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Applicant	Merck Sharp and Dohme Corp.
Established Name	Pneumococcal 15-Valent Conjugate Vaccine [CRM197 Protein], (b) (4)
(Proposed) Trade Name	Vaxneuvance
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Contains 15 Streptococcus pneumoniae serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F)
Dosage Form(s) and Route(s) of Administration	Suspension for intramuscular injection (0.5 mL dose), supplied as a single-dose prefilled syringe
Dosing Regimen	0.5 mL dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of invasive pneumococcal disease and pneumonia caused by Streptococcus pneumoniae serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in adults 18 years of age and older.

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List of Abbreviations and Definitions of Terms

AE	Adverse event
ANCOVA	Analysis of Covariance
APaT	All Participants as Treated
BLA	Biologic license application
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CSR	Clinical study report
eVRC	electronic Vaccination Report Card
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HAI	Hemagglutination inhibition
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
(b) (4)	(b) (4)
IPD	Invasive pneumococcal disease
ISS	Integrated Summary of Safety
LLOQ	Lower limits of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MOPA	Multiplexed opsonophagocytic assay
NA	Not applicable
OPA	Opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
PCV7	Prevnar™ (Serotypes 4, 9V, 6B, 14, 18C, 19F, 23F)
PCV13	Prevnar 13™ or Prevenar 13™ (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)
Pn ECL	Pneumococcal electrochemiluminescence
PP	Per-Protocol
PPV	Pneumococcal polysaccharide vaccine
PPV23	PNEUMOVAX™23 (Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F)
QIV	Quadrivalent influenza vaccine
SAE	Serious adverse event
V114	Pneumococcal 15-valent Conjugate Vaccine [CRM197 protein], (b) (4) (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F)
VRC	Vaccination report card

1. EXECUTIVE SUMMARY

The applicant, Merck Sharp & Dohme Corp., submitted a Biologics License Application (BLA) for Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4) (V114). The proposed indication for V114 is active immunization for the prevention of invasive pneumococcal disease and pneumonia caused by *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in adults 18 years of age and older.

The immunogenicity and safety results are summarized below:

Immunogenicity:

This submission includes two studies in Pneumococcal vaccine-naïve adults ≥ 50 years of age

- The pivotal study V114-019 was a Phase 3, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 in healthy adults 50 years of age or older. The study success criteria for immunogenicity were met. Specifically, the primary immunogenicity analyses showed that:
 - V114 was noninferior to Prevnar 13 for the 13 shared serotypes and superior to Prevnar 13 for the 2 unique serotypes in V114 as assessed by serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination. The lower bounds of the 2-sided 95% confidence intervals (CIs) of the OPA GMT ratios (V114/Prevnar 13) were greater than 0.5 for the shared serotypes and greater than 2.0 for the 2 unique serotypes.
 - V114 was superior to Prevnar 13 for the 2 unique serotypes in V114 as assessed by the proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from pre-vaccination to 30 days postvaccination. The lower bounds of the 2-sided 95% CIs of the differences (V114-Prevnar 13) between the proportions of participants with a ≥ 4 -fold rise were >0.1 for the 2 unique serotypes.

The key secondary immunogenicity analyses showed that V114 was superior to Prevnar 13 for serotype 3 as assessed by the OPA GMTs at 30 days postvaccination and the proportions of participants with a ≥ 4 -fold rise in OPA responses from pre-vaccination to 30 days postvaccination. The lower bounds of the 2-sided 95% CIs were greater than 1.2 for the GMT ratio (V114/Prevnar 13) and >0 for the difference (V114 - Prevnar 13) between the proportions of participants with a ≥ 4 -fold rise.

- Study V114-020 was a Phase 3, multicenter, randomized, double-blind, active comparator-controlled, lot-to-lot consistency study to evaluate the safety, tolerability, and immunogenicity of V114 in healthy adults 50 years of age or older. The primary immunogenicity analyses showed that all 3 lots of V114 met equivalence criteria, as assessed by the serotype-specific OPA GMTs for the 15 serotypes in V114 at 30 days postvaccination. The lower and upper limits of the 95% CIs of the serotype-specific GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all 15 serotypes.

The applicant conducted the Phase-3 study V114-017 in immunocompetent, pneumococcal vaccine-naïve adults 18 to 49 years of age with or without at-risk conditions. Using descriptive statistics, the study showed that serotype-specific OPA GMTs and IgG geometric mean concentrations (GMCs) at 30 days postvaccination with PCV were comparable for the 13 shared serotypes between V114 and Prevnar 13 and higher in the V114 group for the 2 serotypes unique to V114. The study also showed that V114 was immunogenic in immunocompetent adults 18 to 49 years of age with risk factors for pneumococcal disease, including underlying comorbidities (diabetes mellitus, chronic liver disease, chronic lung disease including asthma, chronic heart disease) and behavioral factors (current smoker, increased alcohol use).

The Phase-3 study V114-018 showed that V114 elicited an immune response in HIV-positive adults as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine at 30 days postvaccination. Serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination were comparable for the 13 shared serotypes between V114 and Prevnar 13 and higher in the V114 group for the 2 unique serotypes.

Study V114-016 demonstrated that serotype-specific OPA GMTs at 30 days postvaccination with PNEUMOVAX23 (PPV23, Month 13) were comparable between participants administered V114 or Prevnar 13 12 months prior to receipt of PPV23 for all 15 serotypes in V114. In addition, between-group comparisons of IgG GMCs at 30 days postvaccination with PPV23 (Month 13) were consistent with those observed in the primary analysis of OPA GMTs.

Study V114-021 showed that V114 administered concomitantly with quadrivalent influenza vaccine (QIV) met noninferiority criteria for the 15 serotypes in V114 as assessed by serotype-specific OPA GMTs at 30 days postvaccination with V114. The lower bounds of the 2-sided 95% CIs of the OPA GMT ratios (concomitant/non-concomitant) were >0.5 for all 15 serotypes in V114. In addition, QIV administered concomitantly with V114 met noninferiority criteria for the 4 strains in QIV as assessed by strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV. The lower bounds of the 2-sided 95% CIs of the HAI GMT ratios (concomitant/non-concomitant) were >0.5 for all 4 strains in QIV.

Safety:

V114 had a generally comparable safety profile with Prevnar 13 when administered as a single dose to adults ≥ 18 years of age with and without prior pneumococcal vaccination.

- In pneumococcal vaccine-naïve adults ≥ 18 years of age, the most frequently reported AEs were the solicited AEs. Injection site pain, fatigue, and myalgia occurred most frequently.
- In pneumococcal vaccine-naïve adults ≥ 50 years of age, the proportion of participants with solicited injection site pain was higher among those who received V114 compared with Prevnar 13.
- Across the studies, the proportion of participants who experienced SAEs was low following vaccination with V114 or Prevnar 13, and comparable across intervention groups; no SAEs were considered by the investigator to be vaccine-related.

V114 showed a similar safety profile with that observed in immunocompetent, pneumococcal vaccine-naïve adults, in the following populations:

- Adults 18 to 49 years of age with risk factors for pneumococcal disease
- Adults ≥ 18 years of age considered immunocompromised due to HIV infection
- Adults ≥ 65 years of age with prior pneumococcal vaccination

V114 administered sequentially with PPV23 or concomitantly with inactivated influenza vaccine showed a similar safety profile with that of V114 in immunocompetent, pneumococcal vaccine-naïve adults.

The immunogenicity and safety results support this application for the proposed indication.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Invasive pneumococcal disease and pneumonia caused by *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

PNEUMOVAX23 (pneumococcal vaccine polyvalent, PPV23) was first licensed in the US in 1983. Prevnar was introduced in 2000 and has been widely adopted in national childhood vaccination schedules worldwide. Synflorix and Prevnar 13 were licensed in 2009 and 2010, respectively, and replaced Prevnar for pediatric immunization worldwide.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N.A.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

This application for licensure is based on the inference of V114 effectiveness for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of noninferior immune responses to the 13 shared serotypes in Prevnar 13. Licensure of Prevnar 13 in adults was based on demonstration of noninferiority of OPA responses to those elicited by PPV23. The CAPiTA study subsequently confirmed protective efficacy of Prevnar 13 for the prevention of invasive pneumococcal disease (IPD) and pneumococcal pneumonia, validating the results of immunobridging. Based on this precedent and the infeasibility of conducting efficacy studies for new pneumococcal vaccines in settings where uptake of currently approved vaccines is high, immunobridging to Prevnar 13 for shared serotypes and demonstration of superior OPA responses to serotypes 22F and 33F had been proposed to regulatory agencies and accepted as basis for V114 licensure.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review.

3.2 Compliance with Good Clinical Practices and Data Integrity

The submission presented no data integrity issues.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

N/A

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on six Phase 3 studies V114-019, V114-020, V114-017, V114-018, V114-016 and V114-021.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- STN 125741/1 Module 2.5. Clinical Overview
- STN 125741/1 Module 2.7.3. Summary of Clinical Efficacy
- STN 125741/1 Module 2.7.4. Summary of Clinical Safety
- STN 125741/1 Module 5.3.5.1. Study V114-019 Clinical Study Report
- STN 125741/1 Module 5.3.5.1. Study V114-020 Clinical Study Report
- STN 125741/1 Module 5.3.5.1. Study V114-017 Clinical Study Report
- STN 125741/1 Module 5.3.5.1. Study V114-018 Clinical Study Report
- STN 125741/1 Module 5.3.5.1. Study V114-016 Clinical Study Report
- STN 125741/1 Module 5.3.5.1. Study V114-021 Clinical Study Report
- STN 125741/1 Module 5.3.5.4. Statistical Report: Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an ^{(b) (4)} Test (b) (4) OPA Testing
- STN 125741/1 Module 5.3.5.3. Integrated Summary of Safety
- STN 125741/40 Module 1.11.3. Response to CBER Information Request

5.3 Table of Studies/Clinical Trials

The clinical development program includes six Phase-3 studies (Table 1).

Table 1 Overview of individual studies in the V114 clinical development program

Trial ID and Title	Trial Design	Dosing regimen	Trial population	Subject exposure
V114-016 A Phase 3, Multicenter, Randomized, Double blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX23 One Year Later in Healthy Adults 50 Years of Age or Older (PNEU-PATH)	Multicenter, randomized, double-blind, parallel-group, placebo-controlled	0.5 mL intramuscular dose of V114 or Plevnar 13 on Day 1 0.5 mL intramuscular dose of PPV23 at Month 12	Healthy adult males/females without prior administration of any pneumococcal vaccine Age: ≥50 years of age	V114: 327 Plevnar 13: 324 PPV23: 600
V114-017 A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX23 Six Months Later in Immunocompetent Adults Between 18 and 49 Years of Age at Increased Risk for Pneumococcal Disease (PNEU – DAY)	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	V114 group: 0.5 mL intramuscular dose of V114 at Day 1 and 0.5 mL intramuscular dose of PNEUMOVAX23 at Month 6 Plevnar 13 group: 0.5mL intramuscular dose of Plevnar 13 at Day 1 and 0.5 mL intramuscular dose of PNEUMOVAX23 at Month 6	Pneumococcal vaccine-naïve participants 18 to 49 years of age (inclusive) with or without risk factors for pneumococcal disease.	V114 group: 1133 participants received V114 and 1035 received PNEUMOVAX23 Plevnar 13 group: 378 participants received Plevnar 13 and 1 was incorrectly vaccinated with V114; and 346 received PNEUMOVAX23
V114-018 A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX23 Eight Weeks Later in Adults Infected with HIV (PNEU–WAY)	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	V114 group: 0.5 mL intramuscular dose of V114 at Day 1 and 0.5 mL intramuscular dose of PNEUMOVAX23 at Week 8 Plevnar 13 group: 0.5 mL intramuscular dose of Plevnar 13 at Day 1 and 0.5 mL intramuscular dose of PNEUMOVAX23 at Week 8	Pneumococcal vaccine-naïve males or females who were infected with human immunodeficiency virus (HIV) and had CD4+ T-cell count ≥50 cells/μL and plasma HIV ribonucleic acid (RNA) <50,000 copies/mL at screening. Age: ≥18 years of age	V114 group: 152 participants received V114 and 150 received PNEUMOVAX23 Plevnar 13 group: 150 participants received Plevnar 13 and 148 received PNEUMOVAX23
V114-019 A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Adults 50 Years of Age or Older (PNEU-AGE)	Multicenter, randomized, double-blind, active comparator-controlled	V114 group: 0.5 mL intramuscular single dose of V114 at Visit 1 (Day 1) Plevnar 13 group: 0.5 mL intramuscular single dose of Plevnar 13 at Visit 1 (Day 1)	Healthy adult males/females without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine. Age: 50-92 years	V114: 602 Plevnar 13: 600
V114-020 A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and	Multicenter, randomized, double-blind, parallel-group, active-controlled	0.5 mL intramuscular dose of V114 Lot 1, V114 Lot 2, V114 Lot 3, or Plevnar 13 on Day 1	Healthy adult males/females without prior administration of any pneumococcal vaccine Age: ≥50 years of	V114 Lot 1: 699 V114 Lot 2: 704 V114 Lot 3: 700 Plevnar 13: 230

Trial ID and Title	Trial Design	Dosing regimen	Trial population	Subject exposure
Immunogenicity of V114 in Healthy Adults 50 Years of Age or Older (PNEU-TRUE)			age	
V114-021 A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 When Administered Concomitantly With Influenza Vaccine in Healthy Adults 50 Years of Age or Older (PNEU-FLU)	Multicenter, randomized, double-blind, parallel-group, placebo-controlled	Concomitant group: 0.5 mL intramuscular doses of V114 (Day 1), QIV (Day 1), and placebo (Day 30). Non-concomitant group: 0.5 mL intramuscular doses of placebo (Day 1), QIV (Day 1), and V114 (Day 30)	Healthy adult males/females with or without prior administration of PPV23. Age: ≥50 years of age	V114: 1186 QIV: 1197 Placebo: 1180

Source: adapted from 5.2 Tabular Listing of All Clinical Studies.

5.4 Consultations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Pivotal Study V114-019: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Adults 50 Years of Age or Older (PNEU-AGE)

6.1.1 Objectives

6.1.1.1 Primary Objectives

- To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).
- To compare the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination (Day 30) with V114 versus Prevnar 13.
 - Hypothesis (H1): V114 is noninferior to Prevnar 13 as measured by the serotype-specific OPA GMTs for 13 shared serotypes at 30 days postvaccination. The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% confidence interval (CI) of the OPA GMT ratio (V114/ Prevnar 13) to be greater than 0.5.
 - Hypothesis (H2): V114 is superior to Prevnar 13 as measured by serotype-specific OPA GMTs for 2 unique serotypes in V114 at 30 days postvaccination. The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio (V114/ Prevnar 13) to be greater than 2.0.
- To compare serotype-specific proportions of participants with a ≥4-fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses for the 2 unique serotypes in V114 for participants administered V114 versus participants administered Prevnar13.

- Hypothesis (H3): V114 is superior to Prevnar 13 for the 2 unique serotypes in V114 as measured by proportions of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for serotype-specific OPA responses. The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the differences (V114 - Prevnar 13) between the proportions of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) to be greater than 0.1.

6.1.1.2 Secondary Objectives

- To compare the serotype 3 OPA GMT at 30 days postvaccination (Day 30) with V114 versus Prevnar 13.
 - Hypothesis (H4): V114 is superior to Prevnar 13 as measured by the serotype 3 OPA GMTs at 30 days postvaccination. The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio (V114/Prevnar 13) to be greater than 1.2.
- To compare proportions of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for the serotype 3 OPA responses for participants administered V114 versus participants administered Prevnar 13.
 - Hypothesis (H5): V114 is superior to Prevnar 13 for serotype 3 as measured by proportions of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses. The statistical criterion for superiority requires the lower bound of the 2-sided 95% CI of the difference (V114 - Prevnar 13) between the proportions of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) to be greater than 0.
- To evaluate the serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination (Day 30) with V114 compared with Prevnar 13.
- To evaluate the serotype-specific Geometric Mean Fold Rises (GMFRs) and proportions of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13.

6.1.2 Design Overview

This was a randomized, active-controlled, parallel-group, multisite, double-blind study of V114 in adults 50 years of age or older. Approximately 1200 individuals were to be randomly assigned in a 1:1 ratio to receive either V114 (600 participants) or Prevnar 13 (600 participants) at Visit 1 (Day 1). Randomization was stratified by participant age at enrollment (50 to 64 years, 65 to 74 years, and ≥ 75 years). At least 800 participants were to be ≥ 65 years of age.

6.1.3 Population

Healthy male and female participants ≥ 50 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Experimental treatment: V114
- Active Comparator: Prevnar 13

6.1.6 Sites and Centers

This study was conducted at 30 centers in 5 countries.

6.1.7 Surveillance/Monitoring

N/A

6.1.8 Endpoints

- Immunogenicity Endpoints
 - Primary immunogenicity endpoints
 - Serotype-specific OPA GMTs at 30 days postvaccination (Day 30) for the 15 serotypes contained in V114
 - Proportion of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for OPA responses for the 2 unique serotypes contained in V114
 - Secondary immunogenicity endpoints
 - Serotype 3 OPA GMT at 30 days postvaccination (Day 30)
 - Proportion of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for serotype 3 OPA responses
 - Serotype-specific IgG GMCs at 30 days postvaccination (Day 30)
 - Serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses
- Safety analysis endpoints include:
 - Proportion of participants with solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) from Day 1 through Day 5 postvaccination
 - Proportion of participants with solicited systemic AEs (muscle pain/myalgia, joint pain/arthralgia, headache, and tiredness/fatigue) from Day 1 through Day 14 postvaccination
 - Proportions of participants with the broad AE categories consisting of any AE and any vaccine-related AE from Day 1 through Day 14 postvaccination
 - Proportions of participants with the broad AE categories consisting of any SAE, any vaccine-related SAE, and death from Day 1 through the duration of participation in the study
 - Proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 5 postvaccination

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Blinding

This study was a double-blind study. The participant and the investigator who was involved in the clinical evaluation of the participants remained blinded to the group assignments. Because V114 and Prevnar 13 are different in appearance, V114 and Prevnar 13 were prepared and/or dispensed by an unblinded pharmacist or unblinded qualified study site personnel. To avoid bias, the unblinded study personnel had no further contact with study participants for any study-related procedures/assessments after administration of study vaccines.

- Randomization

Participants were assigned randomly in a 1:1 ratio to receive either V114 or Prevnar 13. Randomization was stratified by age at time of randomization, i.e., 50 to 64, 65 to 74, and ≥ 75 years of age.

- Definitions of analysis populations

- Immunogenicity Analysis Populations

- Per-Protocol (PP) population: all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. The PP population served as the primary population for the analysis of immunogenicity data in this study.
- Full Analysis Set (FAS): all randomized participants who received at least 1 vaccination and had at least 1 serology result. FAS population was used for supportive analysis.

- Safety Analysis Population: safety analyses were conducted in the All Participants as Treated (APaT) population, which consisted of all randomized participants who received study vaccination.

- Sample size determination

This study randomized approximately 600 participants into the V114 group and 600 participants into the Prevnar 13 group. The applicant expected this study would have $>90\%$ power for demonstrating noninferiority to Prevnar 13 for the 13 shared serotypes and superiority for the 2 unique serotypes for V114 at an overall 1-sided 2.5% alpha level. The applicant suggested that there was an 80% chance of observing at least 1 SAE among 600 participants in V114 group if the underlying incidence of an SAE is 0.27%. There would be a 50% chance of observing at least 1 SAE among 600 participants in the V114 group if the underlying incidence of an SAE is 0.12%.

- Statistical Analysis for Primary Immunogenicity Endpoints

- Primary Endpoints/Hypotheses (H1 and H2)

The first primary objective (to compare the serotype-specific OPA GMTs at 30 days postvaccination with V114 versus Prevnar 13) was assessed via the 2 hypotheses.

For each of the 13 shared serotypes, OPA GMTs between participants administered V114 and Prevnar 13 at 30 days postvaccination were compared via the following noninferiority hypotheses:

H₀: $\text{GMT}_1/\text{GMT}_2 \leq 0.50$ versus

H₁: $\text{GMT}_1/\text{GMT}_2 > 0.50$

where GMT_1 is serotype-specific OPA GMT for the V114 group and GMT_2 is serotype-specific OPA GMT for the Prevnar 13 group. A ratio of 0.50 corresponds to a 2.0-fold decrease of OPA GMT in the V114 group as compared with the Prevnar 13 group. Rejecting the null hypothesis (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (V114/ Prevnar 13) being >0.50 and would lead to the conclusion that the OPA response to V114 for the common serotype is noninferior to that of Prevnar 13.

For the 2 additional serotypes, OPA GMTs between participants administered V114 and Prevnar 13 at 30 days postvaccination were assessed via the following superiority hypotheses:

$H_0: GMT_1/GMT_2 \leq 2.0$ versus

$H_1: GMT_1/GMT_2 > 2.0$

where GMT_1 is serotype-specific OPA GMT for the V114 group and GMT_2 is serotype-specific OPA GMT for the Prevnar 13 group. A ratio of 2 corresponds to a 2.0-fold increase of OPA GMT in the V114 group as compared with the Prevnar 13 group. Rejecting the null hypotheses (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (V114/ Prevnar 13) being >2.0 and would lead to the conclusion that the OPA GMT of V114 for the additional serotype is superior to that of Prevnar 13.

To address the first primary immunogenicity objectives, the serotype-specific OPA GMTs at 30 days postvaccination were compared between vaccination groups. Comparisons were made through the estimation of serotype-specific OPA GMT ratios for each of the 15 serotypes in V114. Estimation of the GMT ratios and 95% CIs was conducted using the constrained longitudinal data analysis (cLDA, Liang, K-Y and Zeger, S. L. 2000). In this model, the response vector consisted of the log-transformed antibody titers at baseline and 30 days postvaccination. The repeated-measures model included terms for vaccination group, time, the interaction of time-by-vaccination group (with a restriction of the same baseline mean across groups), age stratum (i.e., 50 to 64 years, 65 to 74 years, and ≥ 75 years) at baseline, and age stratum-by-time interaction. This model allowed for different baseline means for each stratum, but restrict the baseline mean within the age stratum levels to be the same for both vaccination groups.

○ Primary Endpoints/Hypotheses (H3)

The second primary objective (proportions of participants with a ≥ 4 -fold rise from pre-vaccination to 30 days postvaccination for OPA responses for participants administered V114 versus participants administered Prevnar 13) was assessed via the following superiority hypotheses for the 2 serotypes that are unique to V114:

$H_0: p_1 - p_2 \leq 0.1$ versus

$H_1: p_1 - p_2 > 0.1$

where p_1 is the proportion of participants with a ≥ 4 -fold rise for the V114 group and p_2 is the proportion for the Prevnar 13 group. A difference of 0.1 corresponds to the V114 group having a 10% higher proportion of participants with a ≥ 4 -fold rise in OPA responses from pre-vaccination to 30 days postvaccination than the Prevnar 13 group. Rejecting the null hypotheses (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower

bound of the 2-sided 95% CI on the difference (V114 - Prevnar 13) being >0.1 and would lead to the conclusion that the proportion of participants with a ≥ 4 -fold rise in OPA responses in the V114 group for the unique serotype is superior to that in the Prevnar 13 group.

To address the second primary immunogenicity objective, the serotype-specific proportion of participants with a ≥ 4 -fold rise was compared between vaccination groups. Comparisons were made through the estimation of the difference in the serotype-specific proportion of participants with a ≥ 4 -fold rise for each of the 2 unique serotypes in V114. Estimation of the proportion difference and 95% CI was conducted using the stratified M&N method (Miettinen, O. and Nurminen, M. 1985).

- Statistical Analysis for Secondary Immunogenicity Endpoints
 - Secondary Endpoints/Hypotheses (H4)

The first secondary objective (to compare the serotype 3 OPA GMTs at 30 days postvaccination with V114 versus Prevnar 13) was assessed via the following superiority hypotheses:

$$H_0: \text{GMT}_1/\text{GMT}_2 \leq 1.2 \text{ versus}$$

$$H_1: \text{GMT}_1/\text{GMT}_2 > 1.2$$

where GMT_1 is the serotype 3 OPA GMT for the V114 group and GMT_2 is the serotype 3 OPA GMT for the Prevnar 13 group. A ratio of 1.2 corresponds to the V114 group having an OPA GMT that is 1.2-fold higher than the OPA GMT in the Prevnar 13 group. Rejecting the null hypotheses (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (V114/ Prevnar 13) being >1.2 . To address the first secondary immunogenicity objective, the cLDA method was used.

- Secondary Endpoints/Hypotheses (H5)

The second secondary objective (proportion of participants with a ≥ 4 -fold rise from pre-vaccination to 30 days postvaccination for OPA responses for participants administered V114 versus participants administered Prevnar 13) was assessed via the following superiority hypotheses for serotype 3:

$$H_0: p_1 - p_2 \leq 0 \text{ versus}$$

$$H_1: p_1 - p_2 > 0$$

where p_1 is the proportion of participants with a ≥ 4 -fold rise for the V114 group and p_2 is the proportion for the Prevnar 13 group. A difference of 0 corresponds to no difference in the proportions of participants with a ≥ 4 -fold rise of OPA responses from pre-vaccination to 30 days postvaccination between V114 and Prevnar 13. Rejecting the null hypotheses (H_0) at the 1-sided $\alpha=0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the difference (V114 - Prevnar 13) being >0 . To address the second secondary immunogenicity objective, the stratified M&N method was used.

- Other Secondary Endpoints

A similar statistical model as used for the first primary objective was used to address the secondary objective that evaluates the serotype-specific IgG GMCs at 30 days postvaccination with V114 compared with Prevnar 13.

Descriptive statistics with point estimates and within-group 95% CIs were provided for all other immunogenicity endpoints. For the continuous endpoints, the point estimates were calculated by exponentiating the estimates of the mean of the natural log values and the within-group CIs were derived by exponentiating the bounds of the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group CIs were calculated based on the exact method proposed by Clopper and Pearson.

- **Statistical Methods for Safety Analyses**

Safety parameters or AEs of special interest identified as “Tier 1” safety endpoints were subject to inferential testing for statistical significance with p-values and 95% CIs for between-treatment differences in the proportion of participants with events; these analyses were performed using the M&N method. Tier 2 parameters were assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events. Only point estimates by treatment group were provided for Tier 3 safety parameters.

- **Multiplicity adjustment**

The study would meet its primary immunogenicity objectives if noninferiority was demonstrated with respect to the OPA GMTs for the 13 shared serotypes and superiority was demonstrated with respect to both OPA GMTs and the proportions of participants with ≥ 4 -fold rises in OPA responses for the 2 additional serotypes. All hypotheses were tested individually for each serotype at a 1-sided 0.025 alpha-level. This approach controls the 1-sided type-I error rate at 0.025, and no multiplicity adjustment was required.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographic characteristics were comparable for vaccinated participants across intervention groups (Table 2). The median age of participants was 66 years (range: 50 to 92 years), with approximately 69% over 65 years of age, and approximately 12% over 75 years of age. The majority of participants were female, white, and of non-Hispanic or Latino ethnicity.

Table 2. Subject Characteristics (All Vaccinated Subjects)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Total n	Total (%)
Subjects in population	602		600		1,202	
Sex						
Male	244	(40.5)	269	(44.8)	513	(42.7)
Female	358	(59.5)	331	(55.2)	689	(57.3)
Age (Years)						
50 to 64	186	(30.9)	186	(31.0)	372	(30.9)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Total n	Total (%)
65 to 74	346	(57.5)	346	(57.7)	692	(57.6)
≥75	70	(11.6)	68	(11.3)	138	(11.5)
Mean	66.2		65.7		65.9	
SD	7.7		7.4		7.5	
Median	67.0		66.0		66.0	
Range	50 to 92		50 to 82		50 to 92	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(0.2)	1	(0.1)
Asian	150	(24.9)	152	(25.3)	302	(25.1)
Black Or African American	36	(6.0)	37	(6.2)	73	(6.1)
Multiple	7	(1.2)	4	(0.7)	11	(0.9)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	0	(0.0)	1	(0.1)
White	408	(67.8)	406	(67.7)	814	(67.7)
Ethnicity						
Hispanic Or Latino	135	(22.4)	129	(21.5)	264	(22.0)
Not Hispanic Or Latino	467	(77.6)	470	(78.3)	937	(78.0)
Not Reported	0	(0.0)	1	(0.2)	1	(0.1)

Source: Table 10-5 in the Study V114-019 CSR.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.1.10.1.3 Subject Disposition

A total of 1205 participants were randomized across 30 study sites. Nearly all participants received either V114 or Prevnar 13 and completed the study. Three participants were randomized but discontinued prior to vaccination. The number of participants who discontinued the study and the reasons for discontinuation were comparable across intervention groups (Table 3).

Table 3. Disposition of Subjects (All Randomized Subjects)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Total n	Total (%)
Subjects in population	604		601		1,205	
Vaccinated with						
PCV	602	(99.7)	600	(99.8)	1,202	(99.8)
Trial Disposition						
Completed	596	(98.7)	594	(98.8)	1,190	(98.8)
Discontinued	8	(1.3)	7	(1.2)	15	(1.2)
Death	1	(0.2)	1	(0.2)	2	(0.2)
Lost To Follow-Up	5	(0.8)	5	(0.8)	10	(0.8)
Physician Decision	1	(0.2)	0	(0.0)	1	(0.1)
Protocol Deviation	0	(0.0)	1	(0.2)	1	(0.1)
Withdrawal By Subject	1	(0.2)	0	(0.0)	1	(0.1)

Source: Table 10-1 in the Study V114-019 CSR.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

The primary endpoint analysis showed that V114 met noninferiority criteria for the 13 shared serotypes as assessed by serotype-specific OPA GMTs at 30 days postvaccination. The lower bounds of the 95% CIs of the estimated OPA GMT ratios (V114/Prevnar 13) were >0.5 for all shared serotypes (Table 4).

The analysis also showed that V114 met superiority criteria for the 2 additional serotypes as assessed by serotype specific OPA GMTs at 30 days postvaccination. The lower bounds of the 95% CIs of the estimated OPA GMT ratios (V114/Prevnar 13) were >2.0 for both additional serotypes (Table 4). Additionally, V114 met superiority criteria for the 2 additional serotypes as assessed by the proportions of participants with a ≥4-fold rise from pre-vaccination to 30 days postvaccination for serotype-specific OPA responses. The lower bounds of the 2-sided 95% CIs of the difference in percentages [V114 - Prevnar 13] were >10 percentage points for both unique serotypes (Table 5).

Table 4. Analysis of OPA GMTs at Day 30 (Per-Protocol Population)
(Based Only on Samples Testing ^{(b) (4)} Negative)

Pneumococcal Serotype	V114 (N=602) n	V114 (N=602) GMT	Prevnar 13 (N=600) n	Prevnar 13 (N=600) GMT	V114 / Prevnar 13 (95% CI) GMT ratio	p-value (1-sided)
13 Shared Serotypes (Non-inferiority [‡])	-	-	-	-	-	-
1	598	256.8	598	320.8	0.80 (0.66, 0.97)	<0.001
3	598	214.8	598	132.9	1.62 (1.40, 1.87)	<0.001
4	598	1109.3	598	1632.8	0.68 (0.57, 0.80)	<0.001
5	598	444.5	598	560.2	0.79 (0.64, 0.98)	<0.001
6A	596	5371.0	596	5275.8	1.02 (0.85, 1.22)	<0.001
6B	598	3984.3	598	3178.9	1.25 (1.04, 1.51)	<0.001
7F	596	4574.9	596	5829.8	0.78 (0.68, 0.90)	<0.001
9V	598	1809.2	597	2192.8	0.83 (0.71, 0.96)	<0.001
14	598	1975.8	598	2618.7	0.75 (0.64, 0.89)	<0.001
18C	598	2749.0	598	2551.7	1.08 (0.91, 1.27)	<0.001
19A	598	3176.9	597	3920.6	0.81 (0.70, 0.94)	<0.001
19F	598	1688.0	598	1884.0	0.90 (0.77, 1.04)	<0.001
23F	598	2029.0	598	1723.1	1.18 (0.96, 1.44)	<0.001
2 Serotypes Unique to V114 (Superiority [§])	-	-	-	-	-	-
22F	594	2381.4	585	73.2	32.52 (25.87, 40.88)	<0.001
33F	598	8009.9	597	1114.4	7.19 (6.13, 8.43)	<0.001

Source: Table 7 in Statistical Report: Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an ^{(b) (4)} Test ^{(b) (4)} OPA Testing.

Table 5. Analysis of the Proportions of Subjects With a ≥ 4 -Fold Rise in OPA Responses at Day 30 (Per-Protocol Population, based only on samples testing $(b) (4)$ negative) (Serotypes 22F and 33F)

Pneumococcal Serotype	V114 (N = 602) Observed Response Percentage (m/n)	Prevnar 13 (N = 600) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)	p-Value (1-sided)
22F	71.7 (369 / 515)	13.9 (68 / 488)	57.7 (52.5, 62.5)	<0.001
33F	56.8 (323 / 569)	6.2 (34 / 547)	50.6 (45.9, 55.0)	<0.001

Note: N=Number of subjects randomized and vaccinated; n=Number of subjects contributing to the analysis; m=Number of subjects with the indicated response.

Source: Table 8 in the Statistical Report: Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an $(b) (4)$ Test $(b) (4)$ OPA Testing.

Reviewer Comments:

- During the Phase 3 clinical program, blinded performance monitoring of the $(b) (4)$ test revealed $(b) (4)$ positivity rates within the historical range for Studies V114-018 and V114-021; however, a higher than expected number of serum samples tested $(b) (4)$ positive in studies completed later in the program (V114-016, V114-017, V114-019, V114-020) following a change to a critical reagent. The $(b) (4)$ positive samples were retested using a revised $(b) (4)$ assay and the positivity rates were found to be lower and within the expected range. Considering the low proportion (<5%) of participants reporting systemic antibiotic use around the time of blood draws for immunogenicity testing, $(b) (4)$ OPA testing and analysis for the 4 studies. The evaluation of OPA-related endpoints presented in the CSRs for these studies (V114-016, V114-017, V114-019, V114-020) was based on results from all available OPA data, regardless of $(b) (4)$ status. The review team discussed the issue and decided that the evaluation of OPA-related endpoints should be performed only on the data from the samples tested negative in an $(b) (4)$ test. Therefore, the primary and key secondary OPA endpoint analysis results for these studies are based on the applicant’s report “Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an $(b) (4)$ Test $(b) (4)$ OPA Testing” instead of the CSRs of these studies.*
- My analysis using cLDA showed similar results for the primary immunogenicity endpoint analysis of serotype-specific OPA GMTs at 30 days postvaccination. The applicant’s cLDA model restricted the baseline mean within the age stratum levels to be the same for both vaccination groups. To evaluate this assumption, I conducted additional analysis to compare the serotype-specific OPA GMTs at 30 days postvaccination between the V114 and Prevnar 13 groups, using ANCOVA to adjust for baseline values. The additional analyses showed similar results.*

6.1.11.2 Analyses of Secondary Endpoints

- Serotype 3 OPA Responses at 30 Days Postvaccination

The secondary endpoint analysis showed that V114 met the superiority criterion for serotype 3 as assessed by the OPA GMTs at 30 days postvaccination. The lower bound of the 95% CI of the OPA GMT ratio (V114/Prevnar 13) was >1.2 (Table 6). Also, V114 met the superiority criterion for serotype 3 as assessed by the proportions of participants with a ≥4-fold rise from pre-vaccination to 30 days postvaccination for OPA responses. The lower bound of the 2-sided 95% CI of the difference in percentages (V114-Prevnar 13) was > 0% (Table 7).

Table 6. Analysis of OPA GMTs at Day 30 (Serotype 3)
(Per-Protocol Population, based only on samples testing ^{(b) (4)} negative)

Serotype	V114 (N=602) n	V114 (N=602) GMT	Prevnar 13 (N=600) n	Prevnar 13 (N=600) GMT	V114 / Prevnar 13 GMT Ratio (95% CI)	p-value (1-sided)
3	598	214.8	598	132.9	1.62 (1.40, 1.87)	<0.001

Note: N=Number of subjects randomized and vaccinated; n=Number of subjects contributing to the analysis.

Source: Table 9 in Statistical Report: Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an ^{(b) (4)} Test ^{(b) (4)} OPA Testing.

Table 7. Analysis of the Proportions of Subjects With a ≥4-Fold Rise in OPA Responses at Day 30 (Serotype 3)
(Per-Protocol Population, Based Only on Samples Testing ^{(b) (4)} Negative)

Serotype	V114 (N=602) Observed Response Percentage (m/n)	Prevnar 13 (N=600) Observed Response Percentage (m/n)	Percent Point Difference (V114 – Prevnar 13) Estimate (95% CI)	p-Value (1-sided)
3	70.2 (401 / 571)	58.3 (328 / 563)	12.0 (6.4, 17.5)	<0.001

Note: N=Number of subjects randomized and vaccinated; n=Number of subjects contributing to the analysis; m=Number of subjects with the indicated response.

Source: Table 10 in Statistical Report: Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an ^{(b) (4)} Test ^{(b) (4)} OPA Testing.

- Serotype-specific IgG Responses at 30 Days Postvaccination

Between-group comparisons of IgG GMCs at 30 days postvaccination were similar with the primary analysis of OPA GMTs (Table 8).

Table 8. Analysis of IgG GMCs at Day 30 (Per-Protocol Population)

Serotype	V114 (N=602) n	V114 (N=602) GMC	Prevnar 13 (N=600) n	Prevnar 13 (N=600) GMC	V114 / Prevnar 13 GMC Ratio (95% CI)
13 Shared Serotypes					
1	598	5.30	598	7.34	0.72 (0.62, 0.83)
3	598	0.96	598	0.64	1.51 (1.33, 1.71)
4	598	1.88	598	2.62	0.72 (0.62, 0.83)
5	598	4.57	598	5.56	0.82 (0.70, 0.96)

Serotype	V114 (N=602) n	V114 (N=602) GMC	Pprevnar 13 (N=600) n	Pprevnar 13 (N=600) GMC	V114 / Pprevnar 13 GMC Ratio (95% CI)
6A	598	7.21	598	7.01	1.03 (0.87, 1.21)
6B	598	8.60	598	6.19	1.39 (1.17, 1.64)
7F	598	6.18	598	8.09	0.76 (0.66, 0.89)
9V	598	4.77	598	5.52	0.86 (0.75, 1.00)
14	598	9.39	598	12.30	0.76 (0.65, 0.89)
18C	598	8.99	598	10.00	0.90 (0.77, 1.05)
19A	598	14.60	598	17.38	0.84 (0.73, 0.97)
19F	598	8.77	598	9.70	0.90 (0.78, 1.05)
23F	598	6.67	598	6.13	1.09 (0.92, 1.28)
2 Serotypes Unique to V114					
22F	598	3.44	598	0.32	10.62 (9.37, 12.03)
33F	598	11.05	598	1.23	8.98 (8.00, 10.07)

Source: Table 11-5 in the Study V114-019 CSR.

- Additional Serotype-specific OPA and IgG Endpoints at 30 Days Postvaccination Serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise from pre-vaccination to 30 days postvaccination for both OPA responses and IgG responses were comparable in both intervention groups for the shared serotypes and higher in the V114 group compared with the Pprevnar 13 group for serotype 3 and the 2 serotypes unique to V114.

6.1.11.3 Subpopulation Analyses

Serotype-specific OPA GMT ratios at 30 days postvaccination were similar across sex, race and ethnicity subgroups and had similar trend across serotypes. It is noted that, within each intervention group, there was a trend toward lower serotype-specific OPA GMTs in the older age groups (65 to 74 and ≥ 75 years of age) compared with the younger age group (50 to 64 years of age). Within all subgroups, the OPA GMT ratios and the proportions of participants with a ≥ 4 -fold rise from pre-vaccination to 30 days postvaccination for serotype-specific OPA responses for the 2 serotypes unique to V114 (22F, 33F) were substantially higher in the V114 group than in the Pprevnar 13 group.

6.1.11.4 Dropouts and/or Discontinuations

Please refer to section 6.1.10.1.3.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

The majority of participants in both intervention groups experienced 1 or more AEs (Table 9). There was a higher proportion of participants with AEs in the V114 group

(67.9%) compared with the Prevnar 13 group (58.2%), mainly due to a higher proportion of participants with injection-site AEs following vaccination with V114. The proportions of participants with systemic AEs and vaccine-related systemic AEs were comparable across intervention groups.

The proportions of participants with solicited AEs were generally comparable across intervention groups, with the exception of solicited injection-site pain, which was substantially higher in the V114 group (Table 10).

The proportions of participants who experienced SAEs were low in the study and comparable across intervention groups, and none of the SAEs were considered by the investigator to be vaccine-related. Two deaths were reported (one in each intervention group), and neither death was considered by the investigator to be vaccine-related.

Table 9. Analysis of Adverse Event Summary
(All Participants as Treated Population) (Following PCV)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Difference in % vs. Prevnar 13 Estimate (95% CI)
Subjects in population	602		600		
with one or more adverse events	409	(67.9)	349	(58.2)	9.8 (4.5, 15.2)
injection-site	362	(60.1)	293	(48.8)	
systemic	231	(38.4)	208	(34.7)	
with no adverse event	193	(32.1)	251	(41.8)	
with vaccine-related adverse events	385	(64.0)	329	(54.8)	9.1 (3.6, 14.6)
injection-site	362	(60.1)	293	(48.8)	
systemic	169	(28.1)	156	(26.0)	
with serious adverse events	9	(1.5)	13	(2.2)	-0.7 (-2.3, 0.9)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
who died	1	(0.2)	1	(0.2)	-0.0 (-0.8, 0.8)

Note: Reported adverse events include nonserious adverse events within 14 days of vaccination and serious adverse events occurring Day 1 through Month 6.

Source: Table 12-1 in the Study V114-019 CSR.

Table 10. Analysis of Subjects with Solicited Adverse Events
(Incidence > 0% in One or More Vaccination Groups)
(All Participants as Treated Population) (Following PCV)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Difference in % vs Prevnar 13 Estimate (95% CI)
Subjects in population	602		600		
with one or more solicited adverse events	391	(65.0)	332	(55.3)	
with no solicited adverse events	211	(35.0)	268	(44.7)	
Solicited injection site adverse events	355	(59.0)	284	(47.3)	
Injection site erythema	54	(9.0)	68	(11.3)	-2.4 (-5.8, 1.1)
Injection site pain	325	(54.0)	254	(42.3)	11.7 (6.0, 17.2)
Injection site swelling	75	(12.5)	67	(11.2)	1.3 (-2.4, 5.0)
Solicited systemic adverse events	200	(33.2)	182	(30.3)	
Arthralgia	32	(5.3)	33	(5.5)	-0.2 (-2.8, 2.4)
Fatigue	105	(17.4)	104	(17.3)	0.1 (-4.2, 4.4)

	V114 n	V114 (%)	Pprevnar 13 n	Pprevnar 13 (%)	Difference in % vs Pprevnar 13 Estimate (95% CI)
Headache	70	(11.6)	78	(13.0)	-1.4 (-5.1, 2.4)
Myalgia	93	(15.4)	72	(12.0)	3.4 (-0.4, 7.4)

Note: Injection site erythema, injection site pain, and injection site swelling were solicited from Day 1 to Day 5 following vaccination. Arthralgia, fatigue, headache, and myalgia were solicited from Day 1 to Day 14 following vaccination.

Source: Table 12-2 in the Study V114-019 CSR.

Reviewer Comments: The applicant used the clinical event data reported by investigator in the Case Report Forms (eCRF) as the primary sources for the safety analyses. It’s noted that there were differences, particularly in the rates of solicited systemic adverse reactions between clinical event data reported by participants on the Vaccination report card (VRC) and those reported by investigator in the Case Report Forms. Nevertheless, the review team does not anticipate that the overall safety profile of V114 differs in a clinically meaningful way between the two approaches.

6.1.12.1 Methods

Please see Statistical Methods for Safety Analyses in section 6.1.9.

6.1.12.3 Deaths

Two deaths were reported (one in each intervention group), and neither death was considered by the investigator to be vaccine-related.

6.1.12.4 Nonfatal Serious Adverse Events

The proportions of participants with SAEs were 1.5% and 2.2% in the V114 and Pprevnar 13 groups, respectively. None of the SAEs were considered by the investigator to be vaccine-related.

6.1.12.5 Adverse Events of Special Interest (AESI)

No additional AEs of special interest were defined for this study.

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

As this study was a single dose study, discontinuation from study intervention due to an AE could not occur.

6.2 Study V114-020: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Healthy Adults 50 Years of Age or Older (PNEU-TRUE)

6.2.1 Objectives

6.2.1.1. Primary Objectives

- To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).
- To compare the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination (Day 30) across 3 different lots of V114.
 - Hypothesis: All 3 lots of V114 are equivalent as measured by the serotype-specific OPA GMTs for 15 serotypes in V114 at 30 days postvaccination. The statistical criterion for equivalence requires the bounds of the 95% confidence interval (CI) of the GMT ratio for each pairwise V114 lot-to-lot comparison of the OPA GMT ratio to be within 0.5 to 2.0.

6.2.1.1. Secondary Objectives

- To evaluate the serotype-specific Immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days post vaccination (Day 30) compared across the 3 different lots of V114 and combined lots of V114 compared to Prevnar 13.
- To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥ 4 -fold rise from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses separately across 3 different lots of V114.

6.2.2 Design Overview

This was a randomized, active-controlled, parallel-group, multisite, double-blind study of V114 in healthy adults. The planned enrollment for this study was approximately 2220 healthy adults 50 years of age or older. Eligible participants were randomized in a 3:3:3:1 ratio to 1 of 4 intervention groups: V114 Lot 1, V114 Lot 2, V114 Lot 3, and Prevnar 13. Randomization was stratified by participant age at enrollment (50 to 64 years, 65 to 74 years, and ≥ 75 years).

6.2.3 Population

Healthy adults 50 years of age or older.

6.2.4 Study Treatments or Agents Mandated by the Protocol

- V114 Lot 1
- V114 Lot 2
- V114 Lot 3
- Prevnar 13

6.2.6 Sites and Centers

This study was conducted at 55 centers in 6 countries.

6.2.7 Surveillance/Monitoring

N/A

6.2.8 Endpoints

- Primary immunogenicity endpoint
Serotype-specific OPA responses for the 15 serotypes in V114 at Day 30.

- Secondary immunogenicity endpoints
 - Serotype-specific IgG responses for the 15 serotypes in V114 at Day 30.
 - Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1 and Day 30.
- Primary safety endpoints
 - Solicited injection-site AEs from Day 1 through Day 5 postvaccination.
 - Solicited systemic AEs from Day 1 through Day 14 postvaccination.
 - Vaccine-related serious adverse events (SAEs) from Day 1 to Month 6 postvaccination

6.2.9 Statistical Considerations & Statistical Analysis Plan

- Blinding

This was a double-blind study. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants were blinded to the intervention assignments. V114 and Prevnar 13 were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel who had no further contact with study participants for any study-related procedures/assessments.
- Randomization

Participants were assigned randomly in a 3:3:3:1 ratio to V114 Lot 1, V114 Lot 2, V114 Lot 3, and Prevnar 13. Randomization was stratified by age at time of randomization: 50 to 64, 65 to 74, and ≥ 75 years of age. Approximately 50% of the participants will be ≥ 65 years of age.
- Definitions of analysis populations
 - Per-Protocol (PP) population: all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s). The Per-Protocol (PP) population served as the primary population for the analysis of immunogenicity data in this study.
 - Full Analysis Set (FAS) population: all randomized participants who received at least 1 vaccination and had at least 1 serology result. FAS was used for supportive immunogenicity analysis.
 - Safety Analysis Set (All Participants as Treated (APaT) population): all randomized participants who received study vaccination.

- Statistical Methods for Primary Immunogenicity Endpoint

The primary objective was assessed by pairwise comparison of lots (Lot 1 to Lot 2, Lot 1 to Lot 3, and Lot 2 to Lot 3). Each pairwise comparison of lots consisted of two 1-sided tests at the $\alpha=0.025$ level. Rejecting the null hypothesis of nonequivalence for any test is equivalent to requiring the bounds of the 95% CI on the pairwise lot-to-lot comparison of the V114 GMT ratios to be between 0.5 and 2.0. For each of the 15 serotypes in V114 and for each pairwise comparison, OPA GMTs between participants administered different lots of V114 at 30 days postvaccination was compared via the following equivalence hypotheses:

$$H_0: \text{GMT}_x/\text{GMT}_y < 0.5 \text{ or } \text{GMT}_x/\text{GMT}_y > 2.0 \text{ versus}$$

$$H_1: 0.5 \leq \text{GMT}_x/\text{GMT}_y \leq 2.0$$

where GMT_x is serotype-specific OPA GMT for one of the V114 lots and GMT_y is serotype-specific OPA GMT for another V114 lot. Estimation of the GMT ratios and 95% CIs, and the hypothesis test were conducted using the cLDA method.

- **Statistical Methods for Secondary Immunogenicity Endpoints**

The cLDA method was used to address the secondary objective that evaluates the serotype-specific IgG GMCs at 30 days postvaccination compared across 3 different lots of V114 and combined lots of V114 compared to Prevnar 13. Descriptive statistics with point estimates and within-group 95% CIs were provided for all other immunogenicity endpoints.

- **Sample size determination**

The applicant planned to randomize approximately 667 participants to receive each of 3 manufactured lots of V114 (Lot 1, Lot 2, and Lot 3) and 220 participants to receive Prevnar 13 in this study. The applicant expected that, for the primary hypothesis, this study would have >90% power to demonstrate equivalent immunogenicity across the 3 V114 lots based on their assumptions.

- **Multiplicity adjustment**

The criteria for study success require demonstrating success on all 15 pneumococcal serotypes for all 3 pairwise comparisons for V114 lots that are evaluated in the primary immunogenicity objective. Since comparisons were made individually for each of the 15 serotypes and for each pairwise comparison, this approach controlled the 2-sided type I error rate at 0.05, and no multiplicity adjustment was required.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

Demographic characteristics were comparable for vaccinated participants across intervention groups. The median age of participants was 65.0 years (range: 50 to 92 years). Approximately 55% of participants were ≥ 65 years of age, and approximately 10% of participants were ≥ 75 years of age. The majority of participants were female, white, and of non-Hispanic or Latino ethnicity.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.2.10.1.3 Subject Disposition

A total of 2340 participants were randomized across 55 study sites. Nearly all randomized participants received either V114 (Lot 1, Lot 2, or Lot 3) or Prevnar 13 and completed the study. The proportions of participants who discontinued the study and the reasons for discontinuation were comparable across intervention groups (Table 11).

Table 11. Disposition of Subjects (All Randomized Subjects)

	V114 Lot 1 n	V114 Lot 1 (%)	V114 Lot 2 n	V114 Lot 2 (%)	V114 Lot 3 n	V114 Lot 3 (%)	Prevnar 13 n	Prevnar 13 (%)	Total n	Total (%)
Subjects in population	702		704		701		233		2,340	
Vaccinated with PCV	698	(99.4)	704	(100.0)	700	(99.9)	231	(99.1)	2,333	(99.7)
Completed	683	(97.3)	689	(97.9)	683	(97.4)	227	(97.4)	2,282	(97.5)
Discontinued	12	(1.7)	9	(1.3)	11	(1.6)	4	(1.7)	36	(1.5)
Death	1	(0.1)	2	(0.3)	0	(0.0)	0	(0.0)	3	(0.1)
Lost To Follow-Up	5	(0.7)	6	(0.9)	8	(1.1)	2	(0.9)	21	(0.9)
Protocol Deviation	2	(0.3)	0	(0.0)	0	(0.0)	1	(0.4)	3	(0.1)
Withdrawal By Subject	4	(0.6)	1	(0.1)	3	(0.4)	1	(0.4)	9	(0.4)
Status Not Recorded [†]	7	(1.0)	6	(0.9)	7	(1.0)	2	(0.9)	22	(0.9)

Source: Table 10-1 in the Study V114-020 CSR

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary endpoint analysis showed that immune response was consistent across the lots of V114 for all 15 serotypes. The 3 lots of V114 met criteria for equivalence, as assessed by the serotype-specific OPA GMTs for the 15 serotypes in V114 at 30 days postvaccination. The lower and upper limits of the 95% CI of the serotype-specific OPA GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all 15 serotypes (Table 12).

Table 12. Analysis of OPA GMTs at Day 30 (Comparison Across V114 Lots)
(Per-Protocol Population, Based Only on Samples Testing ^{(b) (4)} Negative)

Serotype	Group A vs. Group B	V114 Group A N	V114 Group A n	V114 Group A Estimated GMT	V114 Group B N	V114 Group B n	V114 Group B Estimated GMT	GMT Ratio Group A / Group B (95% CI)
13 Shared Serotypes								
1	Lot 1 vs. Lot 2	698	693	245.8	704	693	249.2	0.99 (0.83, 1.18)
	Lot 1 vs. Lot 3	698	693	245.8	700	687	238.3	1.03 (0.86, 1.23)
	Lot 2 vs. Lot 3	704	693	249.2	700	687	238.3	1.05 (0.88, 1.25)
3	Lot 1 vs. Lot 2	698	693	194.0	704	693	230.1	0.84 (0.74, 0.96)
	Lot 1 vs. Lot 3	698	693	194.0	700	687	212.5	0.91 (0.80, 1.04)
	Lot 2 vs. Lot 3	704	693	230.1	700	687	212.5	1.08 (0.95, 1.23)
4	Lot 1 vs. Lot 2	698	693	1057.6	704	692	1287.1	0.82 (0.70, 0.97)
	Lot 1 vs. Lot 3	698	693	1057.6	700	686	1058.0	1.00 (0.85, 1.18)
	Lot 2 vs. Lot 3	704	692	1287.1	700	686	1058.0	1.22 (1.03, 1.43)
5	Lot 1 vs. Lot 2	698	693	380.1	704	693	460.7	0.83 (0.68, 1.00)
	Lot 1 vs. Lot 3	698	693	380.1	700	687	382.8	0.99 (0.82, 1.20)
	Lot 2 vs. Lot 3	704	693	460.7	700	687	382.8	1.20 (1.00, 1.45)
6A	Lot 1 vs. Lot 2	698	684	5686.6	704	690	5944.8	0.96 (0.82, 1.12)

Serotype	Group A vs. Group B	V114 Group A N	V114 Group A n	V114 Group A Estimated GMT	V114 Group B N	V114 Group B n	V114 Group B Estimated GMT	GMT Ratio Group A / Group B (95% CI)
	Lot 1 vs. Lot 3	698	684	5686.6	700	685	6020.9	0.94 (0.81, 1.11)
	Lot 2 vs. Lot 3	704	690	5944.8	700	685	6020.9	0.99 (0.84, 1.16)
6B	Lot 1 vs. Lot 2	698	693	5057.9	704	692	5257.9	0.96 (0.82, 1.12)
	Lot 1 vs. Lot 3	698	693	5057.9	700	687	5043.4	1.00 (0.86, 1.17)
	Lot 2 vs. Lot 3	704	692	5257.9	700	687	5043.4	1.04 (0.89, 1.22)
7F	Lot 1 vs. Lot 2	698	692	3718.8	704	692	4555.3	0.82 (0.72, 0.93)
	Lot 1 vs. Lot 3	698	692	3718.8	700	686	4151.6	0.90 (0.79, 1.02)
	Lot 2 vs. Lot 3	704	692	4555.3	700	686	4151.6	1.10 (0.97, 1.25)
9V	Lot 1 vs. Lot 2	698	690	1662.3	704	693	1675.7	0.99 (0.87, 1.14)
	Lot 1 vs. Lot 3	698	690	1662.3	700	687	1744.5	0.95 (0.83, 1.09)
	Lot 2 vs. Lot 3	704	693	1675.7	700	687	1744.5	0.96 (0.84, 1.10)
14	Lot 1 vs. Lot 2	698	693	2336.0	704	693	2508.5	0.93 (0.80, 1.09)
	Lot 1 vs. Lot 3	698	693	2336.0	700	686	2042.5	1.14 (0.98, 1.34)
	Lot 2 vs. Lot 3	704	693	2508.5	700	686	2042.5	1.23 (1.05, 1.43)
18C	Lot 1 vs. Lot 2	698	693	3802.4	704	692	3507.0	1.08 (0.95, 1.24)
	Lot 1 vs. Lot 3	698	693	3802.4	700	687	3349.5	1.14 (0.99, 1.30)
	Lot 2 vs. Lot 3	704	692	3507.0	700	687	3349.5	1.05 (0.91, 1.20)
19A	Lot 1 vs. Lot 2	698	693	3311.1	704	693	3710.9	0.89 (0.79, 1.01)
	Lot 1 vs. Lot 3	698	693	3311.1	700	687	3473.3	0.95 (0.84, 1.08)
	Lot 2 vs. Lot 3	704	693	3710.9	700	687	3473.3	1.07 (0.94, 1.21)
19F	Lot 1 vs. Lot 2	698	693	1841.9	704	692	2006.8	0.92 (0.81, 1.05)
	Lot 1 vs. Lot 3	698	693	1841.9	700	687	1997.2	0.92 (0.81, 1.05)
	Lot 2 vs. Lot 3	704	692	2006.8	700	687	1997.2	1.00 (0.88, 1.14)
23F	Lot 1 vs. Lot 2	698	690	2207.2	704	691	2361.1	0.93 (0.79, 1.11)
	Lot 1 vs. Lot 3	698	690	2207.2	700	684	2119.0	1.04 (0.88, 1.24)
	Lot 2 vs. Lot 3	704	691	2361.1	700	684	2119.0	1.11 (0.94, 1.32)
Additional Serotypes								
22F	Lot 1 vs. Lot 2	698	687	2554.3	704	691	2752.2	0.93 (0.79, 1.09)
	Lot 1 vs. Lot 3	698	687	2554.3	700	683	2653.7	0.96 (0.82, 1.13)
	Lot 2 vs. Lot 3	704	691	2752.2	700	683	2653.7	1.04 (0.89, 1.22)
33F	Lot 1 vs. Lot 2	698	690	7722.3	704	690	7649.1	1.01 (0.87, 1.17)
	Lot 1 vs. Lot 3	698	690	7722.3	700	687	7387.8	1.05 (0.90, 1.22)
	Lot 2 vs. Lot 3	704	690	7649.1	700	687	7387.8	1.04 (0.89, 1.20)

Source: Table 11 in Statistical Report: Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an ^{(b) (4)} Test ^{(b) (4)} OPA Testing.

Reviewer Comments:

My analysis using cLDA showed similar results for the primary immunogenicity endpoint analysis. The applicant's cLDA model restricted the baseline mean within the age stratum levels to be the same for both vaccination groups. To evaluate this assumption, I conducted additional analysis to compare the serotype-specific OPA GMTs at 30 days postvaccination among three lots, using ANCOVA to adjust for baseline values. The analysis showed similar results.

6.2.11.2 Analyses of Secondary Endpoints

The results of the lot-to-lot comparisons of IgG GMCs at 30 days postvaccination with V114 were similar with the results of the primary analysis of OPA GMTs (Table 13).

Table 13. Analysis of IgG GMCs at Day 30 (Comparison Across V114 Lots) (Per-Protocol Population)

Serotype	Group A vs. Group B	V114 GroupA N	V114 GroupA n	V114 GroupA Estimated GMC	V114 GroupB N	V114 GroupB n	V114 GroupB Estimated GMC	GMC Ratio Group A / Group B (95% CI)
13 Shared Serotypes								
1	Lot 1 vs. Lot 2	698	693	3.91	704	693	4.05	0.96 (0.84, 1.10)
	Lot 1 vs. Lot 3	698	693	3.91	700	688	3.83	1.02 (0.89, 1.17)
	Lot 2 vs. Lot 3	704	693	4.05	700	688	3.83	1.06 (0.92, 1.21)
3	Lot 1 vs. Lot 2	698	693	0.74	704	693	0.86	0.85 (0.77, 0.95)
	Lot 1 vs. Lot 3	698	693	0.74	700	688	0.73	1.01 (0.91, 1.13)
	Lot 2 vs. Lot 3	704	693	0.86	700	688	0.73	1.18 (1.06, 1.32)
4	Lot 1 vs. Lot 2	698	693	1.79	704	692	2.18	0.82 (0.72, 0.94)
	Lot 1 vs. Lot 3	698	693	1.79	700	688	1.67	1.07 (0.94, 1.23)
	Lot 2 vs. Lot 3	704	692	2.18	700	688	1.67	1.31 (1.14, 1.50)
5	Lot 1 vs. Lot 2	698	693	3.81	704	693	4.63	0.82 (0.72, 0.95)
	Lot 1 vs. Lot 3	698	693	3.81	700	688	3.96	0.96 (0.84, 1.11)
	Lot 2 vs. Lot 3	704	693	4.63	700	688	3.96	1.17 (1.02, 1.35)
6A	Lot 1 vs. Lot 2	698	693	8.09	704	693	8.84	0.92 (0.78, 1.07)
	Lot 1 vs. Lot 3	698	693	8.09	700	688	8.16	0.99 (0.85, 1.16)
	Lot 2 vs. Lot 3	704	693	8.84	700	688	8.16	1.08 (0.93, 1.27)
6B	Lot 1 vs. Lot 2	698	693	10.92	704	693	11.46	0.95 (0.82, 1.11)
	Lot 1 vs. Lot 3	698	693	10.92	700	688	10.44	1.05 (0.90, 1.22)
	Lot 2 vs. Lot 3	704	693	11.46	700	688	10.44	1.10 (0.94, 1.28)
7F	Lot 1 vs. Lot 2	698	693	5.71	704	693	7.11	0.80 (0.70, 0.92)
	Lot 1 vs. Lot 3	698	693	5.71	700	688	5.94	0.96 (0.84, 1.10)
	Lot 2 vs. Lot 3	704	693	7.11	700	688	5.94	1.20 (1.04, 1.37)
9V	Lot 1 vs. Lot 2	698	693	4.20	704	693	4.44	0.95 (0.83, 1.08)

Serotype	Group A vs. Group B	V114 Group A N	V114 Group A n	V114 Group A Estimated GMC	V114 Group B N	V114 Group B n	V114 Group B Estimated GMC	GMC Ratio Group A / Group B (95% CI)
	Lot 1 vs. Lot 3	698	693	4.20	700	688	4.26	0.99 (0.87, 1.13)
	Lot 2 vs. Lot 3	704	693	4.44	700	688	4.26	1.04 (0.91, 1.19)
14	Lot 1 vs. Lot 2	698	693	9.82	704	693	11.38	0.86 (0.75, 1.00)
	Lot 1 vs. Lot 3	698	693	9.82	700	688	8.66	1.13 (0.98, 1.31)
	Lot 2 vs. Lot 3	704	693	11.38	700	688	8.66	1.31 (1.14, 1.52)
18C	Lot 1 vs. Lot 2	698	693	14.07	704	693	11.81	1.19 (1.04, 1.36)
	Lot 1 vs. Lot 3	698	693	14.07	700	688	10.66	1.32 (1.15, 1.51)
	Lot 2 vs. Lot 3	704	693	11.81	700	688	10.66	1.11 (0.97, 1.27)
19A	Lot 1 vs. Lot 2	698	693	15.45	704	693	17.34	0.89 (0.78, 1.02)
	Lot 1 vs. Lot 3	698	693	15.45	700	688	15.81	0.98 (0.86, 1.11)
	Lot 2 vs. Lot 3	704	693	17.34	700	688	15.81	1.10 (0.96, 1.25)
19F	Lot 1 vs. Lot 2	698	693	9.78	704	693	11.22	0.87 (0.76, 1.00)
	Lot 1 vs. Lot 3	698	693	9.78	700	688	10.65	0.92 (0.80, 1.05)
	Lot 2 vs. Lot 3	704	693	11.22	700	688	10.65	1.05 (0.92, 1.21)
23F	Lot 1 vs. Lot 2	698	693	7.38	704	693	7.97	0.93 (0.80, 1.07)
	Lot 1 vs. Lot 3	698	693	7.38	700	688	7.44	0.99 (0.86, 1.15)
	Lot 2 vs. Lot 3	704	693	7.97	700	688	7.44	1.07 (0.93, 1.24)
2 Serotypes Unique to V114								
22F	Lot 1 vs. Lot 2	698	693	4.12	704	693	4.41	0.93 (0.81, 1.08)
	Lot 1 vs. Lot 3	698	693	4.12	700	688	3.80	1.08 (0.93, 1.26)
	Lot 2 vs. Lot 3	704	693	4.41	700	688	3.80	1.16 (1.00, 1.35)
33F	Lot 1 vs. Lot 2	698	693	9.92	704	693	10.88	0.91 (0.79, 1.06)
	Lot 1 vs. Lot 3	698	693	9.92	700	688	9.45	1.05 (0.90, 1.22)
	Lot 2 vs. Lot 3	704	693	10.88	700	688	9.45	1.15 (0.99, 1.34)

Source: Table 11-2 in the Study V114 P020 CSR

Additional Serotype-Specific OPA and IgG Endpoints at 30 Days Postvaccination
 Serotype-specific GMTs, GMFRs and proportions of participants with a ≥ 4 -fold rise from Pre-vaccination to 30 days postvaccination with V114 were comparable across each of the 3 V114 lots (Lot 1, Lot 2, Lot 3) for both OPA and IgG responses for all 15 serotypes.

6.2.11.3 Subpopulation Analyses

Serotype-specific OPA GMT ratios between any 2 lots of V114 at 30 days postvaccination were similar among age subgroups (50 to 64, 65 to 74, and ≥ 75 years of age). Within each of the 3 lots of V114, there was a trend toward lower serotype-specific OPA GMTs in the older age groups (65 to 74 and ≥ 75 years of age) compared with the younger age group (50 to 64 years of age). Serotype-specific OPA GMT ratios between

any 2 lots of V114 at 30 days postvaccination were similar across sex, race and ethnicity subgroups.

6.2.11.4 Dropouts and/or Discontinuations

Please refer to section 6.2.10.1.3.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

- Adverse Events Across V114 Lots

Overall, the majority of participants in each of the V114 lots experienced 1 or more AEs (Table 14). The proportions of participants with injection-site AEs, systemic AEs, and vaccine-related AEs were comparable across the 3 lots of V114. The proportion of participants with SAEs was 1.7%, 2.7% and 1.0% for Lot 1, 2, and 3 of V114. None of the SAEs were considered by the investigator to be vaccine related.

Table 14. Summary of Adverse Event by V114 Lots
(All Participants as Treated Population) (Following PCV)

	V114 Lot 1 n	V114 Lot 1 %	V114 Lot 1 95% CI	V114 Lot 2 n	V114 Lot 2 %	V114 Lot 2 95% CI	V114 Lot 3 n	V114 Lot 3 %	V114 Lot 3 95% CI
Subjects in population	699			704			700		
with one or more adverse events	566	81.0	(77.9,83.8)	545	77.4	(74.1,80.5)	546	78.0	(74.7,81.0)
injection-site	495	70.8		498	70.7		495	70.7	
systemic	374	53.5		358	50.9		362	51.7	
with no adverse event	133	19.0		159	22.6		154	22.0	
with vaccine-related adverse events	537	76.8	(73.5,79.9)	528	75.0	(71.6,78.2)	527	75.3	(71.9,78.4)
injection-site	495	70.8		498	70.7		495	70.7	
systemic	305	43.6		289	41.1		316	45.1	
with serious adverse events	12	1.7	(0.9,3.0)	19	2.7	(1.6,4.2)	7	1.0	(0.4,2.0)
with serious vaccine-related adverse events	0	0.0	(0.0,0.4)	0	0.0	(0.0,0.4)	0	0.0	(0.0,0.4)
who died	1	0.1	(0.0, 0.8)	2	0.3	(0.0,1.0)	0	0.0	(0.0,0.4)

Source: Table 12-1 in the Study V114-020 CSR

- Adverse Events in V114 (Combined Lots) and Prevnar 13 Groups

Overall, the majority of participants experienced one or more AEs (Table 15). There was a higher proportion of participants with AEs in the V114 (combined lots) group compared with the Prevnar 13 group, mainly due to a higher proportion of participants with injection-site AEs following vaccination with V114. The proportions of participants with systemic AEs and vaccine-related systemic AEs were comparable across the V114 (combined lots) and Prevnar 13 intervention groups. The proportion of participants who experienced SAEs was 1.8% and 2.2% for the V114 (combined lots) and Prevnar 13 groups, respectively; none of the SAEs were considered by the investigator to be related to study vaccine.

Table 15. Summary of Adverse Event between V114 Combined Lots and Prevnar 13
(All Participants as Treated Population) (Following PCV)

	V114 Combined Lots n (%)	Prevnar 13 n (%)	Difference in % vs Prevnar 13 Estimate (95% CI)
Subjects in population	2103	230	
with one or more adverse events	1657 (78.8)	159 (69.1)	9.7 (3.8, 16.1)
injection-site	1488 (70.8)	133 (57.8)	
systemic	1094 (52.0)	112 (48.7)	
with no adverse event	446 (21.2)	71 (30.9)	
with vaccine-related adverse events	1592 (75.7)	147 (63.9)	11.8 (5.6, 18.4)
injection-site	1488 (70.8)	133 (57.8)	
systemic	910 (43.3)	87 (37.8)	
with serious adverse events	38 (1.8)	5 (2.2)	-0.4 (-3.2, 1.1)
with serious vaccine-related adverse events	0 (0.0)	0 (0.0)	0.0 (-1.6, 0.2)
who died	3 (0.1)	0 (0.0)	0.1 (-1.5, 0.4)

Source: Table 12-2 in the Study V114 P020 CSR

6.2.12.1 Methods

Safety analysis was performed with descriptive statistics.

6.2.12.3 Deaths

Three deaths were reported during the study. None were considered by the investigator to be related to study vaccine.

6.2.12.4 Nonfatal Serious Adverse Events

The proportion of participants with SAEs was 1.8% and 2.2% in the V114 (combined lots) and Prevnar 13 intervention groups. None of the SAEs were considered by the investigator to be related to study vaccine.

6.2.12.5 Adverse Events of Special Interest (AESI)

N/A

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

As this was a single-dose study, discontinuation from study intervention due to an AE could not occur.

6.3 Study V114-017: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX23 Six Months Later in Immunocompetent Adults Between 18 and 49 Years of Age at Increased Risk for Pneumococcal Disease (PNEU – DAY)

6.3.1 Objectives

6.3.1.1 Primary Objectives

- To evaluate the safety and tolerability of V114 and Prevnar 13 with respect to the proportion of participants with AEs within each vaccination group separately.
- To evaluate the serotype specific OPA GMTs at 30 days postvaccination (Day 30) with V114 and Prevnar 13 within each vaccination group separately.

6.3.1.2 Secondary Objectives

- To evaluate the safety and tolerability of PNEUMOVAX23 (PPV23) administered 6 months following V114 and following Prevnar 13 with respect to the proportion of participants with AEs within each vaccination group separately.
- To evaluate the serotype specific IgG GMCs at 30 days postvaccination (Day 30) with V114 and Prevnar 13 within each vaccination group separately.
- To evaluate the serotype specific GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for participants administered V114 and for participants administered Prevnar 13 within each vaccination group separately.
- To evaluate the serotype specific (1) OPA GMTs and IgG GMCs at 30 days postvaccination with PPV23 (Month 7), (2) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination (Day 1) to 30 days postvaccination with PPV23 (Month 7) for both OPA and IgG responses, (3) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination with PPV23 (Month 6) to 30 days postvaccination with PPV23 (Month 7) for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13 6 months before receipt of PPV23.

6.3.2 Design Overview

Approximately 1500 individuals were randomly assigned in a 3:1 ratio to receive either V114 (1125 participants) or Prevnar 13 (375 participants) at Day 1. Randomization was stratified based on (1) enrollment at Center for American Indian Health (CAIH, approximately 600 Native American participants, 40% of the total enrollment) or not and (2) underlying type/number of risk factors for pneumococcal disease (including diabetes mellitus, chronic liver disease, chronic lung disease including asthma, chronic heart disease, smoking, and AUDIT-C score ≥ 5). All participants received a single dose of PPV23 at Month 6.

6.3.3 Population

Males or females 18 to 49 years of age with ≥ 1 of the following risk conditions for pneumococcal disease: Diabetes mellitus Type 1 or Type 2, Chronic liver disease with compensated cirrhosis, confirmed diagnosis of COPD Stage 1 to 3, confirmed diagnosis of mild or moderate persistent asthma, confirmed diagnosis of chronic heart disease, and current smoker.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Experimental: V114 followed by PNEUMOVAX23.

Active control: Prevnar 13 followed by PNEUMOVAX23.

6.3.6 Sites and Centers

This study was conducted at 79 centers in 7 countries. A total of 77 centers randomized participants.

6.3.7 Surveillance/Monitoring

N/A

6.3.8 Endpoints

- Primary Immunogenicity Endpoints:
Serotype-specific OPA responses for the 15 serotypes in V114 at Day 30
- Primary Safety Endpoints:
Following vaccination with V114 or Prevnar 13:
 - Solicited injection-site AEs from Day 1 through Day 5 postvaccination
 - Solicited systemic AEs from Day 1 through Day 14 postvaccination
 - Vaccine-related SAEs from Day 1 to Month 6
- Secondary Immunogenicity Endpoints
 - Serotype-specific IgG responses for the 15 serotypes in V114 at Day 30
 - Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1 and Day 30
 - Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1, Month 6, and Month 7
- Secondary Safety Endpoints
Following vaccination with PNEUMOVAX23:
 - Solicited injection-site AEs from Day 1 through Day 5 postvaccination
 - Solicited systemic AEs from Day 1 through Day 14 postvaccination
 - Vaccine-related SAEs from Month 6 to Month 7

6.3.9 Statistical Considerations & Statistical Analysis Plan

- Randomization
Participants was assigned randomly in a 3:1 ratio to 2 study intervention arms (V114 or Prevnar 13), respectively. Randomization was stratified based on:
 - whether a participant is enrolled at CAIH (approximately 600 Native American participants, 40% of the total enrollment) or not.
 - the type/number of risk factors for pneumococcal disease a participant has at the time of randomization.
- Blinding
This was a double-blind study.
- Definitions of analysis populations
 - Per-Protocol (PP) population: all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. The PP population served as the primary population for the analysis of immunogenicity data in this study.
 - Full Analysis Set (FAS) population: all randomized participants who received at least 1 study vaccination and had at least 1 serology result. The FAS population was used in supportive analyses.

- Safety Analyses population (All Participants as Treated (APaT) population): all randomized participants who received at least 1 dose of study vaccination.
- Sample size determination

This was a descriptive study. This study planned to randomize approximately 1125 participants into the V114 group and 375 participants into the Prevnar 13 group.

- Statistical Methods for Immunogenicity Analyses

Immunogenicity analyses was conducted for each of the 15 pneumococcal serotypes in the V114 and Prevnar-13 group separately. To address the primary immunogenicity objective, evaluation of the OPA GMTs at 30 days postvaccination with V114 or Prevnar 13 (Day 30) included descriptive summaries, and within-group 95% CIs was calculated for each vaccination group. A similar statistical approach was used to evaluate the IgG GMCs at 30 days postvaccination with V114 or Prevnar 13 (Day 30) and OPA GMTs and IgG GMCs at 30 days postvaccination with PPV23 (Month 7). Descriptive statistics with point estimates and within-group 95% CIs were provided for all other immunogenicity endpoints.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

6.3.10.1.1 Demographics

Demographic and baseline characteristics were comparable for vaccinated participants across intervention groups. Approximately half of the participants were female. The median age of participants was 36 years (range: 18 to 49 years). Approximately 40% of participants were American Indian or Alaska Native.

A majority (54.7%) of participants had a single risk factor for pneumococcal disease at screening and 20.1% of participants had 2 or more risk factors. The most common single risk factors were tobacco use (14.6%), chronic lung disease (14.3%), and diabetes mellitus (13.8%). Approximately 25% of participants had no risk factors.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.3.10.1.3 Subject Disposition

A total of 1515 participants were randomized. All but 3 randomized participants received V114 or Prevnar 13. The majority of participants completed the study (>90%). The proportion of participants who discontinued the study and the reasons for study discontinuation were comparable across intervention groups. The majority of participants also received PPV23 (>90%).

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

V114 was immunogenic in pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease as assessed by OPA GMTs at 30 days postvaccination (Day 30) for all 15 serotypes contained in the

vaccine (Table 16). Prevnar 13 was immunogenic as assessed by OPA GMTs at 30 days postvaccination for all 13 serotypes contained in the vaccine.

Table 16 Summary of OPA GMTs at Day 30
(Per-Protocol Population, Based Only on Samples Testing ^{(b) (4)} Negative)

	V114 (N=1133) n	V114 (N=1133) Observed GMT	V114 (N=1133) 95% CI	Prevnar 13 (N=379) n	Prevnar 13 (N=379) Observed GMT	Prevnar 13 (N=379) 95% CI
13 Shared Serotypes						
1	1004	267.3	(242.3, 294.8)	337	266.9	(219.9, 324.0)
3	990	198.4	(183.6, 214.5)	336	149.5	(129.4, 172.7)
4	1001	1401.2	(1294.3, 1516.9)	338	2567.7	(2267.5, 2907.7)
5	1003	560.0	(507.9, 617.6)	339	731.4	(612.8, 873.0)
6A	994	12763.2	(11771.8, 13838.1)	333	11313.1	(9739.1, 13141.4)
6B	999	10164.1	(9485.9, 10890.8)	338	6957.7	(5986.9, 8085.8)
7F	1004	5725.4	(5382.1, 6090.5)	338	7582.6	(6761.8, 8503.0)
9V	1000	3353.5	(3132.3, 3590.4)	339	3969.4	(3541.2, 4449.5)
14	1001	5244.8	(4860.4, 5659.7)	339	5863.2	(5190.6, 6623.0)
18C	999	5694.8	(5314.3, 6102.6)	339	3050.3	(2684.9, 3465.3)
19A	1001	5335.1	(4984.6, 5710.3)	339	5884.0	(5220.7, 6631.6)
19F	1003	3252.8	(3051.0, 3468.0)	339	3272.0	(2948.5, 3631.0)
23F	1001	4828.5	(4443.4, 5246.9)	337	3875.9	(3322.9, 4520.9)
Additional Serotypes						
22F	991	3938.8	(3654.3, 4245.6)	317	290.9	(220.8, 383.3)
33F	999	11734.1	(10917.2, 12612.2)	334	2181.5	(1826.1, 2606.1)

Source: Table 6 in Statistical Report: Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an ^{(b) (4)} Test ^{(b) (4)} OPA Testing.

Reviewer Comment:

My analysis of the primary immunogenicity endpoints showed similar results.

6.3.11.2 Analyses of Secondary Endpoints

- Serotype-specific OPA Responses

Following sequential vaccination with PPV23, serotype-specific OPA titers were measured for the 15 serotypes in V114, including 14 shared serotypes between V114 and PPV23, and 1 serotype unique to V114 (6A). V114 or Prevnar 13 followed by PPV23 was immunogenic for all 15 serotypes as assessed by serotype-specific OPA GMTs at 30 days postvaccination with PPV23 (Month 7). PPV23 elicited an immune response for serotypes 22F and 33F at 30 days postvaccination with PPV23 in the Prevnar 13 group.

- Serotype-specific IgG Responses

As observed for OPA GMTs, V114 was immunogenic in pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease as assessed by IgG GMCs at 30 days postvaccination (Day 30) for all 15 serotypes contained in the vaccine. Prevnar 13 was immunogenic as assessed by IgG responses at 30 days postvaccination for all 13 serotypes contained in the vaccine. V114 or Prevnar 13 followed by PPV23 was immunogenic for all 15 serotypes as assessed by serotype-specific IgG GMCs at 30 days postvaccination with PPV23 (Month 7). PPV23 elicited an immune response for serotypes 22F and 33F at 30 days postvaccination with PPV23 in the Prevnar 13 group.

6.3.11.3 Subpopulation Analyses

- V114 was immunogenic within age, sex, race and ethnic subgroups as assessed by OPA GMTs for all 15 serotypes contained in the vaccine at 30 days postvaccination (Day 30). It is noted that, within each intervention group, there was a trend toward lower serotype-specific OPA GMTs in the older age group (40 to 49 years of age) compared with the younger age group (18 to 29 years of age).
- V114 was immunogenic in participants enrolled at CAIH sites as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine at Day 30 postvaccination with PCV. V114 followed by PPV23 was immunogenic in participants enrolled at CAIH sites as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine at Month 7 postvaccination with PCV.
- V114 was immunogenic in participants with no risk factors, with a single risk factor, with 2 or more risk factors as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine at Day 30 postvaccination with PCV. V114 followed by PPV23 was immunogenic in participants with no risk factors, with a single risk factor, with 2 or more risk factors as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine at Month 7 postvaccination with PCV.

6.3.11.4 Dropouts and/or Discontinuations

Please refer to 6.3.10.1.3.

6.3.11.5 Exploratory and Post Hoc Analyses

N/A

6.3.12 Safety Analyses

• Following Vaccination With PCV

The majority of participants in both intervention groups experienced at least 1 AE. The proportions of participants who experienced SAEs were 4.3% and 3.2% for the V114 and Prevnar 13 groups, and none of the SAEs were considered by the investigator to be related to study vaccine. Over the duration of the study, 5 participants died (V114: 3 vs. Prevnar 13: 2) and 3 (V114) discontinued study intervention due to AEs. The proportions of participants with injection-site AEs, systemic AEs, and vaccine-related systemic AEs were comparable across intervention groups (Table 17).

Table 17. Summary of Adverse Events
(All Participants as Treated Population) (Following PCV)

	V114 n (%)	V114 (95% CI)	Prevnar 13 n (%)	Prevnar 13 (95% CI)
Subjects in population	1134		378	
with one or more adverse events	960 (84.7)	(82.4, 86.7)	312 (82.5)	(78.3, 86.2)
injection-site	893 (78.7)		272 (72.0)	
systemic	707 (62.3)		238 (63.0)	
with no adverse event	174 (15.3)		66 (17.5)	
with vaccine-related† adverse events	925 (81.6)	(79.2, 83.8)	293 (77.5)	(73.0, 81.6)
injection-site	893 (78.7)		272 (72.0)	
systemic	555 (48.9)		176 (46.6)	
with serious adverse events	49 (4.3)	(3.2, 5.7)	12 (3.2)	(1.7, 5.5)
with serious vaccine-related adverse events	0 (0.0)	(0.0, 0.3)	0 (0.0)	(0.0, 0.8)
who died	3 (0.3)	(0.1, 0.8)	2 (0.5)	(0.1, 1.9)
discontinued vaccine due to an adverse event	3 (0.3)	(0.1, 0.8)	0 (0.0)	(0.0, 0.8)
discontinued vaccine due to a vaccine-related adverse event	0(0.0)		0 (0.0)	
discontinued vaccine due to a serious adverse event	3(0.3)		0(0.0)	
discontinued vaccine due to a serious vaccine-related adverse event	0(0.0)		0(0.0)	

Source: Table 12-1 in the Study V114-017 CSR

- Following Vaccination with PPV23

The majority of participants in both intervention groups experienced at least 1 AE following vaccination with PPV23 (V114 76.0% vs. Prevnar 13 76.5%). The proportions of participants who experienced SAEs were 0.3% in the V114 group and 0.9% in the Prevnar 13 group. One participant in the Prevnar 13 group experienced an SAE that was considered by the investigator to be related to study vaccine. No participants died during the follow-up period for PPV23 (Months 6 to 7). The proportions of participants with injection-site AEs, systemic AEs, and vaccine-related systemic AEs following vaccination with PPV23 were comparable across intervention groups.

6.3.12.1 Methods

Safety analysis was conducted with descriptive statistics.

6.3.12.3 Deaths

There were 5 deaths reported during the study. Three deaths occurred following vaccination with V114 due to SAEs of multiple injuries, hepatic encephalopathy, and completed suicide. Two deaths occurred following vaccination with Prevnar 13 due to SAEs of cardiac failure and haemorrhagic stroke. None of the deaths were considered by the investigator to be related to study vaccine.

6.3.12.4 Nonfatal Serious Adverse Events

- Following vaccination with PCV

The proportion of participants with SAEs were 4.3% and 3.2% in the V114 and Prevnar 13 groups, respectively. None of the SAEs were considered by the investigator to be vaccine related.

- Following vaccination with PPV23

The proportion of participants with SAEs following vaccination with PPV23 were 0.3% and 0.9% in the V114 and Prevnar 13 groups, respectively. One participant in the Prevnar 13 group experienced an SAE of generalized tonic-clonic seizure 2 days following vaccination with PPV23 that was considered by the investigator to be related to study vaccine

6.3.12.5 Adverse Events of Special Interest (AESI)

NA

6.3.12.6 Clinical Test Results

N/A

6.3.12.7 Dropouts and/or Discontinuations

Three participants in the V114 group discontinued study intervention due to serious, non-vaccine-related AEs of colon cancer, nephrotic syndrome, and rheumatoid arthritis, which occurred within the protocol-defined reporting period.

6.4 Study V114-021: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 When Administered Concomitantly with Influenza Vaccine in Healthy Adults 50 Years of Age or Older (PNEU-FLU)

6.4.1 Objectives

6.4.1.1 Primary Objectives:

- To evaluate the safety and tolerability of V114 and quadrivalent influenza vaccine (QIV) when administered concomitantly compared with V114 and QIV when administered non-concomitantly with respect to the proportion of participants with adverse events (AEs).
- To compare the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination with V114 administered concomitantly with QIV versus V114 administered non-concomitantly with QIV.
 - Hypothesis (H1): V114 administered concomitantly with QIV is noninferior to V114 administered non-concomitantly with QIV as measured by serotype-specific OPA GMTs at 30 days postvaccination with V114. The statistical criterion for noninferiority required the lower bound of the 2-sided 95% CI of the OPA GMT ratio (concomitant/non-concomitant) to be greater than 0.50.
- To compare the strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV administered concomitantly with V114 versus QIV administered non-concomitantly with V114.
 - Hypothesis (H2): QIV administered concomitantly with V114 is noninferior to QIV administered non-concomitantly with V114 as measured by strain-specific HAI GMTs at 30 days postvaccination with QIV. The statistical criterion for noninferiority required the lower bound of the 2-sided 95% CI of the HAI GMT ratio (concomitant/non-concomitant) to be greater than 0.50.

6.4.1.1 Secondary Objectives:

- To evaluate the serotype-specific Immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days postvaccination with V114 administered concomitantly with QIV compared with V114 administered non-concomitantly with QIV.
- Within each vaccination group, to evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥ 4 -fold rise from baseline (pre-vaccination with V114) to 30 days postvaccination with V114 for both OPA and IgG responses for participants administered V114 concomitantly with QIV and participants administered V114 non-concomitantly with QIV.
- Within each vaccination group, to evaluate the strain-specific (1) GMFRs from baseline (pre-vaccination with QIV) to 30 days postvaccination with QIV, (2) proportions of participants with an HAI titer $\geq 1:40$ at 30 days postvaccination with QIV, and (3) proportions of participants that seroconverted at 30 days postvaccination with QIV for participants administered QIV concomitantly with V114 and participants administered QIV non-concomitantly with V114.

6.4.2 Design Overview

This was a randomized, placebo-controlled, parallel-group, multisite, double-blind study of V114 in healthy adults. A total of 1200 participants were randomized in a 1:1 ratio to receive either V114 with concomitant QIV or V114 with nonconcomitant QIV.

Randomization was stratified by age (50 to 64 years, 65 to 74 years, and 75 years or older; at least 50% of the participants were to be 65 years of age or older) and by history of prior PPV23 vaccination (yes and no; at least 50% of participants were to be PPV23-naïve).

6.4.3 Population

Healthy males or females ≥ 50 years of age.

6.4.4 Study Treatments or Agents Mandated by the Protocol

- V114 with concomitant QIV, followed by placebo;
- V114 with nonconcomitant QIV.

6.4.6 Sites and Centers

This study was conducted at 45 centers in US.

6.4.7 Surveillance/Monitoring

N/A

6.4.8 Endpoints

- Primary Immunogenicity Endpoints:
 - Serotype-specific OPA responses for the 15 serotypes in V114 at 30 days postvaccination with V114.

- Strain-specific HAI responses for the 4 strains in QIV at 30 days postvaccination with QIV.
- Secondary Immunogenicity Endpoints:
 - Serotype-specific IgG responses for the 15 serotypes in V114 at 30 days postvaccination with V114.
 - Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at pre-vaccination with V114 and 30 days postvaccination with V114.
 - Strain-specific HAI responses for the 4 strains in QIV at pre-vaccination with QIV and 30 days postvaccination with QIV
- Primary Safety Endpoints
 - Solicited injection-site AEs from Day 1 through Day 5 postvaccination
 - Solicited systemic AEs from Day 1 through Day 14 postvaccination
 - Vaccine-related serious adverse events (SAEs) from Day 1 through Month 7

6.4.9 Statistical Considerations & Statistical Analysis Plan

- Blinding

This was a double-blind study.

- Randomization

Subjects were assigned randomly in a 1:1 ratio to receive either V114 concomitantly with QIV or V114 non-concomitantly with QIV. Randomization was stratified by age (50 to 64 years of age, 65 to 74 years of age, and ≥ 75 years of age) or by history of prior PPV23 vaccination.

- Definitions of analysis populations

- Per-Protocol (PP) Population: all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. The PP population served as the primary population for the analysis of immunogenicity data in this study.
- Full Analysis Set (FAS) Population: all randomized participants who received at least 1 study vaccination and had at least 1 serology result. The FAS population was used for supportive analysis.
- Safety Analysis Population (All Participants as Treated (APaT) population): all randomized participants who received at least 1 dose of study vaccination.

- Sample size determination

The applicant planned to randomize approximately 600 participants into the concomitant group and 600 participants into the nonconcomitant group. The applicant indicated that the sample size would have approximately 87% power for demonstrating noninferiority of the serotype-specific OPA GMT ratios for the 15 pneumococcal serotypes included in V114 and >99.9% power for demonstrating noninferiority of the strain-specific HAI GMT ratios for the 4 influenza strains in QIV at an overall 1-sided 2.5% alpha-level. Because the 2 hypotheses were assumed to be independent and the success of the study

required that the statistical criteria be met for both hypotheses, the overall power for the primary immunogenicity hypotheses was estimated to be approximately 87%.

- **Statistical Analysis for Primary Immunogenicity Endpoint**

The primary objective (to compare the serotype-specific OPA GMTs at 30 days postvaccination with V114 between participants administered V114 concomitantly with QIV versus participants administered V114 non-concomitantly with QIV) was assessed via the following noninferiority hypotheses:

$$H_0: \text{GMT}_1/\text{GMT}_2 \leq 0.50 \text{ versus}$$

$$H_1: \text{GMT}_1/\text{GMT}_2 > 0.50,$$

where GMT_1 is the serotype-specific OPA GMT for the concomitant group and GMT_2 is the serotype-specific OPA GMT for the nonconcomitant group.

The primary objective (to compare the strain-specific HAI GMTs at 30 days postvaccination with QIV between participants administered QIV concomitantly with V114 versus participants administered QIV non-concomitantly) was assessed via the following noninferiority hypotheses:

$$H_0: \text{GMT}_1/\text{GMT}_2 \leq 0.50 \text{ versus}$$

$$H_1: \text{GMT}_1/\text{GMT}_2 > 0.50,$$

where GMT_1 is the strain-specific HAI GMT for the concomitant group and GMT_2 is the strain-specific HAI GMT for the nonconcomitant group.

To address the 2 primary immunogenicity objectives, the serotype-specific OPA GMTs at 30 days postvaccination with V114 and strain-specific HAI GMTs at 30 days postvaccination with QIV were compared between intervention groups separately. Comparisons were made through the estimation of serotype-specific OPA GMT ratios for each of the 15 serotypes in V114 and strain-specific HAI GMT ratios for each of the 4 strains in QIV, respectively. Estimation of the ratios, 95% CI, and the hypothesis test (i.e., 1-sided p-value) was calculated using a constrained longitudinal data analysis (cLDA) method. In this model, the response vector consisted of the log-transformed baseline and 30 days postvaccination antibody titers. The repeated-measures model included terms for vaccination group, time, the interaction of time-by-vaccination group (with a restriction of the same baseline mean across groups), age stratum (i.e., 50 to 64 years, 65 to 74 years, and ≥ 75 years) at baseline, history of prior PPV23 stratum (i.e., Yes and No), age stratum-by-time interaction, and history of prior PPV23 stratum-by-time interaction. This model allowed for different baseline means for each stratum, but restricted the baseline mean within both the age stratum levels and the history stratum levels to be the same for both vaccination groups.

- **Statistical Analysis for Secondary Immunogenicity Endpoints**

A similar statistical approach was used to evaluate the serotype-specific IgG GMCs at 30 days postvaccination with V114 for participants administered V114 concomitantly with QIV and participants administered V114 non-concomitantly with QIV. Descriptive statistics with point estimates and within-group 95% CIs were provided for all other immunogenicity endpoints.

- **Multiplicity adjustment**

The overall success of the study required demonstrating success on all 15 pneumococcal serotypes and all 4 influenza strains included in the primary immunogenicity hypotheses. This approach controlled the 1-sided type-I error rate at 0.025, and no multiplicity adjustment was required.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

6.4.10.1.1 Demographics

Demographics and baseline characteristics were comparable for vaccinated participants across intervention groups. Overall, 20.9% of participants reported prior administration of PPV23. Participants with prior administration of PPV23 had a median age of 68.0 years, compared with a median age of 63.0 years among participants without prior administration of PPV23. Prior administration of PPV23 by age group was comparable across intervention groups.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.4.10.1.3 Subject Disposition

A total of 1200 participants were randomized. Nearly all randomized participants received all study vaccinations and completed the study (Table 18). The number of participants who discontinued the study, and the reasons for discontinuation, were comparable across intervention groups.

Table 18 Disposition of Subjects (All Randomized Subjects)

	Concomitant Group n	Concomitant Group (%)	Nonconcomitant Group n	Nonconcomitant Group (%)	Total n	Total (%)
Subjects in population	600		600		1200	
Vaccinated at Vaccination 1						
QIV	599	(99.8)	598	(99.7)	1197	(99.8)
V114	599	(99.8)	2	(0.3)	601	(50.1)
Placebo	0	(0.0)	596	(99.3)	596	(49.7)
Vaccinated at Vaccination 2						
V114	0	(0.0)	586	(97.7)	586	(48.8)
Placebo	583	(97.2)	1	(0.2)	584	(48.7)
Trial Disposition						
Completed	583	(97.2)	583	(97.2)	1166	(97.2)
Discontinued	17	(2.8)	17	(2.8)	34	(2.8)
Death	1	(0.2)	0	(0.0)	1	(0.1)
Lost To Follow-Up	7	(1.2)	7	(1.2)	14	(1.2)
Physician Decision	2	(0.3)	3	(0.5)	5	(0.4)
Withdrawal By Subject	7	(1.2)	7	(1.2)	14	(1.2)

Source: Table 10-1 in the Study V114-021 CSR

6.4.11 Efficacy Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

- Serotype-specific OPA GMTs at 30 Days Postvaccination with V114

V114 administered concomitantly with QIV was noninferior to V114 administered nonconcomitantly with QIV as assessed by serotype-specific OPA GMTs at 30 days postvaccination with V114. The lower bounds of the 2-sided 95% CIs of the OPA GMT ratios were >0.50 for all 15 serotypes (Table 19).

Table 19 Analysis of Postvaccination OPA GMTs (Per-Protocol Population)

Serotype	Concomitant Group (N=599) n	Concomitant Group (N=599) GMT	Nonconcomitant Group (N=598) n	Nonconcomitant Group (N=598) GMT	GMT Ratio Concomitant / Nonconcomitant (95% CI)
1	593	140.1	567	211.5	0.66 (0.54, 0.82)
3	591	137.9	566	147.4	0.94 (0.81, 1.09)
4	591	901.3	561	1078.5	0.84 (0.69, 1.01)
5	593	396.1	567	500.6	0.79 (0.64, 0.98)
6A	581	5564.2	561	6615.9	0.84 (0.71, 1.00)
6B	585	3904.0	563	4436.5	0.88 (0.74, 1.04)
7F	588	3563.2	560	4119.5	0.86 (0.75, 0.99)
9V	591	2859.6	566	2874.1	0.99 (0.86, 1.15)
14	589	2024.8	567	2228.6	0.91 (0.77, 1.08)
18C	591	3022.8	566	3802.7	0.79 (0.68, 0.92)
19A	589	3208.4	564	3849.0	0.83 (0.73, 0.95)
19F	591	2523.2	566	2473.9	1.02 (0.89, 1.17)
22F	586	2243.4	560	2932.5	0.77 (0.64, 0.91)
23F	584	2206.2	556	2592.2	0.85 (0.70, 1.03)
33F	592	8142.9	567	9807.4	0.83 (0.72, 0.96)

Source: Table 11-1 in the Study V114-021 CSR

- Strain-specific HAI GMTs at 30 Days Postvaccination with QIV

QIV administered concomitantly with V114 was noninferior to QIV administered nonconcomitantly with V114 as assessed by strain-specific HAI GMTs at 30 days postvaccination with QIV. The lower bounds of the 2-sided 95% CIs of the HAI GMT ratios were >0.50 for all 4 strains (Table 20).

Table 20 Analysis of Postvaccination HAI GMTs (Per-Protocol Population)

Influenza Strain	Concomitant Group (N = 599) n	Concomitant Group (N = 599) GMT	Nonconcomitant Group (N = 598) n	Nonconcomitant Group (N = 598) GMT	GMT Ratio (Concomitant Group / Non-concomitant Group) (95% CI)
H1N1	592	124.82	593	115.00	1.09 (0.94, 1.25)
H3N2	592	87.85	593	85.62	1.03 (0.90, 1.17)

B-Victoria	592	35.53	593	36.88	0.96 (0.86, 1.08)
B-Yamagata	592	33.47	593	33.13	1.01 (0.90, 1.13)

Source: Table 11-2 in the Study V114-021 CSR

Reviewer Comments: *My analysis using cLDA showed similar results for the primary immunogenicity endpoint analyses. The applicant’s cLDA model restricted the baseline mean within both the age stratum levels and the history stratum levels to be the same for both vaccination groups. To evaluate this assumption, I conducted additional analysis to compare the serotype-specific OPA GMTs at 30 days postvaccination and strain-specific HAI GMTs at 30 days postvaccination with QIV between the intervention groups, using ANCOVA to adjust for baseline values. The analyses showed similar results.*

6.4.11.2 Analyses of Secondary Endpoints

- Serotype-specific IgG GMCs at 30 Days Postvaccination with V114

The point estimates and 95% CIs for IgG GMC ratios at 30 days postvaccination with V114 showed similar trend with those for OPA GMTs in the primary analysis.

- Serotype-specific OPA and IgG Antibody Responses

Some Pneumococcal serotypes showed lower serotype-specific OPA GMTs at baseline (pre-vaccination with V114) and 30 days postvaccination with V114 in the concomitant group compared with the nonconcomitant group. OPA GMFRs and the proportions of participants with ≥ 4 -fold rise in OPA responses from baseline to 30 days postvaccination were comparable across intervention groups.

Serotype-specific IgG GMCs at baseline (prevaccination with V114) were comparable in the concomitant and nonconcomitant group. There was a trend toward lower serotype-specific IgG GMCs at 30 days postvaccination with V114 and lower IgG GMFRs in the concomitant group compared with the nonconcomitant group. The proportions of participants with ≥ 4 -fold rise in IgG responses from baseline to 30 days postvaccination were comparable in both groups.

- Strain-specific HAI Responses

The intervention groups were comparable for HAI GMTs, HAI GMFRs, proportions of participants with HAI titers $\geq 1:40$, and proportions of participants who seroconverted at 30 days postvaccination with QIV.

6.4.11.3 Subpopulation Analyses

Serotype-specific OPA GMT ratios and strain-specific HAI GMT ratios for the concomitant versus nonconcomitant group at 30 days postvaccination were similar across age subgroups (50 to 64, 65 to 74, and ≥ 75 years of age), sex subgroups, race subgroups, ethnicity subgroups, and subgroups for history of PPV23 administration.

6.4.11.4 Dropouts and/or Discontinuations

Please refer to section 6.4.10.1.3.

6.4.11.5 Exploratory and Post Hoc Analyses

N/A

6.4.12 Safety Analyses

The proportions of participants with injection-site AEs, systemic AEs, and vaccine-related systemic AEs were comparable across intervention groups (Table 25). The proportions of participants who experienced SAEs was low (<4%) across intervention groups, and none of the SAEs were considered by the investigator to be related to study vaccine. Over the duration of the study, 1 participant died, and 3 participants discontinued study intervention due to AEs.

Table 21 Summary of Adverse Event
(All Participants as Treated Population) (Following Any Vaccination)

	Concomitant Group n (%)	Non-concomitant Group n (%)	Difference in % vs Non-concomitant Group
Subjects in population	600	596	
with one or more adverse events	482 (80.3)	488 (81.9)	-1.5 (-6.0, 2.9)
injection-site	430 (71.7)	440 (73.8)	
systemic	341 (56.8)	345 (57.9)	
with no adverse event	118 (19.7)	108 (18.1)	
with vaccine-related [†] adverse events	452 (75.3)	460 (77.2)	-1.8 (-6.7, 3.0)
injection-site	430 (71.7)	440 (73.8)	
systemic	222 (37.0)	227 (38.1)	
with serious adverse events	22 (3.7)	14 (2.3)	1.3 (-0.7, 3.4)
with serious vaccine-related adverse events	0 (0.0)	0 (0.0)	0.0 (-0.6, 0.6)
who died	1 (0.2)	0 (0.0)	0.2 (-0.5, 0.9)
discontinued vaccine due to an AE	2 (0.3)	1 (0.2)	0.2 (-0.6, 1.1)
discontinued vaccine due to a vaccine related AE	1 (0.2)	1 (0.2)	
discontinued vaccine due to a serious AE	1 (0.2)	0 (0.0)	
discontinued vaccine due to a serious vaccine-related adverse event	0 (0.0)	0 (0.0)	

Source: Table 12-1 in the Study V114-021 CSR

6.4.12.1 Methods

The safety analyses were performed using descriptive statistics.

6.4.12.3 Deaths

One death due to myocardial infarction was reported for a participant in the concomitant group. The investigator considered that the death was not related to study vaccine.

6.4.12.4 Nonfatal Serious Adverse Events

The proportions of participants with SAEs were 3.7% and 2.3%, respectively, for the concomitant group and non-concomitant group. None of the SAEs were considered vaccine related by the investigator.

6.4.12.5 Adverse Events of Special Interest (AESI)

There were no additional AEs of special interest for this study.

6.4.12.6 Clinical Test Results

N/A

6.4.12.7 Dropouts and/or Discontinuations

Three participants discontinued study intervention due to AEs that occurred within the protocol-defined reporting period (2 in the concomitant group; 1 in the non-concomitant group).

6.5 Study V114-016: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX23 One Year Later in Healthy Adults 50 Years of Age or Older (PNEU-PATH)

6.5.1 Objectives

6.5.1.1 Primary Objectives

- To evaluate the safety and tolerability of V114 compared with Prevnar 13 with respect to the proportion of participants with adverse events (AEs).
- To evaluate the safety and tolerability of PNEUMOVAX23 (PPV23) administered 12 months following V114 compared with PPV23 administered 12 months following Prevnar 13 with respect to the proportion of participants with AEs.
- To evaluate the serotype specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination with PPV23 (Month 13) for participants administered V114 compared with participants administered Prevnar 13 12 months before receipt of PPV23.

6.5.1.2 Secondary Objectives

- To evaluate the serotype specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination with PPV23 (Month 13) for participants administered V114 compared with participants administered Prevnar 13 12 months before receipt of PPV23.
- To evaluate the serotype specific (1) OPA GMTs and IgG GMCs at 30 days postvaccination (Day 30) and (2) Geometric Mean Fold Rises (GMFRs) and proportions of participants with a ≥ 4 -fold rise from prevaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13.
- To evaluate the serotype specific (1) OPA GMTs and IgG GMCs at 12 months postvaccination (Month 12) and (2) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination (Day 1) to 12 months postvaccination (Month 12) for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13.
- To evaluate the serotype specific (1) OPA GMTs and IgG GMCs at 30 days postvaccination with PPV23 (Month 13), (2) GMFRs and proportions of participants with a ≥ 4 -fold rise from prevaccination (Day 1) to 30 days postvaccination (Month 13) with PPV23 for both OPA and IgG responses, and (3) GMFRs and proportions of

participants with a ≥ 4 -fold rise from pre-vaccination with PPV23 (Month 12) to 30 days postvaccination with PPV23 (Month 13) for both OPA and IgG responses for participants administered V114 and separately for participants administered Prevnar 13 12 months before receipt of PPV23.

6.5.2 Design Overview

This was a randomized, active-controlled, parallel-group, multisite, double-blind study of V114 in healthy adults. A total of 600 participants were planned to be randomized in a 1:1 ratio to receive either V114 or Prevnar 13 on Day 1 and PPV23 at Month 12. Randomization was stratified by age (50 to 64 years, 65 to 74 years, and 75 years or older; at least 50% of the participants were to be 65 years of age or older).

6.5.3 Population

Healthy male or female ≥ 50 years of age.

6.5.4 Study Treatments or Agents Mandated by the Protocol

- Experimental: V114 followed by PNEUMOVAX23;
- Active Comparator: Prevnar 13 followed by PNEUMOVAX23.

6.5.6 Sites and Centers

This study was conducted at 22 centers in 4 countries: Spain, South Korea, Taiwan, and the US.

6.5.7 Surveillance/Monitoring

N/A

6.5.8 Endpoints

- Primary Immunogenicity Endpoint:
Serotype-specific OPA responses for the 15 serotypes in V114 at Month 13
- Secondary Immunogenicity Endpoints:
 - Serotype-specific IgG responses for the 15 serotypes in V114 at Month 13
 - Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1 and Day 30
 - Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1 and Month 12
 - Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 1, Month 12, and Month 13
- Safety Endpoints
 - Following vaccination with V114 or Prevnar 13:
 - Solicited injection-site AEs from Day 1 through Day 5 postvaccination
 - Solicited systemic AEs from Day 1 through Day 14 postvaccination
 - Vaccine-related serious adverse events (SAEs) from Day 1 to Month 12
 - Following vaccination with PNEUMOVAX23:
 - Solicited injection-site AEs from Day 1 through Day 5 postvaccination

- Solicited systemic AEs from Day 1 through Day 14 postvaccination
- Vaccine-related SAEs from Month 12 to Month 13

6.5.9 Statistical Considerations & Statistical Analysis Plan

- Blinding

This was a double-blind study.

- Randomization

Participants were assigned randomly in a 1:1 ratio to 2 study intervention arms.

Randomization was stratified by age at time of randomization: 50 to 64 years of age, 65 to 74 years of age, or ≥ 75 years of age.

- Definitions of analysis populations

- Per-Protocol (PP) population: all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint. The PP population served as the primary population for the analysis of immunogenicity data in this study.
- Full Analysis Set (FAS) population: all randomized participants who received at least 1 study vaccination and had at least 1 serology result. The FAS was used for supportive analysis.
- Safety Analyses population (All Participants as Treated (APaT) population): all randomized participants who received at least 1 dose of study vaccination.

- Sample size determination

This was a descriptive study. This study planned to randomize approximately 300 participants into the V114 group and 300 participants into the Prevnar 13 group.

- Statistical Analysis for Primary Immunogenicity Endpoint

This is an estimation study and no formal hypothesis testing was performed. The serotype-specific OPA GMTs at 30 days postvaccination with PPV23 (Month 13) was compared between vaccination groups through the estimation of serotype-specific OPA GMT ratios for each of the 15 serotypes in V114. Estimation of the OPA GMT ratios and computation of the corresponding 95% CIs was calculated using a cLDA method. In this model, the response vector consisted of the log-transformed baseline (Day 1) and post baseline (Day 30, Month 12, and Month 13) antibody titers. The repeated measures model included terms for vaccination group, time, the interaction of time-by-vaccination group (with a restriction of the same baseline mean across groups), age stratum (i.e., 50 to 64 years, 65 to 74 years, and ≥ 75 years) at Day 1, and age stratum-by-time interaction.

- Statistical Analysis for Secondary Immunogenicity Endpoints

A similar statistical approach was used to evaluate the IgG GMCs at 30 days postvaccination with V114 or Prevnar 13 (Day 30), at 12 months postvaccination with V114 or Prevnar 13 (Month 12), and at 30 days postvaccination with PPV23 (Month 13) for participants administered V114 compared with participants administered Prevnar 13. Descriptive statistics with point estimates and within-group 95% CIs were provided for all immunogenicity endpoints.

- Multiplicity adjustment
No adjustment was made for multiplicity.

6.5.10 Study Population and Disposition

6.6.10.1 Populations Enrolled/Analyzed

6.5.10.1.1 Demographics

Demographic characteristics were comparable for vaccinated participants across intervention groups. The median age of participants was 65 years (range: 50 to 90 years). Approximately 12% of participants were ≥ 75 years of age. The majority of participants were female, white, and of non-Hispanic or Latino ethnicity.

6.5.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.5.10.1.3 Subject Disposition

A total of 652 participants were randomized. All but 1 randomized participant received either V114 or Prevnar 13 (1 participant who was randomized to V114 withdrew consent prior to vaccination). The majority of participants completed the study. The number of participants who discontinued the study and the reasons for discontinuation were comparable across intervention groups.

6.5.11 Efficacy Analyses

6.5.11.1 Analyses of Primary Endpoint(s)

Serotype-specific OPA GMTs at 30 days following vaccination with PPV23 (Month 13) were comparable between participants administered V114 or Prevnar 13 12 months prior to receipt of PPV23 for all 15 serotypes in V114, as assessed by OPA GMT ratios.

Table 22 Analysis of OPA GMTs at Month 13 (Per-Protocol Population, Based Only on Samples Testing ^{(b) (4)} Negative)

Serotype	V114 (N=326) n	V114 (N=326) GMT	Prevnar 13 (N=325) n	Prevnar 13 (N=325) GMT	GMT Ratio (V114 / Prevnar 13) (95% CI)
13 Shared Serotypes					
1	321	387.2	323	278.0	1.39 (1.11, 1.75)
3	321	277.6	322	259.2	1.07 (0.90, 1.28)
4	321	1670.1	323	1559.6	1.07 (0.86, 1.34)
5	321	693.0	323	577.2	1.20 (0.93, 1.55)
6A	321	3221.7	323	2791.4	1.15 (0.94, 1.42)
6B	321	3194.1	323	2859.7	1.12 (0.93, 1.35)
7F	321	5100.9	322	4830.9	1.06 (0.90, 1.25)
9V	321	2027.1	323	1864.6	1.09 (0.90, 1.31)
14	321	3370.6	322	2641.0	1.28 (1.06, 1.54)
18C	321	2356.8	323	2086.7	1.13 (0.95, 1.34)

Serotype	V114 (N=326) n	V114 (N=326) GMT	Prevnar 13 (N=325) n	Prevnar 13 (N=325) GMT	GMT Ratio (V114 / Prevnar 13) (95% CI)
19A	321	3651.6	323	3132.7	1.17 (0.97, 1.40)
19F	321	2236.1	323	2151.9	1.04 (0.89, 1.21)
23F	320	1897.6	323	1478.2	1.28 (1.01, 1.62)
Additional Serotypes					
22F	321	3114.2	323	1903.3	1.64 (1.29, 2.07)
33F	321	7932.7	323	8225.9	0.96 (0.78, 1.19)

Source: Table 4 in Statistical Report: Sensitivity Analysis of Primary and Key Secondary OPA Endpoints of Studies V114-016, V114-017, V114-019, and V114-020 Using an ^{(b) (4)} Test ^{(b) (4)} OPA Testing

Reviewer Comments: My analysis showed similar results for the primary immunogenicity endpoint analysis.

6.5.11.2 Analyses of Secondary Endpoints

- Serotype-specific IgG GMCs at 30 Days Postvaccination with PPV23
Between-group comparisons of IgG GMCs at 30 days following vaccination with PPV23 (Month 13) showed similar trend with the primary analysis of OPA GMTs.

- Serotype-specific OPA GMTs and IgG GMCs at 30 Days Postvaccination with PCV
Serotype-specific OPA GMTs and IgG GMCs at 30 days following vaccination with PCV (Day 30) were comparable across intervention groups for the 13 shared serotypes, as assessed by OPA GMT ratios and IgG GMC ratios. OPA GMTs and IgG GMCs at 30 days following vaccination with PCV were higher in the V114 group than in the Prevnar 13 group for the 2 serotypes unique to V114.

- Serotype-specific OPA GMTs and IgG GMCs at 12 Months Postvaccination with PCV
OPA GMTs and IgG GMCs at 12 months following vaccination with PCV (Month 12) were comparable across intervention groups for the 13 shared serotypes, as assessed by OPA GMT ratios and IgG GMC ratios. OPA GMTs and IgG GMCs at 12 months following vaccination with PCV were higher in the V114 group than in the Prevnar 13 group for the 2 serotypes unique to V114.

6.5.11.3 Subpopulation Analyses

Serotype-specific OPA GMT ratios at Month 13 between the intervention groups were similar for age, sex, race, and ethnicity subgroups.

6.5.11.4 Dropouts and/or Discontinuations

Please refer to section 6.5.10.1.3.

6.5.11.5 Exploratory and Post Hoc Analyses

N/A

6.5.12 Safety Analyses

- Following Vaccination with PCV

Following vaccination with PCV (but prior to administration of PPV23), the majority of participants in both intervention groups (V114 72.5% vs. Prevnar 13 62.0%) experienced at least one AE. Overall, AEs were reported for more participants in the V114 group compared with the Prevnar 13 group. Injection-site AEs (V114 61.2% vs. Prevnar 13 48.1%), systemic AEs (V114 49.5% vs. Prevnar 13 38.0%), and vaccine-related AEs (V114 65.7% vs. Prevnar 13 55.2%) were more frequently experienced by participants in the V114 group than in the Prevnar 13 group. The proportions of participants who experienced SAEs were 5.2% and 5.9%, respectively, for the V114 and Prevnar 13 group. None of the SAEs were considered by the investigator to be related to study vaccine.

- Following Vaccination with PPV23

As observed following vaccination with PCV, the majority of participants in both intervention groups experienced at least one AE following vaccination with PPV23 (V114 73.8% vs. Prevnar 13 70.5%). The proportions of participants with injection-site AEs (V114 67.8% vs. Prevnar 13 63.6%), systemic AEs (V114 47.3% vs. Prevnar 13 41.1%), and vaccine-related AEs (V114 71.5% vs. Prevnar 13 67.2%) were comparable across intervention groups. The proportions of participants who experienced SAEs were 0.3% and 0.7%, respectively, for the V114 and Prevnar 13 groups. None of the SAEs were considered by the investigator to be related to study vaccine.

6.5.12.1 Methods

The safety analyses were performed using descriptive statistics.

6.5.12.3 Deaths

No deaths.

6.5.12.4 Nonfatal Serious Adverse Events

- Following Vaccination With PCV

The proportions of participants with SAEs occurring within the 12 months following administration of PCV were low and comparable across intervention groups (V114: 5.2% vs. Prevnar 13: 5.9%). None of the SAEs were considered by the investigator to be vaccine related.

- Following Vaccination with PPV23

The proportions of participants who experienced SAEs were 0.3% and 0.7%, respectively, for the V114 and Prevnar 13 group; none of the SAEs were considered by the investigator to be vaccine-related.

6.5.12.5 Adverse Events of Special Interest (AESI)

No AEs of special interest were defined for this study.

6.5.12.6 Clinical Test Results

N/A

6.5.12.7 Dropouts and/or Discontinuations

Three participants discontinued study intervention (i.e., did not receive PPV23 at Month 12) due to AEs that occurred within the protocol-defined reporting period following administration of PCV.

6.6 Study V114-018: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX23 Eight Weeks Later in Adults Infected with HIV (PNEU-WAY)

6.6.1 Objectives

6.6.1.1 Primary Objectives

- To evaluate the safety and tolerability of V114 and Prevnar 13 with respect to the proportion of participants with adverse events (AEs) within each vaccination group separately.
- To evaluate the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) and Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination (Day 30) with V114 and Prevnar 13 within each vaccination group separately.

6.6.1.2 Secondary Objectives

- To evaluate the safety and tolerability of PNEUMOVAX23 (PPV23) administered 8 weeks following V114 and of PPV23 administered 8 weeks following Prevnar 13 with respect to the proportion of participants with AEs within each vaccination group separately.
- To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PPV23 (Week 12) for participants administered V114 and separately for participants administered Prevnar 13 8 weeks before receipt of PPV23.

6.6.2 Design Overview

Approximately 300 individuals were randomly assigned in a 1:1 ratio to receive either V114 (150 participants) or Prevnar 13 (150 participants) at Day 1. Randomization was stratified by CD4+ T-cell count:

- Stratum 1: CD4+ T-cell count ≥ 50 to < 200 cells/ μ L
- Stratum 2: CD4+ T-cell count ≥ 200 to < 500 cells/ μ L
- Stratum 3: CD4+ T-cell count ≥ 500 cells/ μ L

At least 50% of participants were to be enrolled into Stratum 2. All participants were to receive a single dose of PPV23 at Visit 4 (Week 8).

6.6.3 Population

Pneumococcal vaccine-naïve adults ≥ 18 years of age infected with HIV (with CD4+ T-cell count ≥ 50 cells/ μ L and plasma HIV RNA $< 50,000$ copies/mL tested at Screening).

6.6.4 Study Treatments or Agents Mandated by the Protocol

- Experimental: V114 followed by PNEUMOVAX23
- Active Comparator: Prevnar 13 followed by PNEUMOVAX23

6.6.6 Sites and Centers

This study was conducted at 13 centers in 5 countries.

6.6.7 Surveillance/Monitoring

N/A

6.6.8 Endpoints

- Primary Immunogenicity Endpoint:
Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Day 30
- Secondary Immunogenicity Endpoint
Serotype-specific OPA and IgG responses for the 15 serotypes in V114 at Week 12
- Safety Endpoints
 - Following vaccination with V114 or Prevnar 13:
 - Solicited injection-site AEs from Day 1 through Day 5 postvaccination
 - Solicited systemic AEs from Day 1 through Day 14 postvaccination
 - Vaccine-related serious adverse events (SAEs) from Day 1 to Week 8
 - Following vaccination with PPV23:
 - Solicited injection-site AEs from Day 1 through Day 5 postvaccination
 - Solicited systemic AEs from Day 1 through Day 14 postvaccination
 - Vaccine-related SAEs from Week 8 to Month 6

6.6.9 Statistical Considerations & Statistical Analysis Plan

- Blinding: double-blind.
- Randomization: Please see section 6.6.2.
- Definitions of analysis populations
 - The Per-Protocol (PP) population: all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. The PP population served as the primary population for the analysis of immunogenicity data.
 - The Full Analysis Set (FAS) population: all randomized participants who received at least 1 vaccination and had at least 1 serology result. The FAS population was used for supportive analysis.
 - Safety Analysis population (All Participants as Treated (APaT) population): all randomized participants who received at least 1 dose of study vaccination.
- Sample size determination
This was a descriptive study. This study randomized approximately 150 participants into the V114 group and 150 participants into the Prevnar 13 group.
- Statistical Methods for Immunogenicity Analyses

Immunogenicity analyses were conducted for each of the 15 pneumococcal serotypes in V114 separately. To address the primary immunogenicity objective, evaluation of the OPA GMTs and IgG GMCs at 30 days postvaccination with V114 or Prevnar 13 (Day 30) included descriptive summaries and within-group 95% CIs to be calculated for each vaccination group. Point estimates for the OPA GMTs and IgG GMCs were calculated by exponentiating the estimates of the mean of the natural log values. The within-group CIs were derived by exponentiating the CIs of the mean of the natural log values based on the t distribution. A similar statistical approach was used to evaluate the OPA and IgG responses at 30 days postvaccination with PPV23 (Week 12).

6.6.10 Study Population and Disposition

6.6.10.1 Populations Enrolled/Analyzed

6.6.10.1.1 Demographics

Demographic and baseline characteristics were comparable for vaccinated participants across intervention groups. The majority of participants were male, and the majority were between 18 to 49 years of age. Nearly all participants had CD4+ T-cell count ≥ 200 cells/ μL at screening in both intervention groups and more than half of participants had CD4+ T-cell count < 500 cells/ μL at screening in both intervention groups. CD4+ T-cell counts were distributed similarly across age categories.

6.6.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.6.10.1.3 Subject Disposition

A total of 302 participants were randomized. All randomized participants received either V114 or Prevnar 13 and nearly all received PPV23. Nearly all participants completed the study. The number of participants who discontinued the study was comparable across intervention groups. The reasons for study discontinuation were comparable across intervention groups.

6.6.11 Efficacy Analyses

6.6.11.1 Analyses of Primary Endpoint(s)

- Serotype-specific OPA GMTs at 30 Days Postvaccination with PCV
V114 was immunogenic in pneumococcal vaccine-naïve adults infected with HIV as assessed by OPA GMTs at 30 days postvaccination (Day 30) for all 15 serotypes contained in the vaccine (Table 23). Prevnar 13 was immunogenic as assessed by OPA GMTs at 30 days postvaccination for all 13 serotypes contained in the vaccine.

Table 23 Summary of OPA GMTs at Day 30 (Per-Protocol Population)

	V114 (N=152) n	V114 (N=152) Observed GMT	V114 (N=152) 95% CI	Prevnar13 (N=150) n	Prevnar13 (N=150) Observed GMT	Prevnar13 (N=150) 95% CI
13 Shared Serotypes						
1	131	238.8	(173.1, 329.3)	131	200.9	(142.7, 282.7)

	V114 (N=152) n	V114 (N=152) Observed GMT	V114 (N=152) 95% CI	Prevnar13 (N=150) n	Prevnar13 (N=150) Observed GMT	Prevnar13 (N=150) 95% CI
3	131	116.8	(94.9, 143.7)	130	72.3	(58.6, 89.2)
4	130	824.0	(618.8, 1097.2)	131	1465.5	(1154.5, 1860.3)
5	131	336.7	(242.4, 467.7)	130	276.7	(197.9, 386.7)
6A	126	6421.0	(4890.4, 8430.7)	128	5645.1	(4278.9, 7447.4)
6B	129	4772.9	(3628.3, 6278.7)	130	3554.0	(2751.0, 4591.4)
7F	131	6085.8	(4871.6, 7602.8)	131	6144.3	(4982.8, 7576.6)
9V	129	2836.3	(2311.5, 3480.4)	128	2133.9	(1721.8, 2644.5)
14	131	3508.7	(2730.6, 4508.5)	130	3000.3	(2350.0, 3830.5)
18C	129	3002.2	(2435.5, 3700.8)	129	1560.3	(1213.8, 2005.6)
19A	131	4240.7	(3415.4, 5265.3)	131	3715.9	(2949.2, 4681.8)
19F	131	2438.6	(1972.7, 3014.6)	131	2042.0	(1618.9, 2575.5)
23F	129	1757.4	(1276.1, 2420.2)	127	1787.0	(1309.9, 2437.9)
2 Serotypes Unique to V114						
22F	128	3943.7	(3049.2, 5100.5)	116	109.3	(66.2, 180.3)
33F	131	11342.4	(9184.3, 14007.6)	129	1807.6	(1357.3, 2407.3)

Source: Table 11-1 in the CSR of Study V114-018

- Serotype-specific IgG GMCs at 30 Days Postvaccination with PCV

As observed for OPA GMTs, V114 was immunogenic in pneumococcal vaccine-naïve adults infected with HIV as assessed by IgG GMCs at 30 days postvaccination (Day 30) for all 15 serotypes contained in the vaccine (Table 24). Prevnar 13 was immunogenic as assessed by IgG GMCs at 30 days postvaccination for all 13 serotypes contained in the vaccine.

Table 24 Summary of IgG GMCs at Day 30 (Per-Protocol Population)

	V114 (N=152) n	V114 (N=152) Observed GMC	V114 (N=152) 95% CI	Prevnar13 (N=150) n	Prevnar13 (N=150) Observed GMC	Prevnar13 (N=150) 95% CI
13 Shared Serotypes						
1	139	3.16	(2.48, 4.01)	138	4.27	(3.31, 5.50)
3	139	0.57	(0.48, 0.68)	136	0.50	(0.41, 0.60)
4	138	1.14	(0.90, 1.44)	138	2.00	(1.56, 2.55)
5	139	2.38	(1.89, 3.01)	138	2.03	(1.56, 2.64)
6A	139	5.13	(3.73, 7.04)	138	4.91	(3.49, 6.91)
6B	139	7.17	(5.34, 9.63)	138	5.23	(3.73, 7.35)
7F	139	2.61	(2.00, 3.41)	138	3.74	(2.91, 4.81)
9V	139	3.35	(2.71, 4.14)	137	3.55	(2.77, 4.56)

	V114 (N=152) n	V114 (N=152) Observed GMC	V114 (N=152) 95% CI	Pprevnar13 (N=150) n	Pprevnar13 (N=150) Observed GMC	Pprevnar13 (N=150) 95% CI
14	139	15.44	(11.69, 20.39)	138	15.22	(11.56, 20.03)
18C	139	5.58	(4.33, 7.18)	138	5.07	(3.97, 6.48)
19A	139	9.09	(7.08, 11.67)	138	9.61	(7.36, 12.56)
19F	139	6.41	(4.89, 8.39)	138	6.21	(4.73, 8.15)
23F	139	3.92	(2.94, 5.22)	138	4.90	(3.54, 6.77)
2 Serotypes Unique to V114						
22F	139	3.97	(3.06, 5.15)	137	0.20	(0.17, 0.25)
33F	139	6.83	(5.14, 9.07)	138	0.77	(0.62, 0.95)

Source: Table 11-2 in the CSR of Study V114-018

Reviewer Comments: My analysis showed similar results for the primary immunogenicity endpoint analyses.

6.6.11.2 Analyses of Secondary Endpoints

- Serotype-specific OPA GMTs at 30 Days Postvaccination with PPV23

Following vaccination with PPV23, serotype-specific OPA titers were measured for the 15 serotypes in V114, including 14 shared serotypes between V114 and PPV23, and 1 serotype unique to V114 (6A). Serotype-specific OPA GMTs at 30 days postvaccination with PPV23 (Week 12) were comparable with those observed at 30 days postvaccination with PCV (Day 30) in the V114 group for all 15 serotypes and in the Pprevnar 13 group for all 13 serotypes contained in the vaccine. PPV23 elicited an immune response for serotypes 22F and 33F at 30 days postvaccination with PPV23 in the Pprevnar 13 group.

- Serotype-specific IgG GMCs at 30 Days Postvaccination with PPV23

As observed for OPA GMTs, serotype-specific IgG GMCs at 30 days postvaccination with PPV23 (Week 12) were comparable with those observed at 30 days postvaccination with PCV (Day 30) in the V114 group for all 15 serotypes and in the Pprevnar 13 group for all 13 serotypes contained in the vaccine. PPV23 elicited an immune response for serotypes 22F and 33F at 30 days postvaccination with PPV23 in the Pprevnar 13 group.

6.6.11.3 Subpopulation Analyses

V114 was immunogenic within each age, sex, race, and ethnicity subgroup, as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine at 30 days postvaccination. V114 was immunogenic in both CD4+ T-cell count subgroups (≥ 200 to < 500 cells/ μ L, ≥ 500 cells/ μ L) as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine at 30 days postvaccination. There was a trend toward higher serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PCV in participants with CD4+ T-cell count ≥ 500 cells/ μ L compared with participants with CD4+ T-cell count ≥ 200 to < 500 cells/ μ L across both intervention groups.

6.6.11.4 Dropouts and/or Discontinuations

Please refer to section 6.6.10.1.3.

6.6.11.5 Exploratory and Post Hoc Analyses

N/A

6.6.12 Safety Analyses

- Following Vaccination with PCV

The majority of participants in both intervention groups experienced at least 1 AE (V114 73.0% vs. Prevnar 13 62.7%). The proportions of participants who experienced SAEs were 2.0% and 0.0% for the V114 and Prevnar 13 group, respectively; none of the SAEs were considered by the investigator to be related to study vaccine. No participants died or discontinued study vaccine due to an AE. The proportions of participants with injection-site AEs, systemic AEs, and vaccine-related systemic AEs were comparable across intervention groups.

- Following Vaccination with PPV23

As observed for postvaccination with PCV, the majority of participants in both intervention groups experienced at least 1 AE postvaccination with PPV23 (V114 60.7% vs. Prevnar 13 71.6%). The proportions of participants who experienced SAEs were 1.3% and 4.1% for the V114 and Prevnar 13 group, respectively; none of the SAEs were considered by the investigator to be related to study vaccine. No participants died. The proportions of participants with injection-site AEs, systemic AEs, and vaccine-related systemic AEs postvaccination with PPV23 were comparable across intervention groups.

6.6.12.1 Methods

The safety analyses were performed using descriptive statistics.

6.6.12.3 Deaths

No deaths were reported during the trial.

6.6.12.4 Nonfatal Serious Adverse Events

- Following Vaccination with PCV

The proportions of participants with SAEs were 2.0% and 0.0% for the V114 and Prevnar 13 group, respectively. None of the SAEs were considered by the investigator to be vaccine-related.

- Following Vaccination with PPV23

As observed for postvaccination with PCV, the proportions of participants with SAEs postvaccination with PPV23 were 1.3% and 4.1% for the V114 and Prevnar 13 groups, respectively. None of the SAEs were considered by the investigator to be vaccine-related.

6.6.12.5 Adverse Events of Special Interest (AESI)

NA

6.6.12.6 Clinical Test Results

N/A

6.6.12.7 Dropouts and/or Discontinuations

No participants discontinued study vaccine due to an AE within the protocol-defined reporting period.

7. INTEGRATED OVERVIEW OF EFFICACY

There were no efficacy studies conducted as part of the V114 Phase 3 development program. No integration of immunogenicity data was conducted.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data were integrated across three Phase 3 studies in pneumococcal vaccine-naïve adults ≥ 50 years of age (V114-016, V114-019, and V114-020). These studies were considered appropriate for integration because of the similarities in study design and study population. Summaries of pooled data included point estimates based on the direct pooling and between group comparisons (risk differences and associated 95% confidence intervals [CI] for pre-specified endpoints) calculated via stratified Miettinen and Nurminen (M&N) method using Cochran-Mantel-Haenszel (CMH) weights.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Three Phase 3 studies in pneumococcal vaccine-naïve adults ≥ 50 years of age (V114-016, V114-019, and V114-020).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

- **Demographics:**
Demographic characteristics in the integrated population of pneumococcal vaccine-naïve adults ≥ 50 years of age were comparable across intervention groups. The majority of participants were female (V114 58.0%, Prevnar-13 55.7%), white (V114 82.5%, Prevnar-13 69.7%), and of non-Hispanic or Latino ethnicity (V114 79.3%, Prevnar-13 81.7%).
- **Treatment Exposure**
In the integrated population of pneumococcal vaccine-naïve adults ≥ 50 years of age, 3032 subjects received V114 and 1154 subjects received Prevnar-13.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

N/A

8.4 Safety Results

8.4.1 Deaths

There were 5 deaths in the integrated population. All deaths occurred more than 50 days following vaccination with PCV. None of the deaths were considered by the investigator to be vaccine-related.

8.4.2 Nonfatal Serious Adverse Events

The proportions of participants with SAEs following vaccination with PCV were low and comparable across intervention groups (Table 25). None of the SAEs were considered by the investigator to be vaccine-related. SAE preferred terms reported in more than 2 participants in the V114 group were cellulitis (n=3 [0.1%]), pneumonia (n=3 [0.1%]), and acute respiratory failure (n=3 [0.1%]). No SAE preferred terms were reported in more than 2 participants in the Prevnar 13 group.

Table 25. Analysis of Adverse Event Summary (All Participants as Treated Population) (Following PCV) (V114-016, V114-019, V114-020)

	V114 n	V114 (%) [†]	Prevnar 13 n	Prevnar 13 (%) [†]	Difference in % vs. Prevnar 13 Estimate (95% CI) [†]
Subjects in population	3,032		1,154		
with one or more adverse events	2,302	(72.3)	705	(62.2)	10.1 (6.6, 13.7)
injection-site	2,050	(63.7)	582	(51.4)	
systemic	1,484	(45.1)	434	(39.1)	
with no adverse event	730	(27.7)	449	(37.8)	
with vaccine-related adverse events	2,192	(68.0)	655	(57.7)	10.3 (6.6, 13.9)
injection-site	2,050	(63.7)	582	(51.4)	
systemic	1,196	(34.6)	321	(29.2)	
with serious adverse events	59	(2.1)	25	(2.2)	-0.0 (-1.2, 1.0)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0.0 (-0.4, 0.2)
who died	4	(0.1)	1	(0.1)	0.0 (-0.4, 0.4)

[†] Percentages, differences and confidence intervals are calculated based on stratified Miettinen & Nurminen method with Cochran–Mantel–Haenszel weights.

Source: Table 2.7.4-adultpnemo: 6 in the Summary of Clinical Safety

8.4.3 Study Dropouts/Discontinuations

The discontinuation rates were similar between V114 and Prevnar 13 groups (57 [1.9%] and 26 [2.3%], respectively). The reasons for premature study discontinuation included lost to follow-up (V114: 29 [1.0%]; Prevnar 13: 13 [1.1%]), withdrawal by subject (V114: 22 [0.7%]; Prevnar 13: 10 [0.9%]), and death (V114: 4 [0.1%]; Prevnar 13: 1 [0.1%]).

8.4.4 Common Adverse Events

The majority of participants in both intervention groups experienced 1 or more AEs. A higher proportion of participants with AEs was observed in the V114 group compared with the Prevnar 13 group, including injection-site AEs, systemic AEs and vaccine-related systemic AEs (Table 25).

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Immunogenicity:

- The pivotal study V114-019 was a Phase 3, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 in healthy adults 50 years of age or older. The study success criteria for immunogenicity were met. Specifically, the primary immunogenicity analyses showed that:
 - V114 was noninferior to Prevnar 13 for the 13 shared serotypes and superior to Prevnar 13 for the 2 unique serotypes in V114 as assessed by serotype-specific OPA GMTs at 30 days postvaccination. The lower bounds of the 2-sided 95% CIs of the OPA GMT ratio (V114/Prevnar 13) were greater than 0.5 for the shared serotypes and greater than 2.0 for the 2 unique serotypes.
 - V114 was superior to Prevnar 13 for the 2 unique serotypes in V114 as assessed by the proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from pre-vaccination to 30 days postvaccination. The lower bounds of the 2-sided 95% CIs of the differences (V114-Prevnar 13) between the proportions of participants with a ≥ 4 -fold rise were >0.1 for the 2 unique serotypes.

The key secondary immunogenicity analyses showed that V114 was superior to Prevnar 13 for serotype 3 as assessed by the OPA GMTs at 30 days postvaccination and the proportions of participants with a ≥ 4 -fold rise in OPA responses from pre-vaccination to 30 days postvaccination. The lower bounds of the 2-sided 95% CIs were greater than 1.2 for the GMT ratio (V114/Prevnar 13) and >0 for the difference (V114-Prevnar 13) between the proportions of participants with a ≥ 4 -fold rise.

- Study V114-020 was a Phase 3, multicenter, randomized, double-blind, active comparator-controlled, lot-to-lot consistency study to evaluate the safety, tolerability, and immunogenicity of V114 in healthy adults 50 years of age or older. The primary immunogenicity analyses showed that all 3 lots of V114 met equivalence criteria, as assessed by the serotype-specific OPA GMTs for the 15 serotypes in V114 at 30 days postvaccination. The lower and upper limits of the 95% CIs of the serotype-specific GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all 15 serotypes.
- The applicant conducted Phase 3 Study V114-017 in immunocompetent and Pneumococcal vaccine-naïve adults 18 to 49 years of age with or without at-risk conditions. Using descriptive statistics, the study showed that serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PCV were comparable for the 13 shared serotypes between V114 and Prevnar 13 and higher in the V114 group for the 2 serotypes unique to V114. The study also showed that V114 was immunogenic in immunocompetent adults 18 to 49 years of age with risk factors for pneumococcal disease, including underlying comorbidities (diabetes mellitus, chronic liver disease,

chronic lung disease including asthma, chronic heart disease) and behavioral factors (current smoker, increased alcohol use).

- The Phase 3 study V114-018 showed that V114 elicited an immune response in HIV positive adults as assessed by OPA GMTs and IgG GMCs for all 15 serotypes contained in the vaccine at 30 days postvaccination with PCV. Serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PCV were comparable for the 13 shared serotypes between V114 and Prevnar 13 and higher in the V114 group for the 2 unique serotypes.
- Study V114-016 demonstrated that serotype-specific OPA GMTs at 30 days postvaccination with PPV23 (Month 13) were comparable between participants administered V114 or Prevnar 13 12 months prior to receipt of PPV23 for all 15 serotypes in V114. In addition, between-group comparisons of IgG GMCs at 30 days postvaccination with PPV23 (Month 13) were consistent with those observed in the primary analysis of OPA GMTs.
- Study V114-021 showed that V114 administered concomitantly with QIV met noninferiority criteria for the 15 serotypes in V114 as assessed by serotype-specific OPA GMTs at 30 days postvaccination with V114. The lower bounds of the 2-sided 95% CIs of the OPA GMT ratios (concomitant/non-concomitant) were >0.5 for all 15 serotypes in V114. In addition, QIV administered concomitantly with V114 met noninferiority criteria for the 4 strains in QIV as assessed by strain-specific HAI GMTs at 30 days postvaccination with QIV. The lower bounds of the 2-sided 95% CIs of the HAI GMT ratios (concomitant/non-concomitant) were >0.5 for all 4 strains in QIV.

Safety:

- V114 had a generally comparable safety profile to Prevnar 13 when administered as a single dose to adults ≥ 18 years of age with and without prior pneumococcal vaccination.
 - In pneumococcal vaccine-naïve adults ≥ 18 years of age, the most frequently reported AEs were the solicited AEs. Injection site pain, fatigue, and myalgia occurred most frequently.
 - In pneumococcal vaccine-naïve adults ≥ 50 years of age, the proportion of participants with solicited injection site pain was higher among those who received V114 compared with Prevnar 13.
 - Across the studies, the proportion of participants who experienced SAEs was low following vaccination with V114 or Prevnar 13 and comparable across intervention groups; no SAEs were considered by the investigator to be vaccine-related.
- V114 showed a similar safety profile with that observed in immunocompetent, pneumococcal vaccine-naïve adults, in the following populations:
 - Adults 18 to 49 years of age with risk factors for pneumococcal disease
 - Adults ≥ 18 years of age considered immunocompromised due to HIV infection
 - Adults ≥ 65 years of age with prior pneumococcal vaccination
- V114 administered sequentially with PPV23 or concomitantly with inactivated influenza vaccine showed a similar safety profile with that of V114 in immunocompetent, pneumococcal vaccine-naïve adults.

10.2 Conclusions and Recommendations

The immunogenicity and safety results support this application for the proposed indication.