stopper with FluroTec® coating on the side in contact with VAX-24 DP. The stopper is capped with a 13 mm crimped aluminum seal with a flip-off white cap for Low strength, a blue cap for Mid strength, and a green cap for the Mixed strength.

The three different strengths of VAX-24 will be identified as:

- Low, 1.1 mcg of Total PS/dose per serotype
- Mid, 2.2 mcg of Total PS/dose per serotype
- Mixed, 2.2 or 4.4 mcg of Total PS/dose per serotype. Conjugate Drug Substance serotypes 3, 6B, 7F, 9V, 18C, 19A, and 19F are present at the higher level, with the other 17 serotypes present at the lower level.

The vaccine must be stored in a temperature-controlled refrigerator at 2°C to 8°C with controlled, limited access, and accessible to authorized personnel only. The temperature should be monitored by checking and recording current and maximum/minimum temperature readings inside the vaccine storage unit at least once each working day.

4.1.1 Active Comparator

Prevnar 20™ (PCV20), 20-valent pneumococcal conjugate vaccine is a sterile suspension of saccharides of the capsular antigens of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F individually linked to non-toxic diphtheria CRM197 protein. PCV20 is manufactured by Wyeth Pharmaceuticals, LLC (subsidiary of Pfizer Inc.) and is commercially available in the US. Each 0.5 mL dose of the vaccine is formulated to contain approximately 2.2 mcg of each *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F; 4.4 mcg of the

polysaccharide from serotype 6B; 51 mcg CRM197 carrier protein; and 100 mcg polysorbate 80, 295 mcg succinate buffer, 4.4 mg sodium chloride, and 125 mcg aluminum as aluminum phosphate adjuvant. PCV20 pre-filled syringe (PFS) are to be stored at 2°C to 8°C (36°F to 46°F), as required by the manufacturer.

Refer to PCV20 Package Insert for clinical dosage and administration, storage and handling, contraindications, warnings and precautions, and summary of clinical trial results.

4.1.2 Other Supplies

The following supplies are provided by the Sponsor for preparation and administration of study vaccine:

- 1 mL BD Luer-Lok™ Syringe sterile, single use polycarbonate
- 25 Gauge BD™ Needle 1 inch single use, sterile
- 25 Gauge BD™ Needle 1 1/2 inch single use, sterile

4.2 Dose Preparation of Study Vaccines

A central supply depot will provide study vaccines and ancillary supplies.

Unblinded site personnel will manage all aspects of the vaccine inventory; prepare the vaccine for administration; administer the vaccine and active comparator to study subjects; and store and monitor the vaccine in a secure area and maintain all accountability documentation. All study site personnel who complete subject assessments will be blinded to the vaccines being administered to study subjects. Unblinded site personnel will be trained in all aspects of vaccine management, preparation, and administration, and will be provided a Pharmacy Manual regarding such procedures.

All study vaccines are parenteral drug products that should be inspected visually for particulate matter and discoloration prior to administration. The product should not be used if particulate matter or discoloration is found. VAX-24 and PCV20 are suspensions containing ALPO and should be shaken vigorously immediately prior to use to obtain a homogenous, white suspension in the vaccine container. The vaccines should not be used if they cannot be resuspended.

All VAX-24 doses are to be withdrawn into Sponsor-provided syringes using sterile technique. No dilution or reconstitution is necessary. VAX-24 vial must be brought to room temperature and administered ≥ 10 minutes and ≤ 60 minutes. Once VAX-24 is withdrawn into a syringe, the dose must be administered within ≤ 60 minutes. Detailed instructions on packaging, preparation, administration, and accountability are found in the VAX24-101 Pharmacy Manual.

PCV20 will be supplied to the clinical sites as single-use PFS packaged by the manufacturer. PCV20 should be administered by IM injection as soon as possible after being removed from

refrigeration. Preparation and administration instructions are found in the PCV20 Prescribing Information (manufacturer's package insert) and should be adhered to.

Each vaccine is administered IM in the deltoid muscle of the upper arm as a single dose of VAX-24 or PCV20.

4.3 Accountability Procedures for Study Vaccines

It is the responsibility of the Investigator to supervise accurate monitoring of the receipt, storage, dispensing and accounting of all study material according to accepted industry practice. Sites must maintain and retain accurate, original site records of study material inventory as well as copies of all invoices of study material shipments and records of study material distribution.

Drug accountability information will be collected in electronic source document format for tracking study vaccines (eg, date material was received, dispensed to individual subjects, and amount used and unused on site etc).

Each site must keep all used and unused study material until the unblinded CRA has performed vaccine accountability and arranges return to the central repository vendor or gives instruction for used vaccine disposal. Expired vaccine should be separately quarantined until the unblinded CRA has completed accountability monitoring.

Shipment of vaccine will be contingent on enrollment at the study sites. Detailed instructions on packaging, preparation, administration, and accountability are found in the VAX24-101 Pharmacy Manual.

5 STUDY PROCEDURES

Source documents and source data will be captured electronically, meeting the same elements of data quality and integrity (ALCOA: attributable, legible, contemporaneous, original, and accurate) as paper records. Data will be collected into a fully validated system, with changes to data captured by automatic audit trail. The clinical trial site will use their own tablets or laptops to directly record subject data and clinical observations into electronic forms. Designated site staff will receive access to the system after appropriate training. As the trial uses electronic source documents as the original point of data capture, there is no additional data transcription step for the site to enter the CRF data into the application, except for the signed informed consent form (ICF).

Some data may be captured via paper and subsequently transcribed into the eSource system. These source data will be verified by the clinical research associate and the location of the source data (ie, paper, local electronic system, etc) documented before the start of the trial. Copies of the paper source records will be uploaded into the eSource system for real-time access.

Remote monitoring of original electronic source records will be performed, but on-site monitoring would occur for review of any paper source documents and their transcription into the system, etc.

5.1 Informed Consent

The Investigator must obtain informed consent from study subjects at the Screening visit prior to starting any study-related activities. All prospective subjects must sign and date an Institutional Review Board (IRB)-approved ICF. For further details on informed consent, refer to Section 10.3.

5.2 Screening

Screening procedures are listed in the Schedule of Events (APPENDIX A).

Upon entry of a subject into the Screening Form within the electronic data capture (EDC) system, each Subject will be automatically assigned a unique Subject identifier. This Subject ID will be in the following format:

Each subject who signs an ICF will receive a sequential three-digit identification number unique to the site (eg, 001, 002…). When screening information is subsequently entered into the EDC, each subject will be assigned a subject identification number with the following format:

VAX24-101 ─ two-digit site number ─ three-digit identification number

An example of a subject identification number is: VAX24-101 – 01 – 001. Subject numbers will also be sequential since screen-failed subjects will be entered into the EDC system.

[redacted]

Each site is required to record the reason(s) for screen failure for all subjects who receive a subject identification number within the EDC system. Sites may elect to use a pre-screening consent form, and maintain a pre-screening log for those subjects contacted for the study and will provide that log to the Sponsor or designee upon request.

Re-screening

A subject who meets exclusion criterion of having a current acute febrile illness at the time of scheduled enrollment may be re-screened after resolution of the acute illness. A subject who meets exclusion criteria of taking an investigational product, licensed vaccines, or medications (ie, systemic corticosteroid) within 30 days (or blood or blood product within 90 days) prior to Day 1 may be re-screened after the appropriate duration has passed. If an eligible subject is not able to be randomized and treated within 30 days of the Screening period, all screening procedures must be conducted again, including re-consenting and use of a new subject ID number. A subject may be re-screened one time only. Re-screening is not otherwise permitted.

If a subject is re-screened, a new subject number will be assigned as they are entered into the EDC for a new Screening visit and the previous subject number will be captured in the source file of the newly assigned subject number.

5.3 Medical History

Medical history information will be collected from subjects at the Screening Visit and confirmed at the Day 1 (Baseline) Visit. Medical history will include (but not be limited to) demographic information, current and past medical conditions, and prior and concomitant medications taken within 30 days prior to Day 1, including history of vaccinations.

In consideration of the availability of commercial pneumococcal vaccines and ongoing investigational vaccine clinical research, the history of pneumococcal vaccination must be collected and, if the subject's medical records and/or state-mandated vaccine registry are available, the site is required to maintain this documentation as part of the eligibility review.

5.4 Physical Examination

A complete physical examination will be performed on subjects during the Screening visit.

The examination should include:

- Height

- Body weight
- Vital signs
- General appearance
- Eyes-ears-nose-throat
- Head-neck
- Lungs-chest
- Heart
- Abdomen
- Musculoskeletal
- Lymph nodes
- Skin
- Extremities
- Neurological

A physical exam may be performed on subjects at additional time points if indicated by AE reporting.

5.5 Vital Signs

Vital signs collected from subjects will include blood pressure, heart rate, respiratory rate, and oral temperature. The first set of Screening vitals are to be collected for inclusion of the subject into the study. Repeat measurements on abnormal vital parameters are allowed one additional time for inclusion into the study. After Day 1, abnormal vital signs can be repeated for confirmation of clinical significance. Vital signs should be taken after at least 5 minutes in supine position.

5.6 Laboratory Tests

5.6.1 Blood Volume

Blood is collected by venipuncture, in the appropriate blood container tubes according to the schedule of sample collection shown in APPENDIX A and Table 3.

. The maximum volume of blood taken from a subject is up to ~54 mL, [redacted]
Phlebotomy will observe the American Red Cross limit of no more than 450 mL in any 8-week period.

Unscheduled laboratory tests may be performed if indicated by a change in medical condition (including clinically significant abnormal values). The volume to be collected will be appropriate to the tests performed.

NOTE: ALL CRYOVIALS SHOULD BE FROZEN AND STORED AT -20° C OR COLDER AND SHIPPED ON DRY ICE.

Table 3 Blood Collections

Study Day	Blood volume (mL)	Laboratory Tests	Tube Type/volume	Minimum # of 2 mL cryovials
Screening -30 to -1	14	Hematology Clinical Chemistry Serology (HIV, HCV, HBsAg) Serum HCG (females only)	1 EDTA 2 mL 1 SST 3.5 mL 1 SST 3.5 mL (+5 mL for confirmation) Run off SST tube	N/A
Day 1	17 (or 33)*	Immunogenicity* [redacted] Additional research	2 SST 8.5 mL [redacted] Run off SST	8 [redacted] 4
Day 29	5.5 22.5 (or 38.5)*	Hematology Clinical Chemistry Immunogenicity* [redacted] Additional research	1 EDTA 2 mL 1 SST 3.5 mL 2 SST 8.5 mL [redacted] Run off SST tube	N/A N/A 8 [redacted] 4
Total: ~20 mL for subjects aged 18 to 49 years; ~54 mL for subjects aged 50 to 64 years; [redacted]				30

Abbreviations: HBsAg = Hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = Hepatitis C virus; HIV = human immunodeficiency virus; N/A = not applicable; [redacted]

* Immunogenicity and PBMC sample collection would only be collected from subjects aged 50 to 64 years old.

Samples are obtained during the trial according to APPENDIX A. At each time point, blood is collected in the appropriate blood tube(s).

Upon review and approval by the sponsor, the clinical sites will adhere to their standard operating procedures for collecting and storing PBMCs. Upon receipt at the central laboratory, these samples will be stored in liquid nitrogen.

To minimize the impact of lost or damaged shipments, the frozen serum [redacted] samples will be sent in separate consignments (primary, backup) to the central laboratory.

Further details regarding specimen collection, processing, and shipping will be provided in the Central Laboratory Manual.

5.6.2 Safety Laboratory Assessments

Biological samples will be collected for the following clinical laboratory tests and shipped to the central laboratory for analysis:

Hematology: Hemoglobin, White blood cell count (absolute), Neutrophils (absolute), Eosinophils (absolute), Platelet count

Clinical Chemistry: Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Bilirubin (total and direct), Blood urea nitrogen, Calcium, Carbon dioxide, Chloride, Cholesterol and triglycerides, Creatinine, Glucose (random), Gamma-glutamyl transferase (GGT), Lactate dehydrogenase, Phosphate, Potassium, Sodium, Total serum protein, Uric acid

Urinalysis: Specific gravity, pH, Glucose, Protein (Total), Ketones, Bilirubin, Urobilinogen, Hemoglobin, Leucocyte esterase, Nitrite

Serology: HIV 1/2 antibody/antigen test, HBsAg, Hepatitis C virus antibody (HCV Ab)

Pregnancy: Serum test at Screening visit only

Urine pregnancy tests will be conducted at the site using a dipstick before vaccination.

Screening safety lab results are required for subject eligibility in order to be enrolled in the study at Day 1. Screening safety labs will be used as baseline if a subject meets eligibility for enrollment into the study. Screening laboratory tests reported as minor abnormalities are considered acceptable if not clinically significant (eg, MCV). Repeating the screening tests once is permitted for out-of-range values, provided there is an alternative explanation for the out-of-range value. This alternative explanation should be documented in the subject's source documents.

Unscheduled laboratory tests will be performed if indicated by a change in medical condition (including clinically significant abnormal values). The volume to be collected will be appropriate to the tests performed. The toxicity grading scales for clinical laboratory values (FDA 2007) must be used when assigning severity to an out-of-range laboratory value; however, not all out of range laboratory values are considered AEs and need to be evaluated according to Section 7.1.1, Adverse Events.

Further details regarding specimen collection, processing, and shipping will be provided in the Central Laboratory Manual.

5.6.3 Immune Response Assessments

Serum antibody responses to pneumococcal polysaccharides induced by vaccination will be measured using 2 standard assays, OPA and multiplexed Meso Scale Discovery (MSD).

The OPA assay has been developed and qualified by Nexelis, a GCP-compliant central laboratory, to analyze the 24 polysaccharide antigens contained in VAX-24. The OPA assay has been consistently used as the method for measuring the functional capacity of pneumococcal antibodies, as antibodies to pneumococcal PS protect the host by opsonizing pneumococci (marking pneumococci for destruction) for phagocytosis (Burton and Nahm 2006).

The MSD assay has been developed and qualified by Nexelis to measure IgG responses against the 24 polysaccharide antigens contained in VAX-24. The MSD multiplex electrochemiluminescent assay is an immunoassay platform that allows simultaneous measurement of responses against multiple antigens and has been used to evaluate responses to various pneumococcal conjugate vaccines (Marchese 2009, Goldblatt 2011, Feyssaguet 2019, and Nolan 2020).

The immune responses (as assessed by OPA and IgG assays) against the 20 polysaccharide antigens common to PCV20 and VAX-24 (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F) will be compared in the various treatment groups (VAX-24 at 3 different dose levels, and the comparator vaccine), and the 4 incremental polysaccharide antigens contained in VAX-24 (2, 9N, 17F and 20B) will be evaluated separately.

Immunogenicity samples will be collected for subjects aged 50 to 64 years only. [redacted]

5.7 Pregnancy Testing and Contraception

Female subjects of childbearing potential will undergo a serum Human Chorionic Gonadotropin (HCG) pregnancy test at Screening and a urine pregnancy test prior to each injection. The subject must have a negative pregnancy test prior to study vaccine administration. The Investigator must report any pregnancies as described in Section 7.7.1. Female subjects of childbearing potential must also use an acceptable method of contraception from prior to Day 1 through Day 180 (throughout the study). The Investigator must confirm that contraception methods were initiated prior to Day 1 (eg, hormonal contraception) to be considered fully effective.

For reporting a pregnancy, refer to Section 7.7.1, Pregnancy.

5.8 Randomization

Subject eligibility will be confirmed and documented by the Investigator immediately prior to randomization of each subject.

Unblinded study staff will indicate on a Randomization eCRF within the EDC system that they want to generate a randomization number for the subject. When they indicate yes, a randomization number and treatment assignment will be generated from the EDC randomization module. The randomization number is separate from, and does not replace, the subject identification number which is assigned at Screening. The Unblinded Pharmacist or designee will prepare the treatment assigned and dispense the appropriate treatment to the Unblinded Administrator for administration.

Randomization will be 1:1:1:1 for the four treatment groups within each age group (18 to 49, 50 to 64). Within the 50 to 64 year group, subjects will be further stratified into two groups: 50 to 59 and 60 to 64 years. The total sample size expected within the 50 to 64 year age group is 800 subjects; there will be a minimum number of 100 subjects in the 60 to 64 year age group (25 per treatment arm). See Section 9.3 for further details on the sample sizes within each age group.

A subject will be considered enrolled once a randomization number has been assigned within the EDC system. The study will be conducted as an observer-blind study. Neither subjects, clinical site evaluators including the investigators, nor the Sponsor will know subjects' individual treatment assignments until all subjects have completed their participation in the study and the database has been cleaned and locked.

The following safeguards will be employed to reduce the risk of inadvertent unblinding:

- Each clinical site is required to have a blinding plan that outlines its process on blinding the subject in situations such as administration of IM injection with different syringe types, transfer of study vaccine to the clinic room for administration, providing initial training and reminders to the subjects to not disclose their experiences with the injections except with unblinded study staff.
- No Sponsor personnel other than the designated unblinded monitor(s) and third-party unblinded biostatistics and programming staff will have access to the randomization treatment assignments.
- Should any subject or blinded staff member become inadvertently unblinded, the Investigator will promptly (within 24 hours of the Investigator's awareness of the error) disclose the event to the Sponsor clinical study manager and medical monitor in a blinded fashion (disclosing only subject number, not treatment) so that corrective action can be initiated. The unblinding sequence of events will be documented as a protocol deviation and retained as source documents. See Section 5.15 for details on Emergency Unblinding.

5.9 Study Vaccine Administration

On Day 1 before study vaccine administration, the medical history, including physical exam (if indicated by updated medical history) and vital signs, and concomitant medications will be collected and updated in the subject file, serum [redacted] samples will be collected, and females of childbearing potential must have a negative urine pregnancy test. Immediately prior to study vaccine administration, staff should recheck subject eligibility. Once these procedures are performed, study vaccine will be administered. All doses of study vaccine are 0.5 mL in volume and are administered by IM injection with a Sponsor-provided 1 mL syringe and 25 gauge 1" (or 1.5", at the Investigator's discretion) needle as described above or PCV20 PFS, using universal precautions and sterile technique. All injections will be administered into the deltoid muscle. Injections will be administered by an unblinded staff member delegated by the Investigator.

5.10 Acute Observation

The subject will be monitored by blinded study staff for signs of an acute adverse reaction and vital signs will be obtained at least 30 minutes after injection. If a subject reports any symptom collected as Solicited AEs for this study, the blinded study staff will advise them to record the details in their electronic diary at the end of their day.

Allergic reactions to the study vaccine are possible; therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a medically qualified study team member trained to recognize and treat anaphylaxis must be present in the clinic during the entire post-dosing monitoring period.

5.11 Solicited Adverse Events

Solicited AEs will be collected for 7 days after vaccine administration, starting on Day 1. Solicited AEs for this study are local events of pain, erythema (redness) and edema (swelling) at the injection site, and systemic events of oral temperature ≥ 100.4ºF, fatigue, headache, muscle pain, and joint pain.

Subjects will be trained to complete a diary via IBM's ePRO system. This system is accessed via a secure URL and will be used to observe, measure, and record these solicited AEs. A digital thermometer will be provided to the subject to measure oral temperature each day, and it is to be recorded daily in the diary. To record injection site local reaction, a ruler will be provided to the subject to measure the diameter of redness and swelling at the largest point of the reaction each day; it is to be recorded daily in the diary.

Study staff will be provided with a Reference Guide for instructing subjects on accessing the IBM ePRO system. Each user will be provided with login credentials and a temporary password. The IBM ePRO system is web-based and accessed via a secure URL.

Study staff will review the signs and symptoms recorded in the diary and the action taken for the event during the subject's clinic visit. The electronic diary will serve as the primary source document and data will be automatically integrated into the subject visit Solicited AE form in the EDC platform for site staff view-only access. The Investigator will then assess all recorded solicited events for severity and relatedness. Severity will be graded according to the FDA Toxicity Grading Scale (FDA 2007). The results of the Investigator's assessment, if different from the subject's entry, will be recorded in a separate field specified for Investigators within the EDC platform. For solicited injection site reactions, the relationship to study vaccine will be automatically recorded to be probably related, however, the Investigator will determine the relationship for each systemic solicited reaction.

Symptoms continuing beyond the solicited AE collection period (7 days following each injection) will be collected and recorded as an unsolicited AE in the electronic source document (eSD).

5.12 Unsolicited Adverse Events

Unsolicited AEs (any AEs not listed in the diary) will be collected for this study. Details regarding definitions, evaluation, reporting periods, and documentation are outlined in Section 7.

5.13 Prior and Concomitant Medications and Procedures

At the Screening visit, the details of prior and concomitant medications and procedures (through 30 days prior to Day 1) usage will be collected, including history of vaccinations. From Day 1 through Day 29, the details of all concomitant medications and procedures including those associated with solicited AEs and unsolicited AEs will be collected.

Concomitant medications and procedures associated with an SAE, NOCIs, and MAAE will be collected through the end of the study.

5.14 Prohibited Medications and Therapies

Subjects must not have received or be planning to receive:

- Licensed or investigational pneumococcal (pneumonia) vaccine.
- Investigational agents or study product from 30 days prior to Day 1 through the duration of the study.
- Other (non-pneumococcal) licensed vaccines from 30 days prior to Day 1 through Day 29.
- Blood or blood product (including IGIV) from 90 days prior to Day 1 through the duration of the study.
- Systemic immunosuppressant therapy (eg, chemotherapeutics) and immunostimulants.

- Immunomodulatory medications (eg, oral corticosteroids) from 30 days prior to Day 1 or received systemic corticosteroids exceeding physiologic replacement doses within 14 days prior to study vaccination through Day 29.

The history of all prohibited medications at any time during study participation (regardless of association with an AE) will be collected.

5.15 Emergency Unblinding

The Investigator may obtain a treatment assignment for a study subject only in the case of a medical emergency in which knowledge of the treatment is necessary for the management of an AE.

The Investigator must notify the Medical Monitor (and as backup, Medical Director) no later than 24 hours following Unblinding. Additional details for this unblinding process are provided in the Pharmacy Manual.

5.16 Protocol Deviations

The Investigator and delegated staff are responsible for conducting the study in accordance with the protocol. Any deviation from the protocol must be documented in the study file. In addition, deviations must be reported to the IRB as applicable. Subject-specific deviations must be recorded in the subject's source documents. The Sponsor will review all protocol deviations on an ongoing basis and will be responsible for categorizing protocol deviations as exclusionary or not.

5.17 Dosing Errors

The Investigator or designee must report any error in the dosing of study vaccine to the site-assigned unblinded CRA and Medical Monitor or designee within 24 hours of the Investigator's awareness of the error. Additional information regarding the dosing error may be provided as a follow-up report. A dosing error without signs or symptoms is not considered an AE but may be determined to be an important protocol deviation and investigated further.

5.18 Study Completion: For Individual Subjects

An individual subject is considered to complete study participation after completion of the Day 180 visit and completion of any required safety follow-up.

5.19 Early Discontinuation

An individual subject is considered to undergo Early Discontinuation if the subject stops study participation before the Day 180 visit.

An enrolled subject may voluntarily withdraw consent for further participation at any time before the Day 180 visit. The Investigator will request (but cannot require) such subjects to provide the reason(s) for withdrawal of consent and to undergo an Early Discontinuation visit.

In addition, the Investigator, at his or her discretion, may withdraw a subject from further participation in the study. Criteria for withdrawal by the Investigator include:

- Noncompliance with the protocol
- Pregnancy
- Immediate hypersensitivity reaction associated with a study injection
- Loss to follow-up – requires documentation of at least 3 unsuccessful attempts to contact the subject. Lost to follow-up will be determined after the date of the subject's projected last visit.
- Other reason(s) which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject.

The Investigator or designee must report any early discontinuation for safety reasons to the Medical Monitor or designee within 24 hours of discontinuation. Additional information regarding ongoing AEs may be provided as a follow-up report.

5.20 Subject Replacement

Subjects who undergo Early Discontinuation after randomization and before Day 1 vaccine administration may be replaced by randomizing an additional subject at the Sponsor's discretion. Subjects who undergo Early Discontinuation after study vaccination will not be replaced.

5.21 Study Completion: Overall

The study is planned to be completed after all subjects have completed the Day 180 (Month 6) visit (or Early Discontinuation, as appropriate), all necessary safety follow-up has been completed, and all data have been monitored and queries have been resolved. The Sponsor reserves the right to terminate the study prior to the planned study completion.

6 STUDY PROCEDURES BY VISIT

The overall summary of procedures and assessments by visit is given in the Schedule of Events in APPENDIX A and Guidance for Industry, Toxicity Grading Scale, 2007. All visits are relative to the day of vaccine administration, Day 1. Acceptable time windows for the visit schedule are indicated.

6.1 Scheduled Study Visits

6.1.1 Screening (-30 days to Day 1)

The following will take place during the visit, which will occur within 30 days prior to Day 1:

- Informed consent
- Demographics
- Review of eligibility criteria
- Medical history
- Physical exam
- Vital signs
- Biological specimen collection for clinical laboratory tests:
    - Blood for hematology and chemistry
    - Serum for infectious disease screening
    - Serum for HCG pregnancy test (for females of childbearing potential)
    - Urine for urinalysis
- Prior and concomitant medications

6.1.2 Day 1

The following will take place during the visit and ***prior*** to study vaccine administration:

- Updated medical history
- Confirmation Inclusion/Exclusion criteria are met
- Targeted physical examination, if indicated by updated medical history
- Vital signs
- Biological specimen collection (pre-dose) for clinical laboratory tests:
    - Serum samples for immunogenicity (subjects aged 50 to 64 years)
    - [redacted]

- Urine pregnancy test (females of childbearing potential)
- Prior and concomitant medications
- Randomization

All eligible, consented, and randomized subjects will be vaccinated at the Day 1 Baseline visit.

- Study vaccine administration, either VAX-24 or PCV20

The following will take place during the visit and ***after*** study vaccine administration:

- Acute observation for at least 30 minutes after vaccine administration
- Vital signs collected at least 30 minutes after vaccine administration
- AE (solicited and unsolicited) and SAE evaluation
- Concomitant medications
- Instructions on completion of an electronic diary, use of a ruler and thermometer

6.1.3 Day 8 (+3 days)

The following procedures will take place at this visit:

- Visual inspection of injection site location
- Review of diary data with the subject; Investigator's assessment of severity and relationship to study vaccine
- Concomitant medications
- AE (solicited and unsolicited) and SAE evaluation

6.1.4 Day 15 (+3 days)

This visit is a follow-up phone call for safety evaluation. The following procedures will take place at this visit:

- Concomitant medications
- AE (unsolicited) and SAE evaluation

6.1.5 Day 29 (± 3 days)

The following procedures will take place during this visit:

- Concomitant medications
- AE (unsolicited) and SAE evaluation
- Biological specimen collection for clinical laboratory tests:

- Blood for hematology and chemistry
- Urine for urinalysis
- Serum for immunogenicity (subjects aged 50 to 64 years)
- [redacted]

6.1.6 Months 3, 4, 5, 6 (90 to 180 days after Day 1 (± 5 days))

These visits are follow-up phone calls for safety evaluation. The following procedures will take place at each visit:

- SAE, NOCI, and MAAE evaluation
- Concomitant medications or vaccines potentially related to SAE, NOCI, MAAE, or prohibited medications

6.2 Early Discontinuation Visit

All subjects who discontinue study participation before the Month 6 visit will be requested to undergo an Early Discontinuation visit.

If the visit occurs within 7 days after study vaccine administration, the following will be conducted:

- Review of diary data with the subject; Investigator's assessment of severity and relationship to study vaccine
- Review of unsolicited AEs and SAEs
- Review of concomitant medications associated with new or ongoing AEs and any SAEs
- Urine pregnancy test for females of child-bearing potential
- Biological specimen collection for clinical laboratory tests:
  - Blood for hematology and chemistry
  - Urine for urinalysis
  - Serum for immunogenicity (subjects aged 50 to 64 years)
  - [redacted]

If the visit occurs after Day 8 and before Day 29, the following will be conducted:

- Review AEs and SAEs
- Review concomitant medications associated with new or ongoing AEs and any SAEs

- Urine pregnancy test for females of child-bearing potential
- Biological specimen collection for clinical laboratory tests:
  - Blood for hematology and chemistry
  - Urine for urinalysis
  - Serum for immunogenicity (subjects aged 50 to 64 years)

[redacted]

6.3 Unscheduled Visits

Any study procedure, excluding study vaccination, may be conducted at an unscheduled visit as needed. Examples include repeat specimen collection and additional safety follow-up for an AE.

7 SAFETY

7.1 Definitions

7.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a study subject, regardless of the suspected causal relationship with study vaccine.

The definition of an AE includes:

- A new-onset symptom or disease
- An exacerbation of a pre-existing symptom or disease
- A new-onset laboratory abnormality considered by the Investigator to be clinically significant
- A new-onset symptom or disease that occurs as a result of a protocol-specified procedure

The definition of an AE does **not** include:

- A pre-existing symptom or disease that does not worsen during the study (even if first disclosed by the subject after the start of the study)
- A medical or surgical intervention such as surgery, endoscopy, tooth extraction, or transfusion (although the condition leading to the procedure or a complication from the procedure may be an AE)
- An uncomplicated pregnancy
- A dosing error without any resulting signs or symptoms
- Any other situation where an untoward medical occurrence has not occurred (eg, hospitalization for cosmetic elective surgery or social admissions)

The definition of a treatment emergent AE (TEAE) is an event that occurs after vaccination and within the 28 days after vaccination (ie, excluding those after a subject has given informed consent, but before vaccination).

The definition of a NOCI includes:

A new-onset of chronic illness is a disease or condition, that is newly diagnosed, requires ongoing medical attention and/or limits activity of daily living, eg, heart disease, cancer, diabetes.

The Investigator will attempt to establish a diagnosis based on signs, symptoms, and other clinical information. Whenever possible, the Investigator will report an AE as a diagnosis rather than one or more signs or symptoms. If a clinically significant laboratory abnormality meets the

definition of an AE, a diagnosis or clinical signs and symptoms rather than the abnormal laboratory finding should be reported if possible. If no diagnosis is known and clinical signs and symptoms are not present, but the laboratory abnormality is clinically significant by itself, then it should be reported as the AE.

7.1.2 Solicited Adverse Event

A solicited AE is a protocol-specified AE about which the Investigator or designee proactively asks the subject during a protocol-specified time period. Solicited AEs for this study are local events of pain, erythema (redness) and edema (swelling) at the injection site, and systemic events of fever (oral temperature ≥ 100.4ºF), fatigue, headache, muscle pain, and joint pain.

7.1.3 Unsolicited Adverse Event

An unsolicited AE is an AE that is spontaneously reported by the subject or discovered by the Investigator. New onset of chronic illness(s) would be recorded as part of the collection of unsolicited AEs as specified in the visit procedures. Unsolicited AEs will be collected separately from solicited AEs.

7.1.4 Serious Adverse Event

An SAE is an AE (either solicited or unsolicited) which meets any of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongs an existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Important medical event that may jeopardize the patient or subject and/or may require medical or surgical intervention to prevent one of the above outcomes

The Investigator will evaluate all AEs for seriousness using the above criteria.

“Life-threatening” means that, in the opinion of the Investigator, the subject was at immediate risk of death from the event as it occurred. It does not mean that the event might have caused death had it occurred in a more severe form.

Hospitalization for observation or for elective treatment of a pre-existing condition that did not worsen during the study is not considered an SAE.

Important medical events may be considered serious at the discretion of the Investigator.

[redacted]

7.2 Severity Grading

The Investigator will grade all AEs for severity. AEs listed in the Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007 will be graded according to the criteria in the table. AEs not listed in the Toxicity Grading Scale will be graded as follows:

- Mild (Grade 1) – No interference with activity
- Moderate (Grade 2) – Some interference with activity
- Severe (Grade 3) – Significant; prevents daily activity
- Potentially Life-Threatening (Grade 4) – ER visit or hospitalization

7.3 Causality Assessment

The Investigator will assess all AEs, including solicited AEs, for causality (relationship to study vaccine), assigning one of these three categories: Not Related, Possibly Related, or Probably Related.

An AE will be considered "Not Related" to study vaccine if **any** of the following conditions are met:

- An unreasonable temporal relationship between administration of the study vaccine and the onset of the AE (eg, the event occurred either before, or too long after, administration of the study vaccine for it to be considered related);
- A causal relationship between the study vaccine and the AE is biologically implausible (eg, injury as a passenger in an automobile accident);
- A clear alternative causality for the AE is present (eg, typical adverse reaction to a concomitant medication).

An AE will be considered "possibly related" if there is a reasonable possibility that the AE may have been caused by the study vaccine.

- A single occurrence of an event that is uncommon and known to be strongly associated with vaccine exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with vaccine exposure, but is otherwise uncommon in the population exposed to the vaccine (eg, tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of vaccine administration) that

indicates those events occur more frequently in the vaccine treatment group than in a concurrent or historical control group

An AE will be considered "Probably related" if there is evidence that the AE was caused by the study vaccine.

7.4 Follow-up of Adverse Events

The Investigator must follow all AEs until resolution, until the condition stabilizes or is no longer clinically significant, or until the subject is lost to follow-up.

The Investigator is responsible for ensuring the conduct of any supplemental investigations considered necessary to evaluate the AE. These may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

In the event of a non-fatal SAE, subjects will be instructed to contact the Investigator (or designee) immediately. All subjects experiencing an SAE will be evaluated by the Investigator or designee as soon as is feasible following the report of the SAE by the subject. In the event of a fatal SAE, the Investigator must provide the Sponsor with any available post-mortem findings, including histopathology.

Additionally, the Sponsor may request that the Investigator perform or arrange for the conduct of supplemental investigations for one or more AEs.

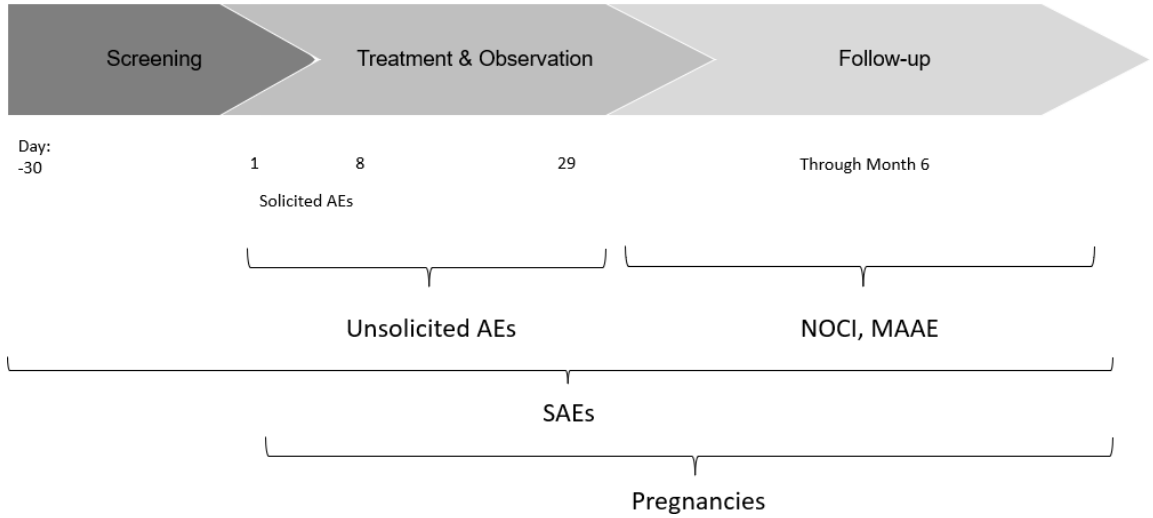
7.5 Reporting of Adverse Events

7.5.1 Reporting Periods

The four reporting periods for solicited AEs begin immediately after study vaccine administration and continue for 7 days after the injection. The reporting period for unsolicited AEs is immediately after study vaccine administration on Day 1, continuing through Day 29. AEs that correspond to solicited AE terms but occur outside of (or continue past) the solicited AE collection periods are also collected through the unsolicited AE reporting periods. The reporting period for SAEs begins at the time of informed consent and continues for the duration of study participation.

A summary of the reporting periods is presented in Figure 3.

Figure 3 Safety Events Reporting Periods



7.5.2 Documentation

The Investigator or designee will document all AEs in the subject's source documents and solicited AEs into the source document file within 24 hours of awareness.

All AEs should include:

- Event term
- Start and stop date
- Severity
- Seriousness (Yes/No) and if Yes, which Seriousness criteria were met
- Relationship to Study Vaccine
- Action taken in response to the AE
- Action taken with Study Vaccine

7.6 SAE Reporting

The Investigator or designee must report all SAEs to Vaxcyte Clinical Safety Team within 24 hours of becoming aware of the event, using the SAE Form. The Investigator or designee must also enter SAEs into the eSD.

E-mail transmission of the SAE Report Form is the preferred method to transmit thisinformation to the Vaxcyte Clinical Safety Team. If initial notification is provided via telephone, this does

not replace the need for the investigator to complete and sign the SAE Report Form within the designated reporting time frames.

Communication Methods to the Vaxcyte Clinical Safety Team:

E-mail (primary): clinicalsafety@vaxcyte.com

Telephone (emergency): 1 (650) 275-4554

The SAE Form should be completed as thoroughly as possible and be signed by the Investigator or designee before reporting to Vaxcyte. The SAE Form must include an assessment of causality and should include a preliminary diagnosis if possible. All SAEs assessed as not related must include an alternate causality.

In order to avoid delays in initial reporting, additional information regarding the SAE may be provided as a follow-up report. The Investigator may also modify the diagnosis, seriousness, and/or causality assessment based on this information.

Vaxcyte will notify the Investigator of SAEs that meet criteria for expedited reporting to regulatory authorities. The Investigator is responsible for notifying the applicable IRB of these events and adhering to any other applicable local reporting requirements.

The Sponsor will report AEs to FDA in accordance with 21 CFR 312.32. Specifically, the Sponsor will report unexpected fatal or life-threatening suspected adverse reactions no later than 7 days after initial receipt of the information, and serious and unexpected suspected adverse reactions (SUSARs) no later than 15 calendar days after determining that the information qualifies for expedited reporting.

It is also the responsibility of Vaxcyte to make the determination of which SAEs are SUSARs, as defined in 21 CFR 312.32.

- *Suspected adverse reaction* means any AE for which there is a reasonable possibility that the drug caused the AE.
- *Unexpected adverse reaction* means an AE that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

All SUSARs, as agreed upon by the IND Sponsor, will be reported to FDA. SUSARs will be provided to all participating Investigators.

7.7 Other Events Requiring Immediate Reporting

7.7.1 Pregnancy

The Investigator or designee must report all pregnancies to the Vaxcyte Clinical Safety Team within 24 hours of becoming aware of the pregnancy, using the Pregnancy Report Form. All pregnancies will be followed to outcome. Additional information regarding the pregnancy may be provided as a follow-up report.

An uncomplicated pregnancy is not considered an AE. Complications of pregnancy may qualify as AEs or SAEs and would therefore be documented and reported as specified above.

7.8 Medical Monitor

The Medical Monitor will be the first point of contact regarding safety and eligibility questions for the study and will work closely with the Medical Director to assess subject eligibility, AEs and SAEs that trigger the stopping and halting rules, and all other safety related questions from the sites.

[redacted]

The Sponsor Medical Director will provide oversight for the study, review blinded safety data, subject eligibility, and assess causality of SAEs on an ongoing basis.

[redacted]

7.9 Data Monitoring Committee

The DMC will consist of two persons (independent Subject Matter Experts) and an unblinded statistician to compile the data and present to the members. The DMC will independently review the 7 days post-vaccination unblinded safety data for the subjects aged 18 to 49 years before

advancing the study into the older adult population. Stopping rules will be observed during the active study vaccine administration periods (see Section 7.10) and the DMC will conduct ad hoc reviews if the study is paused, triggered by one of the Stopping Rules, in order to identify any emerging safety concerns.

The DMC will refer to the DMC Charter for procedures.

7.10 Study Stopping Rules

The rules governing the halting or stopping of the study vaccine administration at any time during the study are defined by age groups 18 to 49 and 50 to 64 years in the Phase 1 and Phase 2 segments of the clinical study, respectively. During the vaccination period(s), if any of the stopping rules are triggered, no further administration of study vaccine(s) will occur until safety data are reviewed by the DMC in communication with the Medical Director and the Investigator at the site where the event occurred, as needed. Study dosing may be resumed if the DMC determines it is safe to proceed with no modifications or with modifications to the protocol plans.

Phase 1: Subjects aged 18 to 49 years

- One (1) SAE regardless of relationship
- One (1) or more subjects with a Grade 4 (potentially life threatening) assessed as at least possibly related to investigational product
- Three or more subjects with a Grade 3 (severe) AE assessed as at least possibly related to investigational product

Phase 2: Subjects aged 50 to 64 years

- One (1) SAE assessed as at least possibly related to investigational product
- One (1) or more subjects with a Grade 4 (potentially life threatening) assessed as at least possibly related to investigational product
- Two or more subjects with the same or similar Grade 3 (severe) AE, including laboratory abnormalities, assessed as at least possibly related to investigational product other than solicited events
- Eight (8) or more subjects with the same or similar Grade 3 (severe) solicited AE

The appropriate regulatory authority will be informed in writing when either of the following occurs:

- Study dosing is stopped
- DMC has decided to resume or discontinue study activities

Enrollment may be resumed following review of available safety data by the Sponsor.

Vaxcyte clinical safety team will refer to the VAX24-102 Safety Medical Monitoring Plan for detailed procedures on stopping rule reporting and safety oversight for the study.

8 DATA HANDLING

8.1 Source Documentation

The Investigator must maintain source documentation of all study conduct data and observations relevant to the study. This source documentation includes, but is not limited to, ICFs, original medical records, progress notes from the Investigator and study staff, laboratory reports, diary for solicited AEs, and documentation of study vaccine accountability.

This study will not employ eCRFs but rather have the data fields incorporated into eSD within a validated system that is 21 CFR Part 11 compliant. All clinical information requested in this protocol will be recorded on these eSD. The only planned paper source documents will be the signed consent form and copies of medical records, and these can be uploaded as copies into the EDC platform. The Investigator is responsible for the adequacy and accuracy of all data entered on the eSD. The Investigator is also responsible for signing all eSD, after which they will be locked by the Sponsor to prevent further data entry or modification.

For further information on eSD, please refer to the eSD Completion Guidelines. Details on data handling will be described in the CRO Data Management Plan.

8.2 Retention of Study Documentation

The Investigator will maintain all study documentation, including copies of ICFs, eSD, and documentation of study vaccine accountability, for either 2 years following FDA or other regulatory approval of VAX-24, or 2 years after clinical development of VAX-24 is discontinued, unless a longer period is required by applicable law or regulation. The Investigator will destroy study documentation only upon instruction by the Sponsor and must notify the Sponsor upon completion of such destruction. Subject identity information will be maintained for 15 years unless a longer period is required by applicable law or regulation.

8.3 Data Monitoring

The Sponsor or designee will monitor completed eSD at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Investigator must make hard copy source documentation accessible to the Sponsor or designee as needed to verify the information in the eSD. The Investigator agrees to cooperate with the Sponsor or designee to ensure that any problems detected in the course of data monitoring are resolved.

8.4 Electronic Patient Reported Outcome Data

This study will employ electronic transfers of external diary data generated from subjects recording solicited AEs and actions taken for 7 days post-vaccination within a validated system

that is 21 CFR Part 11 compliant. The Investigator is responsible for the adequacy and accuracy of data associated with severity and relationship to study vaccine.

8.5 Laboratory Data

This study will employ electronic transfers of external laboratory data generated from clinical specimens collected by the Investigator. The Investigator is responsible for the adequacy and accuracy of data associated with collection of these specimens, and for determining clinical significance for all out of range values.

8.6 Audit Compliance

The Investigator must permit the Sponsor and/or designee, regulatory agencies, and/or the IRB direct access to facilities and study documentation for the purpose of auditing study conduct. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study.

9 STATISTICAL ANALYSIS

This Phase 1/2a study is designed to achieve both safety and immunogenicity objectives.

The primary objectives are to evaluate the safety of a single injection of VAX-24 at three dose levels, and to compare the safety of VAX-24 to that of PCV20 administered to two control groups: 1) subjects 18 to 49 years of age receiving PCV20; and 2) subjects 50 to 64 years of age receiving PCV20.

The secondary immunogenicity objectives are to assess the induction of OPA and IgG antibody responses by VAX-24 at three dose levels compared to the 20 PCV20 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F), as measured at 28 days after the injection (Day 29) and 4 non-PCV20 serotypes (2, 9N, 17F, 20B), measured at 28 days after the injection (Day 29) for subjects aged 50 to 64 years.

Endpoints will be analyzed by age group (18 to 49, 50 to 59, 60 to 64, and 50 to 64 years of age). Safety will also be summarized for all subjects combined (18 to 64 years of age).

A statistical analysis plan will be generated and approved prior to the data freeze and treatment group unblinding for the primary safety and secondary immunogenicity endpoints through Day 29 visits. Individual treatment unblinding will occur after the data is cleaned through the last Month 6 visits and final database lock. A single completed Clinical Study Report (CSR) will summarize safety findings through Month 6 for all 864 subjects and immunogenicity for 800 subjects 50 to 64 years of age.

9.1 Sample Size Calculation

For subjects 18 to 49 years of age, sample size is not driven by statistical assumptions for formal hypothesis testing but was based on the safety objective for the study. With 16 subjects, events that occur at a frequency of 15% or more will be detected with at least 92% probability and events that occur at a frequency of 10% or more will be detected with 81% probability. Therefore 16 subjects in each treatment group are proposed as the basis for the number of subjects in whom to conduct the first safety assessment.

For subjects 50 to 64 years of age, sample size is not based on statistical justification. A total of 800 subjects should provide sufficient information to assess safety and immunogenicity in the 50 to 59 and 60 to 64 age groups. The sample size will also be adequate to plan future studies.

9.2 Treatment Period

The Treatment period begins at the time of study vaccine administration and extends through the Day 29 visit. The Follow-up period spans the time following the Day 29 visit through Day 180 (6 months after study vaccine administration).

9.3 Treatment Groups

Subjects will be randomized into 8 treatment groups as displayed in Table 4.

Table 4 Treatment Groups

Treatment Group	Age Cohort	N	Treatment Administered (VAX-24, mcg Total PS/dose per serotype; PCV20)
			Day 1
1	18 to 49	16	VAX-24, 1.1 mcg
2	18 to 49	16	VAX-24, 2.2 mcg
3	18 to 49	16	VAX-24, 2.2/4.4 mcg
4	18 to 49	16	PCV20
5	50 to 64	200	VAX-24, 1.1 mcg
6	50 to 64	200	VAX-24, 2.2 mcg
7	50 to 64	200	VAX-24, 2.2/4.4 mcg
8	50 to 64	200	PCV20
Total		864	

9.4 Populations for Analysis

Randomized Population: All screened subjects who provide informed consent, provide demographic and other Baseline Screening measurements, are randomized, and are assigned a study subject ID (number). Each subject will be analyzed as randomized (ie, according to the vaccine regimen to which the subject was randomized).

Exposed Population: All subjects who receive at least one study vaccination.

Safety Population: All subjects in the Exposed Population who provide safety assessment data. This generally includes any subjects not lost to follow-up at Day 1, as they will be at risk for reporting an SAE. Each subject will be analyzed as treated (ie, according to the vaccine regimen a subject received, rather than the vaccine regimen to which the subject may have been randomized).

Immunogenicity Evaluable Population: For this Phase 1/2 study, the immunogenicity population will be analyzed as treated (ie, according to the vaccine regimen a subject receives, which may be different from the vaccine regimen to which the subject is randomized in the case of treatment errors). The Phase 1 subjects aged 18 to 49 years are not included in this population.

The Immunogenicity Evaluable Population (IEP) includes all subjects in the Exposed Population who:

- Have no major protocol deviation that would impact immunogenicity assessment or other reason to be excluded as defined prior to unblinding or analysis.
- Have not received a prohibited medication or vaccine.
- Provide evaluable serum sample results for baseline, the relevant post-vaccination time points, and within the required time frames:
    - Baseline: Day 1 or within 30 days before study vaccine administration
    - Day 29: Day 26 through Day 34, inclusive

9.5 Demographic and Baseline Characteristics Analysis

The demographic and baseline characteristics will be summarized descriptively according to age group, treatment group, and overall. Age, height, weight, and body mass index at enrollment will be summarized by reporting the mean, standard deviation, median, minimum, and maximum. The frequencies and percentages of subjects by sex, race, and ethnicity will be presented.

Demographic data will be tabulated for the Randomized, Immunogenicity Evaluable, and Safety Populations.

9.6 Safety Analysis

All safety analyses will be based on the Safety Population.

9.6.1 Analysis of Extent of Exposure

The frequencies and percentages of subjects with vaccinations will be summarized by age group and treatment group for the Randomized Population.

9.6.2 Solicited AEs

With the exception of redness and swelling, all solicited AEs (local and systemic) will be summarized according to severity grading scales defined in Section 7.2, from "mild" to "potentially life-threatening."

Solicited AEs will be recorded daily until 7 days post-injection within an electronic diary. The analyses of solicited AEs (any event, after any injection, and after each injection) will be performed by maximum severity and by treatment group. In addition, solicited AEs ongoing after 7 days post-injection will also be recorded as unsolicited AEs.

Frequencies and percentages of subjects experiencing each solicited AE will be presented by maximum severity. Summary tables showing the occurrence of any local or systemic solicited AE overall and at each time point will also be presented.

The severity of redness and swelling recorded as diameters (cm) will be summarized according to categories based on the largest diameter linear measurement when the local reaction is present:

- Grade 0/absent: 0 - 2.4 cm
- Grade 1/mild: > 2.5 - 5.0 cm.
- Grade 2/moderate: > 5.1 - 10.0 cm.
- Grade 3/severe: > 10.0 cm.

The following summaries of subjects will be performed:

- Solicited events by day post-injection, for each event and for any event.
- Time of first onset of solicited AEs, after injection, for each event and any event.
- Solicited AEs by maximum event severity, after injection, for each event and for any event.
- Duration of solicited AEs, after injection, for each event and maximum duration of any event.
- Solicited AEs, occurrence of at least one event by category (local, systemic), after injection.

For each of the time points or time intervals presented in the summaries, only subjects with at least one observation (ie, any non-missing values but excluding “Not done/unknown”) for the solicited AEs will be summarized.

9.6.3 Unsolicited AEs

All the unsolicited AEs occurring during the study will be recorded, regardless of their assessment of relatedness by the Investigator.

The original verbatim terms used by Investigators to identify AEs in the eSD will be mapped to preferred terms using the MedDRA dictionary. The unsolicited AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC). All reported AEs, as well as AEs judged by the Investigator as at least possibly related to study vaccine, will be summarized by treatment group, according to SOC and preferred term within SOC. When an unsolicited AE occurs more than once for a subject, the maximum severity reported and strongest reported relationship to the treatment group will be counted.

Only TEAEs will be summarized as defined in Section 7.1.1. The selection of unsolicited AEs and their assignment to time intervals will be done by day of onset and not by days ongoing/persisting.

Unsolicited AEs will be summarized by alphabetic SOC and preferred term as follows:

- Any unsolicited TEAE
- Possibly or probably related unsolicited TEAEs
- SAEs
- Possibly or probably related SAE
- Unsolicited TEAE leading to withdrawal
- Any AE leading to death

Listings of all TEAEs will be provided by subject.

9.6.4 Combined Solicited and Unsolicited AEs

Solicited AEs continuing beyond 7 days after any injection will be coded by MedDRA and combined with the unsolicited AEs. An overall summary of subjects with all combined solicited and unsolicited AEs, by SOC and preferred term, will be provided as well.

9.6.5 Analysis of Other Safety Data

The frequencies and percentages of concomitant medications will be tabulated by age group, treatment group, and overall. Medications will be coded using the WHODRUG dictionary.

9.7 Immunogenicity Analysis (50 to 64 years)

9.7.1 GMT/GMR

Immunogenicity analyses will be performed by age group (50 to 59 and 60 to 64) and overall (50 to 64 years). Analyses will be performed for both OPA titers (log_{10}) and IgG titers (mcg/mL). All immunogenicity analyses will be based on the IEP and Exposed Population.

The GMTs and GMCs will be analyzed via linear models. The primary model is an analysis of variance (ANOVA), with logarithmically-transformed titers (log_{10}) as the dependent variable and treatment group and study site as the fixed effects in the model. The results included in the main tables of this report will be based on this basic ANOVA model. As a secondary analysis, in order to remove the effect of baseline concentration on the GMTs, an analysis of covariance (ANCOVA) will also be performed. The ANCOVA includes treatment group and study site as the fixed effects and log_{10} baseline titer as the covariate in the model. The rationale for including

baseline values as a covariate is that prior data have shown vaccine response is correlated with baseline antibody levels.

The least squares means and their 95% confidence intervals (CIs) calculated based on the ANOVA and ANCOVA will be back transformed and reported as the group GMT and GMC values (adjusted for the mean baseline in the case of the ANCOVA). GMRs will also be calculated from the ANCOVA and ANOVA models.

Comparisons between relevant groups will be based on the estimated adjusted GMTs measured at Day 29 for 24 serotypes in VAX-24 (of those 20 in PCV20), and mean square error calculated from the basic ANOVA model using contrast statements. The analysis of GMFR relative to Day 1 will also be computed using similar models.

The main comparison of interest will be the three VAX-24 dose levels group versus the PCV20 (20 serotypes) group. However, the three VAX-24 dose groups will also be compared in a pairwise fashion on a serotype by serotype basis. No adjustment for multiplicity will be applied and missing data will not be imputed.

9.7.2 Threshold analyses

For the 4 non-PCV20 serotypes that are in VAX-24, the % of subjects with a ≥ 4-fold increase in OPA titer will be evaluated using a logistic regression model, with an indicator variable for achieving a ≥ 4-fold increase in OPA titer as the dependent variable, and treatment group and study site as fixed effects and $\log_{10}$ baseline titer as a covariate. The difference in proportions achieving a ≥ 4-fold increase in OPA titer in each of the three VAX-24 dose levels group versus the PCV20 and the corresponding 95% CIs will be calculated. If the lower bound of the 95% CI is > 0.1, the VAX-24 dose will be deemed statistically superior to PCV20.

The percentage of subjects achieving specified thresholds (eg, GMFR ≥ 4 in serotype-specific OPA and IgG, achieving OPA titer of at least serotype-specific LLOQ of the assay), and associated Wilson (score) 95% CI, will be calculated for the Day 29 visit data for each treatment group. A reverse cumulative distribution curve will be provided. Differences between pair-wise treatment groups may be determined via Fisher's exact tests.

9.8 Defined Safety Evaluation

A defined safety evaluation will be conducted for the Phase 1 cohort of subjects aged 18 to 49 years, based on the safety data collected through Day 8. The results will be reported to the DMC by treatment group preserving the double-blind status on the subject level, unless the DMC requests unblinded individual treatments. After the interim safety analysis and DMC concludes that no safety concerns exist, the study will resume enrollment of subjects aged 50 to 64 years.

10 ADDITIONAL INFORMATION

10.1 Ethical Conduct of the Study

The study will be performed in accordance with the protocol and consistent with ICH GCP Guidelines and applicable local regulatory requirements and laws.

10.2 IRB Oversight

The study (protocol, informed consent form, recruiting materials, and any documents seen by the subject) will be reviewed and approved by an IRB appropriate to each study site. Subjects will not be recruited, consented, screened, or enrolled until the IRB has approved the required documentation. In addition, the IRB will review amendments to the protocol before their implementation.

The Investigator will retain all correspondence with the IRB in the trial master file and forward copies of all IRB approvals to the Sponsor.

10.3 Informed Consent

The Sponsor or designee will provide a master ICF template to each site for development of a site-specific ICF. At the Investigator's discretion, the site may develop a separate ICF for pre-screening as described in Section 5.2.

All site-specific ICFs must be approved by the Sponsor or designee and the IRB and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The Sponsor or designee will advise the Site of required changes to the master ICF template during the course of the study.

The Investigator will ensure that each potential study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. Before informed consent is obtained, the Investigator, or a qualified person designated by the Investigator, will provide the potential study subject with ample time and opportunity to inquire about the details of the trial, and will answer all relevant questions to the potential study subject's satisfaction. The potential study subject will then decide whether or not to participate in the trial. The Investigator, or a qualified person designated by the Investigator, will obtain written informed consent from each study subject before any study-specific activity is performed.

The Investigator will retain the original and any amended signed and dated Informed Consent Form(s) at the study site and provide a copy to each study subject.

10.4 Subject Confidentiality

The Investigator will ensure that each subject's anonymity is maintained. In all documents submitted to the Sponsor and/or its designee, subjects can be identified by subject ID number and initials. Documents not intended for submission to the Sponsor and/or its designee (eg, signed ICFs) must be maintained by the Investigator securely and must be in compliance with all federal laws and regulations and ICH GCP Guidelines.

10.5 Compensation for Injury

The Sponsor will adhere to local regulations and guidelines regarding clinical trial compensation to subjects whose health is adversely affected by taking part in the study. The applicable policy for compensation for injury will be described in the master ICF template.

10.6 Clinicaltrials.gov

For purposes of reporting to clinicaltrials.gov, the Sponsor is the responsible party and will provide information regarding this study in accordance with applicable regulations.

10.7 Public Disclosure and Publication Policy

All publication rights are delineated in the Clinical Study Agreement with the Investigator(s).

10.8 Amendments

The protocol may be amended only by the Sponsor.

The IRB must generally be informed of all amendments prior to implementation. In addition, the Investigator must obtain IRB approval for any amendments likely to affect the safety of study subjects prior to implementation.

The Sponsor may implement an amendment prior to IRB notification or approval only in order to eliminate an apparent, immediate hazard to study subjects. In that event, the Sponsor will notify the IRB in writing within 7 calendar days after the implementation.

Amendments, including descriptions and rationales, will be documented in this section of the protocol.

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APPENDIX A: SCHEDULE OF EVENTS

	Visit Number:	--	01	02	03	04	05 to 08	--
	Study Visit:	**Screening**	**Day 1**	**Day 8**	**Day 15 (Phone)**	**Day 29**	**Months 3, 4, 5, 6 (Phone)**	**Early Termination**
Study Event	**Window:**	**-30d**		**+3d**	**+3d**	**±3d**	**±5d**	
Informed Consent		X						
Demographics, Medical History		X	X[a]					
Concomitant Medications		X	X	X	X	X[c]	X[c]	
Physical Exam(s), targeted		X	X[a]					
Vital Signs		X	X[b]					
Confirmation of Eligibility		X	X					
Randomization			X					
Study Vaccine Administration			X					**Refer to Section 6.2 for Procedures**
Post-vaccination Observation (at least 30 min)			X					
Issue e-Diary instructions, Ruler, Thermometer; Conduct Training			X					
Review e-Diary Data				X				
AE Evaluation (Solicited and/or Unsolicited)			X	X	X	X	X[c]	
Clinical Labs[d]								
Hematology, Chemistry, Urinalysis Tests		X				X		
Pregnancy Tests (Urine or Serum)[e]		X	X					
HIV EIA, HBsAg, HCV Ab		X						
Serum for Immunogenicity, [redacted] (50 to 64 yo only)			X			X		

Abbreviations: AE = adverse event; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus antibody; HIV EIA = human immunodeficiency virus, enzyme immunoassay; [redacted] SAE = serious adverse event; yo = years old

[a] Conduct or collect prior to study vaccination (if indicated by updated medical history or change in health status, as applicable).
[b] Vitals to be taken prior and after study vaccine administration (≥ 30 min).
[c] New onset of chronic illnesses and SAEs, and associated concomitant medications collected after Day 29.
[d] All samples collected prior to study vaccine administration.
[e] Serum pregnancy test at Screening and urine pregnancy test prior to vaccine administration.