BLA Clinical Review Memorandum

Application Type	Biologics License Application
STN	125741/0
CBER Received Date	November 17, 2020
PDUFA Goal Date	July 18, 2021
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	Yes-Priority Review
Clinical Reviewers	Anuja Rastogi, MD MHS Nicholas Geagan, D.O.
Review Completion Date	July 14, 2021
Supervisory Concurrence	Lucia Lee, MD Team Leader, CRB1, DVRPA, OVRR, CBER Douglas Pratt, MD, MPH Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	Merck & Co., Inc
Established Name	Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4)
Proposed Trade Name	VAXNEUVANCE
Pharmacologic Class	Vaccine
Formulation	Each dose (0.5 mL) contains 4 µg PS of serotype 6B 2 µg PS for each of the following serotypes: 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F CRM197 carrier protein (30 micrograms) 125 µg aluminum (as AlPO4) adjuvant
Dosage Form and Route of Administration	Dosage form: Suspension Route of Administration: Intramuscular
Dosing Regimen	Single dose
Indication and Intended Population	Indication: active immunization for the prevention of invasive disease (IPD) 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.
Orphan Designated (Yes/No)	No

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Glossary

AE	adverse event
AESI	adverse event of special interest
ACIP	Advisory Committee on Immunization Practices
APaT	All Participants as Treated
AR	adverse reaction
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
BLA	Biologics License Application
CAIH	Center for American Indian Health
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
cLDA	constrained longitudinal data analysis
COPD	chronic obstructive pulmonary disease
CRM_{197}	diphtheria toxin-related protein
DVRPA	Division of Vaccines and Related Products Applications
ECL	electrochemiluminescence
eDMC	External Data Monitoring Committee
EOC	Executive Oversight Committee
eVRC	electronic vaccination report card
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMFR	geometric mean fold increase
GMC	geometric mean concentration
GMT	geometric mean titer
H_0	null hypothesis
HAI	hemagglutination inhibition
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
(b) (4)	(b) (4)
IgG	immunoglobulin G
IM	intramuscular
IPD	invasive pneumococcal disease
LB	lower bound
MedDRA	Medical Dictionary for Regulatory Activities
MOPA	multiplexed opsonophagocytic killing assay
NI	non-inferiority
OPA	opsonophagocytic activity
OVRR	Office of Vaccines Research and Review
PCV13	Prevnar 13 (13-valent pneumococcal conjugate vaccine)
PCV15	pneumococcal 15-valent conjugate vaccine (CRM_{197} Protein) (b) (4)
PI	prescribing information
PPAS	Per-Protocol Analysis Set
PPV23	Pneumovax 23 (23-valent pneumococcal polysaccharide vaccine)
PREA	Pediatric Research Equity Act
QIV	quadrivalent influenza vaccine
SAE	serious adverse event
SOC	System Organ Class
STN	Submission Tracking Number

ULN	upper limit of normal
US	United States
V114	PCV15 (pneumococcal 15-valent conjugate vaccine (CRM_{197} Protein) (b) (4)
VRC	vaccination report card
WHO	World Health Organization
WOCBP	woman of childbearing potential

1. Executive Summary

An original Biologics License Application (BLA) has been submitted by Merck Sharp & Dohme Corp. (subsidiary of Merck & Co., Inc.) for candidate pneumococcal 15-valent conjugate vaccine (CRM_{197} protein), (b) (4) (PCV15) (trade name VAXNEUVANCE, investigational product name V114) with a proposed indication for active immunization for the prevention of invasive disease 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 Applicant has submitted data from 7 clinical studies as part of this BLA, including 4 Phase 3 trials which provided the principal data to support the safety and effectiveness of PCV15 for the intended indication in individuals 18 years of age and older, as well as clinical data to support manufacturing consistency (lot consistency). These 4 trials (V114-019, V114-020, V114-016, V114-017) enrolled participants ≥18 years without prior history of pneumococcal vaccination at over 180 sites in 14 countries, including the United States (US). Study V114-016 which enrolled participants ≥50 years and Study V114-017 which enrolled participants 18 to 49 years each evaluated sequential administration of Pneumovax 23-valent pneumococcal polysaccharide vaccine (PPV23) 12 months and 6 months after PCV15 administration, respectively. Two additional Phase 3 studies (V114-021 and V114-018) evaluated PCV15 when administered concomitantly with a quadrivalent influenza vaccine (QIV) (Fluarix Quadrivalent, GlaxoSmithKline Biologicals) and PCV15 when administered to HIV-infected adults ≥18 years of age. One supportive Phase 2 study (V114-007) in the US evaluated PCV15 in participants ≥65 years with a prior history of pneumococcal vaccination with PPV23.

Immunogenicity Analyses:
In all 4 studies, immunogenicity endpoints were used to infer PCV15 effectiveness for prevention of invasive pneumococcal disease (IPD) in participants 18 years of age and older when administered as a single dose. The PCV15 licensure approach relied on immunologic comparability to Prevnar 13 (PCV13), by evaluation of opsonophagocytic activity (OPA) titers analyzed using pre-specified non-inferiority criteria for the 13 common serotypes. For the 2 serotypes not represented in PCV13, and for serotype 3, pre-specified success criteria were used in superiority analyses to infer effectiveness. Although there is no established immune correlate of protection for prevention of IPD in adults, opsonophagocytosis is considered the main mechanism of protection against pneumococci and OPA measured *in vitro* reflects this mechanism of protection. Evaluation of OPA has been used to support approval of other higher valency pneumococcal conjugate vaccine for the prevention of IPD caused by vaccine serotypes that include the 13 serotypes in PCV13.[1] PCV13 is a licensed pneumococcal 13-valent conjugate vaccine for which effectiveness for the prevention of IPD caused by vaccine serotypes was demonstrated in adults (Pfizer 2017).

Study V114-019 was the main study evaluating the effectiveness of PCV15 in adults ≥50 years of age without prior history of pneumococcal conjugate vaccination. For the 13 shared serotypes in PCV15 and PCV13, noninferiority was determined if the lower bound (LB) of the of the 2-sided 95% CI of the OPA geometric mean titer (GMT) ratio (PCV15 to PCV13) was >0.5, for each serotype. For the two unique serotypes in PCV15, 22F and 33F, effectiveness was based on statistical superiority of OPA responses in PCV15 recipients compared to those in recipients ofPCV13 using the following success criteria: LB of the 95% CI of the OPA GMT ratio >2.0 and LB of the 2-sided 95% CI of the difference (PCV15 minus PCV13) in the proportions of participants with a ≥4-fold increase >10%. As a secondary objective, the Applicant evaluated the statistical superiority of serotype 3 in PCV15 compared to serotype 3 in PCV13 because the immunological profile and effectiveness of PCV13 serotype 3 in post-licensure observational

[1] Based on the efficacy confirmed in the Pfizer's PCV13 Study 6115A1-3006: Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA)

studies has not been consistent with the performance of other PCV13 vaccine serotypes.[2] For serotype 3, statistical superiority of PCV15 compared to PCV13 was demonstrated if the LB of the 2-sided 95% CI of the OPA GMT ratio (PCV15 to PCV13) was >1.2, and if LB of the 2-sided 95% CI of the difference (PCV15 minus PCV13) in the proportions of participants with a ≥4-fold increase was >0.

Study V114-019 demonstrated noninferior OPA responses for the 13 shared serotypes in PCV15 and PCV13, and statistically superior OPA responses for serotypes 22F, 33F and 3 in PCV15 compared to those in PCV13 based on the pre-specified criteria described above.

Study V114-017 descriptively evaluated the immunogenicity of PCV15 in pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease. The OPA GMTs following PCV15 vaccination for most shared serotypes were similar to those observed following PCV13 vaccination. Following the sequential administration of PPV23 six month after PCV15, OPA GMTs were similar to those observed following PPV23 six months after PCV13 for all shared serotypes.

Study V114-016 demonstrated comparable OPA GMTs for the 13 shared serotypes in PCV15 and PCV13 when each vaccine was followed by administration of PPV23 twelve months later. Similarly, for the 14 shared serotypes in PCV15 and PPV23, comparable OPA GMTs were observed in participants who received PCV15 followed by PPV23 as in those who received PCV13 followed by PPV23. For the unique serotype 22F, OPA GMTs were higher in the PCV15 group compared to the PCV13 group at one month after PPV23 and were comparable across groups for the unique serotype 33F.

The supportive Study V114-007 descriptively evaluated the impact of prior receipt of PPV23 on the immunogenicity of a single dose of PCV15 compared to PCV13 in adults ≥65 years of age. The OPA data support the findings of the primary analyses for the shared and unique serotypes, however, in the exploratory analyses differences were observed in the proportion of participants in both study groups who achieved ≥4-fold rise in OPA titers based on time since receipt of PPV23. In general, a greater proportion of participants 65 to 74 years achieved ≥4-fold rise when a longer duration of time had elapsed since receipt of PPV23 (>3 years compared to >1 to 3 years).

Safety Analyses

Post-vaccination safety data were reviewed from 5630 recipients of PCV15 who were enrolled in 7 randomized clinical trials (the 4 aforementioned studies plus V114-018 and V114-007) in 18 countries including the US. The most frequently reported adverse (solicited) reactions included injection site pain, fatigue, and myalgia. Across all studies, there were 8 PCV15 recipients and 3 PCV13 recipients who died during the safety follow-up (≥40 days post-vaccination). None of the deaths were considered related to study vaccination. Rates of reported serious adverse events (SAEs) were low and the types of SAEs across groups were similar and included clinical events that are often reported in the evaluated populations. None of the reported SAEs were considered related to study vaccination.

[2] CDC surveillance data following routine PCV13 vaccination in adults and infants suggested that PCV13 may not have substantively (directly or indirectly) impacted the incidence of serotype 3 invasive pneumococcal disease in adults following ACIP recommendations for use in the US.

Lot Consistency
The Applicant satisfactorily demonstrated consistency of lot performance in Study V114-020 based on comparisons of OPAGMTs of 3 different lots of PCV15. Safety profiles across lots were consistent.

Concomitant Vaccination
The safety and effectiveness of PCV15 when administered concomitantly with QIV compared to 30 days after QIV in adults ≥50 years of age was evaluated in Study V114-021. There was no evidence of immune interference to PCV serotypes as assessed by OPA GMTs across study groups and by influenza strain-specific hemagglutination inhibition (HAI) GMTs for all 4 influenza strains. There was no notable increase in frequency or severity of reported AEs when PCV15 and QIV were administered concomitantly compared to when PCV15 was administered 30 days after QIV.

Pediatric Assessment and Pediatric Research Equity Act
A Pediatric Study Plan was presented to FDA's Pediatric Review Committee on May 4, 2021. Safety and effectiveness of PCV15 have not been established in individuals younger than 18 years of age in the US. The Applicant's plans for an assessment of PCV15 in individuals 0 to <6 weeks was waived because the candidate vaccine did not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and is not likely to be used in this age group. The Applicant's assessment in children 6 weeks through 17 years of age (<18 years) was deferred because the candidate vaccine was ready for approval in individuals 18 years of age before all pediatric studies are complete. The Applicant's deferred studies include Study V114-029 to be conducted in infant/toddlers 6 weeks through 15 months of age evaluating a 4-dose series; Study V114-024 to be conducted in children 7 months through 17 years of age evaluating catch-up vaccination schedules; Study V114-0027 in infants/toddlers 6 weeks through 15 months of age evaluating the interchangeability of PCV15 and PCV13 on a 4-dose schedule; and Study V114-030 evaluating PCV15 in HIV-infected children 6 years through 17 years of age. The committee agreed with the Pediatric Study Plan, including the partial waiver, partial deferral, and the proposed timelines for each study's completion and submission.

Clinical Reviewer Recommendation:
The totality of clinical data presented in this application support approval of PCV15 candidate vaccine for active immunization for the prevention of invasive disease 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.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed individually.

Immunogenicity
For all serotypes, there was an age-dependent decrease in OPA GMTs from early adulthood (18 years through 29 years) to older age cohorts (≥75 years of age). The clinical relevance of the observed differences in OPA GMT responses across age cohorts is unknown. Serotype-specific OPA GMTs by sex were generally similar to those among all participants in the primary analysis. Subgroup analyses based on race/ethnicity were limited by smaller cohort size for certain racial/ethnic groups, including American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander (1 participant), multiple racial origin, and Hispanic ethnicity. However, for racial cohorts with greater number of participants enrolled (White, Asian, and Black), OPA GMTs were generally similar to those among all participants in the primary analysis.

Safety
Subgroup analyses of adverse events (AEs) by age demonstrated lower rates of solicited adverse reactions (ARs) and unsolicited AEs in older PCV15 recipients compared to younger recipients however, rates of SAEs across age cohorts were similar. Rates of AEs by sex were similar to overall rates of AEs. Among participants of White, Black, and Asian racial subgroups, rates of ARs and AEs were comparable to overall rates, though differences were observed in other racial subgroups with small numbers of participants.

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Conditions Studied

Streptococcus pneumoniae (pneumococcus)is associated with significant clinical disease and is a leading cause of death among older adults in the United States (US). It can cause non-invasive disease, including pneumonia without bacteremia or invasive pneumococcal disease (IPD), defined by isolation of *S. pneumoniae* from a normally sterile site (i.e., blood, cerebrospinal fluid, pleura, or peritoneum). The most common manifestations of IPD in adults ≥50 years of age include invasive (bacteremic) pneumonia, bacteremia without a focus, and meningitis (Gruber et al. 2008; Neuzil and Jackson 2008). Pneumococci cause over 50% of all cases of bacterial meningitis in the US. Signs and symptoms of bacterial meningitis may include headache, lethargy, vomiting, irritability, fever, nuchal rigidity, cranial nerve signs, seizures, and/or coma (Gierke 2015).

In North America, mortality rates for invasive pneumococcal disease range from 11% to 30% in adults with higher rates in in adults ≥65 years of age (Centers for Disease Control and Prevention 2018). The overall case-fatality rate for pneumococcal bacteremia is approximately 20% in the general public, and as high as 60% in the elderly. The case-fatality rate of pneumococcal meningitis is approximately 22% among adults (Centers for Disease Control and Prevention 2020).

Approximately 100 different serotypes of pneumococci have been identified that vary by chemical structure of their sero-reactive capsular polysaccharides and in their ability to cause disease, with the majority of disease caused by a relatively limited number of serotypes.

Following the introduction of pneumococcal conjugate vaccines in the US, rates of infection due to vaccine serotypes decreased, while rates of infection due to non-vaccine serotypes increased and were often associated with antibiotic resistance (Obolski et al. 2018). After the licensure and widespread use of a pneumococcal 7-valent conjugate vaccine (PCV7) in 2000, the prevalence of the 7 vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) decreased, while non-vaccine serotype 19A became the most prevalent in the US. Following the subsequent introduction of Prevnar 13 (PCV13; PCV7 plus serotypes 1, 3, 5, 6A, 7F and 19A) in 2010, the incidence of 19A serotype decreased, as it was included among the serotypes in PCV13. (PCV13 USPI)

According to data from the Active Bacterial Core Surveillance (ABCs) in the decade between 2007-08 and 2017-18, for adults ≥65 years the incidence rates of all IPD decreased by 38% and PCV13+6C serotypes decreased by 67%, while non-vaccine serotypes decreased by 5% and Pneumovax 23-valent pneumococcal polysaccharide vaccine (PPV23) serotypes not included in PCV13 decreased by 12% (CDC, 2021). In the 2018 ABCs Report for *Streptococcus pneumoniae* there was an overall estimate of 31,400 (9.6/100,000) cases of IPD and 3,480 (1.06/100,000) deaths due to IPD. The following includes

the reported number of IPD cases [incidence rate per 100,000 population] in 2018 by age (2018 ABC Report):

- 35-49 years: 483 cases [7.1%]
- 50-64 years: 1110 cases [16.6%]
- 65-74 years: 615 cases [20.2%]
- 75-84 years: 374 cases [25.5%]
- ≥85 years: 249 cases [38.7%]

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

Based on guidelines from the Infectious Diseases Society of America (IDSA) for management of bacterial meningitis, recommended empiric therapy for bacterial meningitis is a broad-spectrum antibiotic (e.g., third generation cephalosporin) with the addition of vancomycin (Tunkel et al. 2004). In children, ampicillin is added to the standard therapeutic regimen when *Listeria monocytogenes* is considered and to an aminoglycoside if a gram-negative enteric pathogen is of concern. If the *S. pneumoniae* isolate is susceptible to penicillin, vancomycin should be discontinued, and penicillin G should be started. Per IDSA guidelines, in adults with severe community-acquired pneumonia an empiric regimen could include a ß-lactam plus a macrolide or a ß-lactam plus a respiratory fluoroquinolone.

2.3 Safety and Efficacy of Pharmacologically Related Products

Three pneumococcal vaccines are licensed and available for the use in the United States. Prevnar 20 (PCV20) and Prevnar 13 (PCV13) are both indicated for the prevention of invasive disease and pneumonia.[3] Pneumovax 23 (PPV23), a vaccine comprised of unconjugated purified polysaccharides from 23 pneumococcal serotypes, is approved for use in persons 50 years of age or older and persons ages ≥2 years who are at increased risk for pneumococcal disease and is administered as a single dose. Information about the safety and immunogenicity of each vaccine is described in the corresponding package inserts.

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

At the time of this review, PCV15 vaccine has not been licensed in any other country.

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

Regulatory Pathway to Licensure:
The basis of the licensure approach relied OPA titers measured in blood samples following vaccination to support approval of new, pneumococcal conjugate vaccines for the prevention of IPD caused by vaccine serotypes.[4] Protection against pneumococcal disease in *vivo* is conferred mainly by opsonophagocytic killing of *S. pneumoniae* and OPA measured in *vitro* reflects this mechanism of protection. Because there is no established immune correlate of protection in adults (i.e., a threshold level of an immune parameter predictive of protection), effectiveness for each vaccine serotype was evaluated by comparisons of OPA titer following PCV15 to those following Prevnar 13, a licensed vaccine for which effectiveness for the prevention of IPD caused by vaccine serotypes was demonstrated in adults

[3] PCV20 serotypes: 1,3,4,5,6A,6B,7F,8,9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F. The indication for the prevention of pneumonia caused by the 7 serotypes in PCV20 but not PCV13 is approved under accelerated approval based on OPA and continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
[4] Based on the efficacy confirmed in the Pfizer's Study Evaluating the Efficacy of PCV13 against Community-Acquired Pneumonia in Adults (CAPITA) (NCT00744263)

Major Regulatory Activity
The following timeline includes a list of major regulatory activity associated with the submission of this BLA:

- May 28, 2013: Type C Meeting
  - This meeting was held to seek CBER's advice regarding plans to optimize the PCV15 formulation, including the addition of (b) (4) .
- March 1, 2018: End of Phase 2 Meeting
  - End of Phase 2 (Type B) Meeting for PCV15 to discuss Phase 3 adult clinical program.
- May 10, 2019: Breakthrough Therapy Designation Request
  - Breakthrough therapy designation granted.
- October 5, 2020: Type B – Pre-BLA Meeting
  - The Applicant sought to obtain CBER concurrence on the clinical data supporting review of BLA.[3]

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission of this BLA was adequately organized and integrated to accommodate the conduct of a complete review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices And Submission Integrity

Safety and immunogenicity data from six main studies were provided in this application (V114-020, V114-019, V114-021, V114-016, V114-017, V114-018) to support licensure of PCV15, and were conducted in accordance with Good Clinical Practice and International Committee on Harmonisation guidelines. The informed consent form for each study contained all the essential elements as stated in 21CFR 50.25. In accordance with 21 CFR 312.120, the Applicant provided the required elements to ensure that each study conformed with Good Clinical Practice. The studies that enrolled from foreign sites include V114-20, V114-19, V114-16, V114-17, and V114-18.

Bioresearch monitoring (BIMO) inspections were issued for 3 clinical study sites that participant in the conduct of Study V114-019. The inspections did not reveal substantive issues that impact the data submitted in this application.

3.3 Financial Disclosures

Covered clinical study (name and/or number): V114-020, V114-019, V114-021, V114-016, V114-017, V114-018
Was a list of clinical investigators provided: Yes ☒ No ☐ (Request list from applicant)
Total number of investigators identified: 1067
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 3
Is an attachment provided with details of the disclosable financial interests/arrangements: Yes ☒ No ☐ (Request details from applicant) Is a description of the steps taken to minimize potential bias provided: Yes ☒ No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 Is an attachment provided with the reason: Yes ☐ No ☐ (see below) The sponsor certified that 1,065 investigators had absence of financial interests and/or arrangements. However, they reported that 2 investigators had the following: equity interest (n=3) and significant payment of other sorts (n=1). The sponsor provided the following financial information pertaining to these two investigators: • Principal Investigator Pablo E. Campos (Study V114-018/Site 041) received significant payments (b) (4) that was reported as 'Investigator-initiated study research grant in the amount of (b) (4) on 22Aug2019. • Sub-Investigator Susan Edwards (Study V114-007/Site 29, V114-016/Site 0123, and V114-019/Site 1013) had equity interest in Merck shares with stock values between (b) (4), which were reported/updated between 12Aug2015 and 01Oct2020.

Reviewer Comment: *There is no evidence of significant bias based on the financial interests of the investigators that may have affected study results.*

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Manufacturing process development, in-process testing, release and stability testing were reviewed and support licensure. The data supports 18-month expiry dating for Drug Product single-dose prefilled Luer-lock syringes stored at 2-8°C. Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

4.2 Assay Validation

The immunogenicity-based potency tests for the final drug product and clinical serologic assays were adequate to support licensure as determined by CBER Product and Assay reviewers.

With the submission of this application, the Applicant was asked by CBER to address concerns associated with their (b) (4) OPA testing. For immunogenicity assessments for all phase 3 studies, the applicant had used a validated MOPA to measure serotype-specific OPA titers for each of the 15 serotypes

contained in PCV15 that was to include only sera samples that tested negative for (b) (4) OPA titers.

Blinded performance monitoring of the (b) (4) test revealed a higher than expected number of serum samples testing (b) (4) positive (up to 18% postvaccination) following a change to a critical reagent. Given the low proportion of participants reporting (<5%) systemic antibiotic use around the time of blood draws, (b) (4) . As a result, the OPA data presented in the Clinical Study Reports (CSRs) for Studies V114-020, V114-019, V114-016, and V114-017 do not exclude samples that tested (b) (4) positive.

CBER did not accept the OPA data that did not exclude (b) (4) test-positive sera samples and requested that the sponsor modify their (b) (4) test and re-analyze sera samples for these studies. The Applicant modified the (b) (4) test and provided a statistical report for OPA testing results that included only data that excluded (b) (4) positive sera samples for the primary and key secondary OPA analyses. The (b) (4) -negative OPA testing results were submitted to the application for Studies V114-020, V114-019, V114-016, and V114-017. Therefore, the OPA data presented for these studies in the clinical review memo and the USPI excluded (b) (4) -test positive sera.

4.3 Nonclinical Pharmacology/Toxicology

The CBER Toxicology reviewer considered the nonclinical toxicology data to be adequate to support licensure.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Protection against invasive disease is conferred mainly by opsonophagocytic killing of *S. pneumoniae*. PCV15 induces OPA against the serotypes contained within the vaccine.

4.5 Statistical

The CBER Statistical reviewer concluded that the datasets and the analyses provided in this application were adequate to assess the safety and effectiveness of the candidate vaccine.

4.6 Pharmacovigilance

The CBER Epidemiology/Pharmacovigilance (Epi/PV) reviewer did not identify any safety concerns or potential risk for PCV15 that would require a postmarketing study or a Risk Evaluation and Mitigation Strategy. However, missing information pertaining to the safety of more than one dose administered <1 year apart to immunocompromised adults was identified. The Applicant is currently conducting a Phase 3, randomized, double-blind, active comparator-controlled, parallel-group, multicenter study to describe the safety, tolerability, and immunogenicity of PCV15 and PCV13 when administered as a 3-dose regimen in recipients of allogeneic hematopoietic stem cell transplant. The final clinical study report will be submitted in the fourth quarter of 2022. The Epi/PV reviewer recommended routine pharmacovigilance (adverse reactions reporting and signal detection) and agreed with the Applicant's proposed Pharmacovigilance Plan.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This BLA included clinical data from 6 main trials (V114-020, V114-019, V114-021, V114-016, V114-017, V114-018) to support immunogenicity (inferred effectiveness) and safety of a primary dose of PCV15 in individuals 18 years of age and older (no upper age limit). The submission also included one supportive trial including a primary dose study in adults ≥65 years of age with prior 23-valent pneumococcal polysaccharide vaccination. The clinical, labeling, and financial disclosure information section of the application were reviewed with detailed analyses of the main trials' study reports, pertinent line listing, case report forms, and datasets. Advisory Committee on Immunization Practices (ACIP) vaccine recommendations for the prevention of pneumococcal disease and current pneumococcal US surveillance data were also reviewed.

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

The following STN#125741/0 Amendments (Am) were reviewed (listed by modules)

- Am 0: 1.1, 1.2, 1.3, 1.6, 1.9
- Am 1: 1.3, 1.14, 2.5, 2.7, 5.2, 5.3.5.1, 5.3.5.3
- Am 3: 1.16
- Am 4: 1.11
- Am 9: 1.11
- Am 12: 5.3.5.1
- Am 16: 1.11.3
- Am 15: 1.11
- Am 22: 1.11, 1.14
- Am 23: 1.11
- Am 24: 1.11
- Am 35: 1.11
- Am 36: 1.11
- Am 37: 1.14
- Am 38: 1.11
- Am 39: 1.11.3
- Am 40: 1.11
- Am 44: 1.11

5.3 Table of Studies/Clinical Trials

Study Number	Region	Description	Population	Study Groups: # Enrolled
Trial #1: V114-019 Pivotal Immunogenicity Safety	Canada Japan Spain Taiwan US	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	Healthy pneumococcal vaccine-naïve adults ≥50 years of age	PCV15: 600 PCV13: 600
Trial #2: V114-020 Lot Consistency Safety	Australia Chile Denmark Finland Great Britain US	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	Healthy pneumococcal vaccine-naïve adults ≥50 years of age	PCV15 Lot 1: 667 PCV15 Lot 2: 667 PCV15 Lot 3: 667 PCV13: 220

Study Number	Region	Description	Population	Study Groups: # Enrolled
Trial #3: V114-017 18-49 years of age	Australia New Zealand Canada Chile Poland Russia US	Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX™23 Six Months Later in Immunocompetent Adults Between 18 and 49 Years of Age at Increased Risk for Pneumococcal Disease	Adults 18 to 49 years of age, including adults with medical conditions for which ACIP pneumococcal vaccination is recommended	PCV15 + PPV23: 1125 PCV13 + PPV23: 375
Trial #4: V114-021 Concomitant Administration with QIV vaccine	US	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	Healthy adults ≥50 years of age, including those previously vaccinated with PPV23	Concomitant: 600 Nonconcomitant: 600
Trial #5: V114-016 Sequential Administration	Spain South Korea Taiwan US	Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX™23 One Year Later in Healthy Adults 50 Years of Age or Older	Healthy pneumococcal vaccine-naïve adults ≥50 years of age	PCV15 + PPV23: 300 PCV13 + PPV23: 300
Trial #6: V114-007 Phase 2 ≥65 years of age	US	Phase 2, Multicenter, Randomized, Double-blind, Active Comparator controlled Study to evaluate the Safety and Immunogenicity of V114 compared to PCV13 in adults ≥65 years with history Pneumovax23 vaccination ≥1 prior.	Healthy adults ≥65 years with stable underlying chronic illness, and documented prior receipt of PPV23 ≥1 year prior to study entry	PCV15: 127 PCV13:126
Trial #7: V114-018 HIV	France Peru South Africa Thailand US	Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX™ 23 Eight Weeks Later in Adults Infected with HIV	HIV-positive adults ≥18 years of age	PCV15 + PPV23: 150 PCV13 + PPV23: 150

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 (Study V114-019)

NCT03950622
"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"

Study Overview: This study was designed to evaluate the safety and immunogenicity (inferred effectiveness) of PCV15, compared to PCV13, in adults ≥50 years of age (N=1205). The study was conducted in United States, Japan, Canada, Spain, and Taiwan.

6.1.1 Objectives

Primary Objectives (as stated in protocol)

1. To evaluate the safety and tolerability of PCV15.
    - *Endpoints:* % of participants with solicited injection site ARs (redness, swelling, pain), solicited systemic ARs (muscle pain/myalgia, joint pain/arthralgia, headache, fatigue), fever, unsolicited non-serious AEs, serious adverse events (SAEs)

2. To compare serotype-specific OPA GMTs at 30 days after PCV15 vaccination compared to corresponding serotype-specific OPA GMTs after PCV13 vaccination.
    - *Endpoint:* OPA GMTs for the 15 serotypes in PCV15
    - *Hypothesis (H1):* PCV15 is noninferior to PCV13, as measured by the serotype-specific OPA GMTs for 13 shared serotypes at Day 30.
        - 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):* PCV15 is statistically superior to PCV13, as measured by serotype-specific OPA GMTs for serotypes 22F and 33F in PCV15 at Day 30.
  - 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

3. For serotypes 22F and 33F, to compare the proportions of participants with a ≥4-fold increase in OPA titer from pre-vaccination to 30 days following PCV15 vaccination to corresponding proportions of participants after PCV13 vaccination.
   - *Endpoint:* % of participants with a ≥4-fold increase in OPA titer
   - *Hypothesis (H3):* PCV15 is statistically superior to PCV13 for serotypes 22F and 33F, as measured by proportions of participants with a ≥4-fold increase in OPA titer from Day 1 to Day 30
     - 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 prevaccination [Day 1] to 30 days postvaccination [Day 30] to be greater than 0.1

Reviewer Comment for Primary Objectives: Shared Serotypes & Two Unique Serotypes 33F, 33F
Hypothesis 2 evaluates OPA GMTs for the 2 unique serotypes (22F & 33F) in PCV15 at 30 days postvaccination based on the statistical criteria that required the LB of the 95% CI of the OPA GMT ratio >2.0. Subsequently Hypothesis 3 was included as an additional objective evaluating the 2 unique serotypes that evaluated the proportion of participants with a ≥4-fold increase in OPA titer, with statistical criteria that required that the LB of the 2-sided 95% CI of the difference in the proportions of participants with a ≥4-fold increase be >10%.

The proposed testing approach for the two unique serotypes (22F & 33F) reflects a comparable approach taken with licensure of PCV13 for the unique serotype 6A in PCV13, but not in PPV23, and was also considered acceptable for demonstrating effectiveness of the two unique serotypes in PCV15 (22F,33F).

Secondary Objectives

1. For serotype 3, to compare OPA GMT at 30 days after PCV15 vs. PCV13 vaccination.
   - *Endpoint:* serotype 3 OPA GMT
   - *Hypothesis (H4):* PCV15 is statistically superior to PCV13, as measured by serotype 3 OPA GMT at Day 30.
     - 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

2. For serotype 3, to compare proportions of PCV15 and PCV13 participants with a ≥4-fold increase in OPA titer from Day 1 to Day 30.
   - *Endpoint:* % of participants with a ≥4-fold increase in serotype 3 OPA titer
   - *Hypothesis (H5):* For serotype 3, PCV15 is statistically superior to PCV13 for serotype 3 as measured by proportions of participants with a ≥4-fold increase from Day 1 to Day 30 for OPA responses.
     - 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 prevaccination [Day 1] to 30 days postvaccination [Day 30] to be greater than 0

3. To evaluate serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days after PCV15 vs. PCV13 vaccination.
   - *Endpoint:* Serotype-specific IgG GMCs for 15 serotypes in PCV15

4. To evaluate serotype-specific geometric mean fold increases (GMFRs) and proportions of participants with a ≥4-fold increase from Day 1 to Day 30 for OPA and IgG responses in PCV15 participants and separately for PCV13 participants.
   - *Endpoints:* Serotype-specific OPA and IgG GMFRs for 15 serotypes in PCV15

Reviewer Comment for Secondary Objectives: Serotype 3
Under the IND, the Applicant and CBER had discussions pertaining to CDC surveillance data (Pilishvili 2019) following routine PCV13 vaccination in adults and infants that suggested that PCV13 may not have substantively (directly or indirectly) impacted the incidence of serotype 3 invasive pneumococcal disease in adults following ACIP recommendations for use in the US. Furthermore, the immunological profile of serotype 3 in PCV 13 is not consistent with the performance of other PCV13 vaccine serotypes. For these reasons, CBER requested that the Applicant revise the secondary endpoint and statistical analysis plan to evaluate the statistical superiority of serotype 3 OPA antibody responses in PCV15 recipients compared to serotype 3 OPA responses in PCV13 recipients. For serotype 3, a LB of the 2-sided 95% CI of the OPA GMT ratio (PCV15/PCV13) greater than 1.2 was evaluated because this represented a meaningful margin, beyond a level that could be related to OPA assay variability. In addition, for serotype 3, the difference in proportions of participants (PCV15-PCV13) with a ≥4-fold rise in OPA titers was evaluated [success criteria: 95% LB >0] to provide additional evidence of effectiveness.

6.1.2 Design Overview

Study V114-019 is a randomized, active-controlled, parallel-group, multi-site, double-blind study of PCV15 in adults ≥50 years of age. A total of 1205 individuals were randomized (1:1 ratio) to receive PCV15 (n=604) or PCV13(n=601). Randomization was stratified by age at enrollment (50 to 64 years, 65 to 74 years, and ≥75 years).

In countries that recommended sequential administration of PCV13 followed at least 12 months later by PPV23, PPV23 was administered outside of this study protocol.

6.1.3 Population

Individuals were eligible to be included if they were ≥50 years of age and in good health with any underlying chronic illness documented to be in stable condition. Females were eligible to participate if they were not pregnant, not breast feeding, and not a woman of childbearing potential OR a WOCBP who agrees to use 1 of pre-specified (commonly accepted) contraceptive methods during the treatment period and for at least 6 weeks after the last dose of study intervention.

Individuals were not eligible for enrollment if they met any of the following exclusion criteria: History of IPD (i.e., positive blood culture, positive cerebrospinal fluid culture, or positive culture at another sterile site) or known history of other culture-positive pneumococcal disease within 3 years before Visit 1; known hypersensitivity to any component of pneumococcal polysaccharide vaccine, PCV, or any diphtheria toxoid-containing vaccine; known or suspected impairment of immunological function including, but not limited to, a history of congenital or acquired immunodeficiency, documented HIV infection, functional or anatomic asplenia, or history of autoimmune disease; coagulation disorder contraindicating intramuscular vaccination; history of malignancy ≤5 years prior to signing informed

consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer; prior administration of any pneumococcal vaccine or is expected to receive any pneumococcal vaccine during the study outside of the protocol; received systemic corticosteroids (prednisone equivalent of ≥20 mg/day) for ≥14 consecutive days and has not completed intervention at least 30 days before study entry; received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) within 14 days before vaccination; receiving immunosuppressive therapy, including chemotherapeutic agents used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease; currently participating in or has participated in an interventional clinical study with an investigational compound or device within 2 months of participating in the current study.

Temporary exclusion criteria. The Day 1 visit was rescheduled for participants who met the following criteria:

- febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C], axillary or temporal temperature ≥99.4°F [≥37.4°C], or rectal temperature ≥101.4°F [≥38.6°C]) or received antibiotic therapy for any acute illness occurring within 72 hours before receipt of study vaccine
- received any non-live vaccine within the 14 days before receipt of any study vaccine or is scheduled to receive any non-live vaccine within 30 days following receipt of any study vaccine. Exception: Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of any study vaccine or at least 15 days after receipt of any study vaccine
- received any live vaccine within 30 days before receipt of any study vaccine or is scheduled to receive any live vaccine within 30 days following receipt of any study vaccine
- received a blood transfusion or blood products, including immunoglobulin within the 6 months before receipt of study vaccine or is scheduled to receive a blood transfusion or blood product within 30 days of receipt of study vaccine.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Table 1. Vaccinations Administered in Study V114-019

Study Group	Vaccination Schedule (Day 1)
PCV15	Single dose
PCV13	Single dose

PCV15: 15-valent pneumococcal conjugate vaccine

- Dose: 0.5mL
- Composition: Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F
- Presentation: Sterile suspension in a prefilled syringe
- Lot #0000957291

PCV13: 13-valent pneumococcal conjugate vaccine (diphtheria CRM_{197} protein)

- Dose: 0.5mL
- Composition: Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Presentation: Sterile suspension in a prefilled syringe
- Lot # 0000896670 (PCV13 administered in the US)
- Lot # 0000940410 (PCV13 administered in Canada, Spain, Japan, Taiwan)

6.1.5 Directions for Use

A single dose (0.5mL) was administered IM.

6.1.6 Sites and Centers

Thirty sites in United States, Japan, Canada, Spain, and Taiwan enrolled 1205 participants. There were 14 US sites that enrolled 632 participants.

6.1.7 Surveillance/Monitoring

Safety Monitoring

- Clinical Assessments: physical exam before vaccination (Day 1)
- AE *Monitoring:*
  - Immediate ARs: 30 minutes postvaccination observation period
  - Solicited Local/Injection Site: Days 1-5 postvaccination
    - swelling, redness, pain
  - Solicited Systemic: Days 1-14 postvaccination
    - Muscle pain, joint pain, headache, fatigue.
    - Fever (recorded in eVRC: Days 1-5/reported through Days 1-14) defined as oral/tympanic: ≥100.4°F, axillary/temporal: ≥99.4°F
  - Any other unsolicited injection site or systemic AEs. Days 1-14 postvaccination
  - Concomitant medications and non-study vaccinations. Days 1-14 postvaccination.
  - SAEs, AEs leading to withdrawal: Day 1 through Month 6 postvaccination.
  - Pregnancy testing conducted prior to vaccination

Solicited ARs and fever were recorded electronically in an electronic vaccination report card (eVRC).

Investigator Assessment of Vaccination Report Card with Participant
In all studies included in this application, safety was monitored using the eVRC for up to 14 days postvaccination. Study investigators reviewed the data reported on the eVRC by participants at a study visit 15 days postvaccination to ensure consistency with protocol definitions. The applicant clarified during the review of this BLA, that the data reported on the eVRC were used inform the investigator's final assessment of solicited adverse reaction events[5] Therefore, safety data analyses presented for solicited adverse reaction events reflect the information as assessed by the investigators. Safety solicited data include oral body temperature and injection site adverse reactions that were reported on Days 1-5 postvaccination as well as systemic adverse reactions that were reported on Days 1-14 postvaccination. Unsolicited adverse events were reported on Days 1-14 postvaccination.

Study withdrawal/discontinuation: all activities scheduled for the final study visit (Visit 2) were performed at the time of study withdrawal. Any AEs present at the time the participant withdrew from the study were followed to resolution.

Scientific Advisory Committee (SAC): scientific experts who provided input about study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

Executive Oversight Committee: (EOC): Applicant's senior management members. EOC decision-making process took into consideration the eDMC recommendations.

External Data Monitoring Committee (eDMC): members not affiliated with the Applicant, not involved in the trial in any other way, and had no competing interests that could affect their roles with respect to the trial. Following interim safety data review, the eDMC provided recommendations to the EOC about trial continuation.

[5] STN 125701/0.22 (24March2021) Response to Information Request (sent 17March2021)

Immunogenicity Monitoring

- Pneumococcal electrochemiluminescence (ECL) assay, version 2.0: measured IgG serotype-specific antibodies to 15 serotypes contained in PCV15 using ECL detection method. Assays were grouped into two groups of 7 to 8 serotypes. Lower limits of quantitation (LLOQs): 0.5 µg/mL (serotypes 1, 3, 4, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F); 0.10 µg/mL (serotype 5). Laboratory: (b) (4)
- MOPA (validated): immunoassay that measures antibody-dependent, complement-mediated killing of *S. pneumoniae* by phagocytes. Reference sera: (b) (4). LLOQs (1/dil): 9 (serotype 1), 19 (serotype 3), 34 (serotype 4), 27 (serotype 5), 232 (serotype 6A), 40 (serotype 6B), 61 (serotype 7F), 151 (serotype 9V), 62 (serotype 14), 115 (serotype 18C), 31 (serotype 19A), 113 (serotype 19F), 15 (serotype 22F), 55 (serotype 23F), 20 (serotype 33F). Laboratory: (b) (4) .

6.1.8 Endpoints and Criteria for Study Success

See Section 6.1.1 above.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary Hypothesis #1 (H1)

- For each of the 13 shared serotypes, OPA GMTs at 30 days after vaccination with PCV15 or PCV13 were assessed via the following noninferiority hypotheses:
  - Hypothesis #1: H_0: $GMT_1/GMT_2 \leq 0.50$ vs. H_1: $GMT_1/GMT_2 > 0.50$
    - GMT_1 is serotype-specific OPA GMT for the PCV15 group and GMT_2 is serotype-specific OPA GMT for the PCV13 group.
    - A ratio of 0.50 corresponds to a 2.0-fold decrease of OPA GMT in the PCV15 group as compared with the PCV13 group.
    - Rejecting the null hypothesis (H_0) at the 1-sided $\alpha=0.025$ level corresponded to the lower bound of the 2-sided 95% CI on the GMT ratio being >0.50 and would lead to the conclusion that the OPA response to PCV15 for the common serotype was non-inferior to that of PCV13.

Primary Hypothesis #2 (H2)

- For serotypes 22F and 33F, OPA GMTs at 30 days after PCV15 and after PCV13 vaccination were assessed via the following superiority hypotheses:
  - H_0: $GMT_1/GMT_2 \leq 2.0$ vs. H_1: $GMT_1/GMT_2 > 2.0$
    - GMT_1 is serotype-specific OPA GMT for the PCV15 group and GMT_2 is serotype-specific OPA GMT for the PCV13 group.
    - A ratio of 2 corresponds to a 2.0-fold increase of OPA GMT in the PCV15 group as compared with the PCV13 group.
    - Rejecting the null hypothesis (H_0) at the 1-sided $\alpha=0.025$ level corresponded to the lower bound of the 2-sided 95% CI on the GMT ratio being >2.0 and would lead to the conclusion that the OPA response to PCV15 was statistically superior to that of PCV13 for serotypes 22F and 33F.

Estimation of the GMT ratios and 95% CI and the hypothesis test (i.e., 1-sided p-value) was conducted using a constrained longitudinal data analysis (cLDA) method. The Kenward-Roger adjustment (Kenward MG, 1997) was used with restricted maximum likelihood to make the proper statistical inference.

Primary Hypothesis #3 (H3)

- For serotypes 22F and 33F, the proportion of participants with a ≥4-fold increase in OPA titer (Day 30 compared to Day 1) after PCV15 or PCV13 was assessed via the following superiority hypotheses:
  - H_0: $p_1-p_2 \leq 0.1$ vs. H_1: $p_1-p_2>0.1$
    - p_1 is the proportion of participants with a ≥4-fold increase for the PCV15 group and p_2 is the proportion for the PCV13 group.
    - A difference of 0.1 corresponds to the PCV15 group having a 10% higher proportion of participants with a ≥4-fold increase in OPA responses from pre-vaccination to Day 30 than the PCV13 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 being >0.1 and would lead to the conclusion that the OPA response to PCV15 for the two unique serotypes are statistically superior to that of PCV13.

Estimation of the proportion difference and 95% CI and the hypothesis test (i.e., 1-sided p-value) was conducted using the stratified M&N method, an unconditional, asymptotic method.

Secondary Objective #1/Hypothesis (H4)

- For serotype 3, OPA GMTs at 30 days after vaccination with PCV15 or PCV13 vaccination was assessed via the following statistical superiority hypothesis:
  - H_0: $GMT_1/GMT_2 \leq 1.2$ vs. H_1: $GMT_1/GMT_2>1.2$
    - GMT_1 is the serotype 3 OPA GMT for the PCV15 group and GMT_2 is the serotype 3 OPA GMT for the PCV13 group.
    - A ratio of 1.2 corresponds to the PCV15 group having an OPA GMT that is 1.2-fold higher than the OPA GMT in the PCV13 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 being >1.2 and would lead to the conclusion that the serotype 3 OPA GMT in the PCV15 group is statistically superior to the serotype 3 OPA GMT in the PCV13 group.

Secondary Endpoints/Hypotheses (H5)

- For serotype 3, the proportion of participants with a ≥4-fold increase in OPA titer (Day 30 compared to Day 1) after PCV15 and after PCV13 was assessed via the following superiority hypothesis: H_0: $p_1-p_2 \leq 0$ vs. H_1: $p_1-p_2>0$
  - p_1 is the proportion of participants with a ≥4-fold increase for the PCV15 group and p_2 is the proportion for the PCV13 group.
  - A difference of 0 corresponds to no difference in the proportion of participants with a ≥4-fold increase in OPA responses from pre-vaccination to Day 30 than the PCV13 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 being >0 and would lead to the conclusion that the proportion of participants with a ≥4-fold increase in serotype 3 OPA titer in the PCV15 group is statistically superior to that in the PCV13 group.

All hypothesis-driven analyses were based on the Per-Protocol Population. The sample size provided >90% power overall to demonstrate noninferiority to PCV13 for the 13 shared serotypes and superiority for serotypes 22F and 33F using a 1-sided 2.5% alpha-level.

Statistical assumptions:

- 90% evaluable participants

- Based on data from Study V114-006:
  - Serotype-specific OPA GMT ratios for each of the 15 pneumococcal serotypes ranged from 0.78 to 1.86 across the shared serotypes and >6.0 for the PCV15 serotypes 22F and 33F.
  - For serotypes 22F and 33F, the differences in proportions of participants with a ≥4-fold increase in OPA titers from Day 1 to Day 30 were >0.1 for each serotype.

Other Secondary Endpoints
For 15 pneumococcal serotypes in PCV15

- Descriptive comparisons of PCV15 and PCV13 IgG GMCs at Day 30
- OPA and IgG responses: GMFRs and proportions of participants with a ≥4-fold increase from Day 1 to Day 30 described for each study group separately

Analyses were based on the Per-Protocol Population. For continuous variables, point estimates were calculated by exponentiating the estimates of the mean of the natural log values and the natural log values based on the t-distribution. For the dichotomous variables, the within-group CIs were calculated based on the exact method proposed by Clopper and Pearson (Clopper C., et al, 1934).

Safety Endpoints: % of participants with

- Solicited injection site ARs (redness, swelling, pain) during Days 1-5 postvaccination
- Solicited systemic ARs (muscle pain/myalgia, joint pain/arthralgia, headache, fatigue) during Days 1-14 postvaccination
- Maximum temperature measurement
- Any AE, any vaccine-related AE during Days 1-14 postvaccination
- Any SAE, any vaccine-related SAE, and death from Day 1 through Month 6 postvaccination

Analyses: p-values [solicited local reactions and systemic AEs] and 95% CIs [any AE, any SAE] were provided for between-treatment differences in the percentage of participants with events; these analyses were performed using the Miettinen and Nurminen (M&N) method.

Interim Analysis: Performed to support the periodic review of safety and tolerability data across the adult PCV15 Phase 3 program. An external unblinded statistician provided unblinded interim safety summaries to an external Data Monitoring Committee for their review.

Multiplicity: No multiplicity adjustments were applied for immunogenicity or safety comparisons.

Protocol Amendments

- Protocol Amendment 1 (February 13, 2020), original protocol (January 9, 2019):
  Changes to the protocol included 2 additional secondary immunogenicity objectives relating to demonstration of statistically significant greater immune responses for serotype 3 and revised statistical criteria for demonstration of statistically significantly greater immune response for serotypes 22F and 33F.

Significant changes in the Conduct of the Study & Planned Analyses:

- There were no changes in the planned analyses.
- COVID-19 Pandemic: The Applicant implemented measures to manage key aspects of study conduct during the pandemic based on local and national guidance. These measures included study site monitoring to review source data; query of study sites to determine relationship of reported protocol deviations to the pandemic; and measures to manage data, including when sites were unable to perform the 6-month telephone contact, resulting in participant status as “lost to follow-up” and reason discontinued “due to COVID-19 site was unable to complete the visit” or

"due to COVID-19 study participant did not complete visit." As per the Applicant's standard process, missing procedures and study visits were reported as protocol deviations. However, there were no changes in the planned analyses due to the COVID-19 Pandemic.

6.1.10 Study Population and Disposition

A total of 1205 participants were enrolled in the study. Study period: June 13, 2019 (first participant, first visit) to March 30, 2020 (last participant, last visit).

6.1.10.1 Populations Enrolled/Analyzed

- PPAS: The analysis population for primary immunogenicity analyses included all randomized participants without deviations from the protocol that would substantially affect immunogenicity. Final determination of all protocol deviations was made prior to the final unblinding of the database. Participants were analyzed according to the treatment group to which they were randomized. Deviations that may result in exclusion of a participant from the PPAS included:
  - Failure to receive any study vaccine at Visit 1 Day 1
  - Failure to receive correct clinical materials as per randomization schedule (i.e., participants who were cross-treated) at Day 1
  - Receipt of a prohibited medication or prohibited vaccine prior to study vaccination
  - Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection
  - Collection of a blood sample outside of the pre-specified window
- Full Analysis Set (FAS): All randomized participants who received at least 1 vaccination and had at least 1 serology result
- All Participants as Treated (APaT): primary population for the safety analyses; all randomized participants who received at least 1 dose of study vaccination. Analyses performed according to vaccine received.

6.1.10.1.1 Demographics

Table 2. Demographic Characteristics, by Study Group, All Vaccinated Participants, Study V114-019

Demographic Characteristic	**PCV15 (N=602)**	**PCV13 (N=600)**
Sex ratio M:F (%)	244: 358 (40.5%: 59.5%)	269: 331 (44.8%: 55.2%)
Age, years:		
Mean age (SD)	66.2 (7.7)	65.7 (7.4)
Median age	67.0	66.0
Age range	50, 92	50, 82
Age group (years), n (%)		
50-64	186 (30.9%)	186 (31.0%)
65-74	346 (57.5%)	346 (57.7%)
≥75	70 (11.6%)	68 (11.3%)
Racial origin, n (%):		
Am. Indian/A.N.	0 (0.0%)	1 (0.2%)
Asian	150 (24.9%)	152 (25.3%)
Black/A.A.	36 (6.0%)	37 (6.2%)
White	408 (67.8%)	406 (67.7%)
N. Hawaiian/P.I.	1 (0.2%)	0 (0.0%)
Multiple	7 (1.2%)	4 (0.7%)
Not reported	0 (0.0%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)

Demographic Characteristic	PCV15 (N=602)	PCV13 (N=600)
Ethnicity, n (%):		
Hispanic/Latino	135 (22.4%)	129 (21.5%)
Not H/L	467 (77.6%)	470 (78.3%)
Not reported	0 (0.0%)	1 (0.2%)
Unknown	0 (0.0%)	0 (0.0%)

Source: Adapted from STN 125741.0, P019V114 Clinical Study Report, Table 10-5. All Vaccinated Participants Analyses Set.
PCV13: Prevnar 13; SD: standard deviation.
For Sex, Racial Origin, and Ethnicity: X indicates number of participants fulfilling the item followed by (%).
N: total number of participants for the Safety Analyses Set (participants who received 1 dose and had any safety data available).
Sex Ratio M:F indicates Male:Female.
Racial origin: Black/A.A.: Black/African American; Am. Indian/A.N: American Indian/Alaska Native; N. Hawaiian/P.I.: Native Hawaiian/Pacific Islander. Ethnicity: Hispanic/Latino; Not H/L: Not Hispanic/Latino. Not reported ethnicity accounted for 1 participant (0.1%) across both groups.

Among all vaccinated participants, there were more females (~57%) than males, the median age was 66 years, and the proportion of participants 50 to 64 years was 31%, 65 to 74 years was ~58%, and ≥75 years was ~12%. Overall, the majority of participants were White (~68%), followed by Asian (~25%), and Black/African American (~6%), and included ~22% Hispanic/Latin participants. The demographic characteristics of participants were similar between study groups (Table 2, above**).**

6.1.10.1.2 Participant Disposition

Table 3. Participant Disposition, by Study Group, All Randomized Participants, Study V114-019

Population	PCV15 (N=604) n (%)	PCV13 (N=601) n (%)
Enrolled	604 (100%)	601 (100%)
Vaccinated	602 (99.7%)	600 (99.8%)
Completed study	596 (98.7%)	594 (98.8%)
Safety Analysis*	602 (99.7%)	600 (99.8%)
FAS Set**	602 (99.7%)	600 (99.8%)
Per-Protocol OPA***	598 (99.0%)	598 (99.5%)
Per-Protocol IgG***	598 (99.0%)	598 (99.5%)
≥1 Important Protocol Deviation	14 (2.5%)	14 (2.3%)

Source: Adapted from STN 125741.0, P019V114 Clinical Study Report: Table 10-1, Table 11-1, Table 11-5, Table 12-1, Table 14.1-3, Table 14.2-3.
X indicates number of participants fulfilling the item followed by (%).
N: total number of participants enrolled.
≥1 Important Protocol Deviation: participants with one or more important protocol deviations.
*Safety analyses using the APaT population included all randomized participants who received the study intervention.
**FAS: Full Analysis Set: All randomized participants who received the intervention and had at least 1 serology result. Maximum "n" across all serotypes from the primary (OPA) immunogenicity analysis table in the FAS population.
*** Maximum "n" across all serotypes from the primary (OPA) and secondary (IgG) immunogenicity analysis tables in the Per-Protocol Population.

A list of pre-specified protocol deviations is provided in Section 6.2.10.1 of this review memo. Of the approximately 1200 participants in the study, 29 participants (2.4%) had one or more important protocol deviations; 15 (2.5%) in the PCV15 group and 14 (2.3%) in the PCV13 group. Of the important protocol deviations, 4 participants had clinically important deviations, including one woman who had received PCV15 without a negative pregnancy test result and 3 participants (0.5%) in the PCV13 group whose reportable safety events and/or follow-up safety information were not reported per the timelines outlined in the protocol. Other important deviations included 19 participants (9 PCV15 recipients and 10 PCV13 recipients) whose immunogenicity blood samples were drawn outside the protocol-defined windows, and therefore were excluded from the efficacy analyses (OPA and IgG).

***Reviewer Comment*:** *The reported rates of clinically important protocol deviations were low across study groups and do not raise concerns about study conduct.*

6.1.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints, rather OPA serologic endpoints were used to assess the response to vaccination.

6.1.11.1 Analyses of Primary Endpoints

Primary Analyses: OPA GMTs for 13 Shared Serotypes and Unique Serotypes 22F & 33F

The primary immunogenicity analyses evaluated serotype-specific OPA GMTs at Day 30 in the PCV15 group compared to the PCV13 group. For each of the 13 shared serotypes, non-inferiority of the OPA immune response was demonstrated if the LB bound of the 2-sided 95% CI of the OPA GMT ratio (PCV15/PCV13) was greater than 0.5. For the two unique serotypes 22F and 33F, statistically significantly greater OPA responses were demonstrated if the LB of the 2-sided 95% CI of the OPA GMT ratio was greater than 2.0, and if the LB of the 2-sided 95% CI of the difference in the proportions of participants with a ≥4-fold increase from Day 1 to Day 30 was greater than 10%.

The following table provides the OPA GMT responses [95% CI] at Day 30 for the PCV15 group compared to the PCV13 group for the Per-Protocol Analysis Set (PPAS), as well as the differences in the proportion of participants who achieved ≥4-fold increase in OPA titer from Day 1 to Day 30 [95%CI].[6] The non-inferiority criteria for the 13 shared serotypes was met. PCV15 met both criteria for statistical superiority for the 2 unique serotypes based on both criteria.

Table 4. Serotype-Specific Opsonophagocytic Activity Geometric Mean Titers (OPA GMTs) in Pneumococcal Vaccine Naïve Participants ≥50 years, and Proportions of Participants With ≥4-Fold Rise at Day 30, Per-Protocol Analysis Set, Study V114-019

Pneumococcal Serotype	V114 (N=515-598) GMT % 4-Fold Rise	PCV13 (N=488-598) GMT % 4-Fold Rise	GMTR [95% CI] % Difference [95% CI]
1	257 75.1%	321 77.9%	0.80 [**0.66**, 0.97] -2.6 [-7.4, 2.3]
3	215 70.2%	133 58.3%	1.62 [**1.40**, 1.87] 12.0 [**6.4**, 17.5]
4	1109 79.5%	1633 85.0%	0.68 [**0.57**, 0.80] -5.3 [-9.8, -0.9]
5	445 71.5%	560 75.5%	0.79 [**0.64**, 0.98] -3.9 [-9.0, 1.2]
6A	5371 76.5%	5276 74.8%	1.02 [**0.85**, 1.22] 1.9 [-3.2, 7.0]
6B	3984 81.2%	3179 79.0%	1.25 [**1.04**, 1.51] 2.3 [-2.3, 6.9]
7F	4575 66.7%	5830 72.6%	0.78 [**0.68,** 0.90] -5.9 [-11.3, -0.5]
9V	1809 53.8%	2193 59.8%	0.83 [**0.71**, 0.96] -5.9 [-11.6, -0.1]
14	1976 51.8%	2619 60.6%	0.75 [**0.64**, 0.89] -8.7 [-14.4, -3.0]

[6] The OPA data presented for this study are from the modified (b) (4) test and include OPA data that excluded sera samples that tested (b) (4) positive.

Pneumococcal Serotype	V114 (N=515-598) GMT % 4-Fold Rise	PCV13 (N=488-598) GMT % 4-Fold Rise	GMTR [95% CI] % Difference [95% CI]
18C	2749 71.5%	2552 69.0%	1.08 [**0.91**, 1.27] 2.7 [-2.6, 8.0]
19A	3177 70.6%	3921 70.9%	0.81 [**0.70**, 0.94] -0.2 [-5.5, 5.1]
19F	1688 61.9%	1884 64.7%	0.90 [**0.77**, 1.04] -2.7 [-8.3, 2.9]
23F	2029 74.9%	1723 71.4%	1.18 [**0.96,** 1.44] 3.5 [-1.7, 8.8]
22F	2381 71.7%	73 13.9%	32.52 [**25.87**, 40.88] 57.7 [**52.5**, 62.5]
33F	8010 56.8%	1114 6.2%	7.19 [**6.13,** 8.43] 50.6 [**45.9**, 55.0]

Source: Adapted from STN 125741.0 (module 5.3.5.4) 04Nov2020-(b)(4) Statistical Report (Sensitivity Analyses), Tables 7 and Table 14; STN 125741.0/Am 40 (module 5.3.5.4)14June2021-(b)(4) Statistical Reports (Sensitivity Analyses) Tables 8, 9 and 10. OPA GMTs, GMT ratio and 95% CI are estimated from cLDA model. Pn Serotypes: Pneumococcal Serotypes included in PCV15; OPA: Opsonophagocytic activity; PPAS: Per-Protocol Analyses Set; CI: confidence interval; N: # participants in PPAS; GMT: Geometric Mean Titer (1/dil); GMTR: GMT ratio (PCV15/PCV13); GMTs: calculated by exponentiating the estimates of the mean of the natural logarithm values; Within-group 95% CIs: calculated by exponentiating the bounds of the CIs of the mean of the natural logarithm values based on the t-distribution; GMTRs: estimated from cLDA model. % Differences: difference in estimated 4-fold rise rates across groups (PCV15-PCV13) based on the Miettinen & Nurminen method stratified by age group (i.e., 50 to 64 years, 65 to 74 years, and ≥75 years). Bold numbers indicate lower limits of 95% CIs for which statistical testing was performed for the respective endpoint and respective serotypes.

6.1.11.2 Analyses of Secondary Endpoints

Secondary Analyses: OPA GMT Serotype 3

The secondary immunogenicity analyses evaluated the statistical superiority of serotype 3 OPA GMTs at Day 30 for the PCV15 group compared to PCV13 group. Statistically significantly greater OPA responses were demonstrated if the LB of 2-sided 95% CI of the OPA GMT ratio was greater than 1.2, and if the LB of the 2-sided 95% CI of the difference in proportions of participants with a ≥4-fold increase from Day 1 to Day 30 was greater than 0. As shown in the table above, PCV15 met both criteria for statistical superiority for serotype 3.

Secondary Objectives: IgG GMCs

The secondary immunogenicity objective also included descriptive evaluations of IgG GMCs 30 days postvaccination. For the shared serotypes, the GMC ratio point estimates were between 0.72 and 1.51 and the LBs of the 95% CI for the GMC ratios (PCV15/PCV13) were all ≥0.62.

6.1.11.3 Subpopulation Analyses

Subpopulation Analyses by Age:

The serotype specific OPA GMT ratios across groups were descriptively evaluated in participants 50 to 64 years, 65 to 74 years, and ≥75 years. In general, the OPA GMT point estimates were slightly lower in older age cohorts compared to the primary analyses.

Subpopulation Analyses by Sex:

Serotype-specific OPA GMTs by sex were generally similar to those among all participants in the primary analysis. However, for male participants the LB of the 95% CI of the OPA GMT ratio was slightly less than 0.5 (0.46) for serotype 4.

Subpopulation Analyses by Racial/Ethnic Origin:

As noted above in Section 6.1.10.1.1, the majority of vaccinated participants were of White race (~68%), followed by 25% Asian, 6% Black, 0.9% Multiple. There was 1 participant in each of the racial groups

American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander. Subgroup analyses by race were conducted for White, Black, and Asian races, and were generally comparable to the findings among participants overall, however Black participants had low enrollment (36 PCV15 recipients and 37 PCV13 recipients) and the LB of the 95% CI for the GMT ratio was <0.5 for serotypes 1, 4, 5, 7F, 9V, and 14.

Among Hispanic participants (135 PCV15 recipients and 129 PCV13 recipients) as compared to Non-Hispanic participants (467 PCV15 recipients and 470 PCV13 recipients), OPA GMT ratios were lower for several serotypes, with LB of the 95% CI of OPA GMTR <0.5 for serotypes 1, 4, 5,7F, 9V, 14, and 19F.

6.1.11.4 Dropouts and/or Discontinuations
Approximately 98% of randomized participants completed the study (Table 3, above). Missing immunogenicity data was not imputed and no test or search for outliers was performed.

6.1.12 Safety Analyses

6.1.12.1 Methods
See Section 6.1.2 above.

6.1.12.2 Overview of Adverse Events
Safety data were presented for the PCV15 group and PCV13 group. The following table provides an overview of the rates of adverse events during the study period.

Table 5. Proportions of Participants Reporting at Least One Adverse Event Following Pneumococcal Conjugate Vaccination, All Participants as Treated, Study V114-019

AE Type: Monitoring Period*	PCV15 (N=602) % (n participants/N)	PCV13 (N=600) % (n participants/N)
Immediate AEs: 30 minutes	1.7% (10/602)	0.5% (3/600)
Solicited injection site ARs: 5 days	59.0% (355/602)	47.3% (284/600)
Solicited systemic ARs: 14 days	33.2% (200/602)	30.3% (182/600)
Temperature ≥38.0°C: 5 days[1]	0.5% (3/600)	1.3% (8/598)
Unsolicited AEs: 14 days	14.3% (86/602)	16.0% (96/600)
SAEs: 6 months	1.5% (9/602)	2.2% (13/600)
Deaths: 6 months	0.2% (1/602)	0.2% (1/600)

Source: Adapted from STN 125741.0, Study P019V114 Clinical Study Report including Table 12-1, Table 12-2, Table 12-10.
APaT: All Participants as Treated Population was used as the analysis set for safety; n: #participants who experienced the relevant type of AE; N: #participants in APaT; AEs: adverse events; ARs: adverse reactions; SAEs: serious adverse events
* Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.
ł Percentages are calculated based on the number of participants with temperature data.

Rates of different AE types were comparable across study groups except for injection site ARs, which were reported at higher rates in the PCV15 group. Rates of SAEs were similar and none were considered related to vaccinations, and there was one death in each group, none of which were considered related to study vaccination**.**

Subpopulation Analyses
Vaccine recipients in older age groups (65 to 70 years and >75 years) had lower rates of AEs than those in younger age groups (50 to 64 years). The observed differences in rates of AEs between study groups (PCV15 vs PCV13) were maintained across age cohorts. By sex, rates of AEs were generally comparable to the rates among all participants, though females reported consistently higher rates of AEs than males. Rates of AEs among White, Black, and Asian participants were generally similar to the rates reported for all participants, though differences were observed in racial cohorts with small numbers of participants.

Solicited Reactions

The table below shows proportions of participants who reported solicited reactions on their VRC during the 5 days postvaccination for local reactions and fever, and the 14 days postvaccination for systemic reactions. As mentioned in Section 6.2.7, solicited AR data reflect VRC information as assessed and revised by the investigators.

Table 6. Proportion of Participants With Solicited Reactions (Local, Systemic, Fever) Postvaccination, All Participants as Treated, Study V114-019

Solicited Adverse Reaction*	PCV15 (N=602) % (n participants/N)	PCV13 (N=600) % (n participants/N)
Local (injection site)	--	--
Pain:	--	--
Any†	54.0% (325/602)	42.3% (254/600)
Grade 1	45.8% (276/602)	37.5% (225/600)
Grade 2	8.0% (48/602)	4.5% (27/600)
Grade 3	0.2% (1/602)	0.3% (2/600)
Swelling	--	--
Any†	12.5% (75/602)	11.2% (67/600)
0 to ≤2.4 cm	6.8% (41/602)	6.3% (38/600)
>2.4 to ≤5.0 cm	3.7% (22/602)	2.2% (13/600)
>5.0 to ≤10.0 cm	1.8% (11/602)	2.5% (15/600)
>10.0 cm	0.2% (1/602)	0.2% (1/600)
Erythema:	--	--
Any†	9.0% (54/602)	11.3% (68/600)
0 to ≤2.4 cm	5.0% (30/602)	6.2% (37/600)
>2.4 to ≤5.0 cm	2.0% (12/602)	3.2% (19/600)
>5.0 to ≤10.0 cm	1.8% (11/602)	1.5% (9/600)
>10.0 cm	0.2% (1/602)	0.5% (3/600)
Systemic	--	--
Myalgia:	--	--
Any†	15.4% (93/602)	12.0% (72/600)
Grade 1	12.0% (72/602)	9.8% (59/600)
Grade 2	3.5% (21/602)	2.0% (12/600)
Grade 3	0.0% (0/602)	0.2% (1/600)
Fatigue:	--	--
Any†	17.4% (105/602)	17.3% (104/600)
Grade 1	12.3% (74/602)	12.3% (74/600)
Grade 2	5.0% (30/602)	4.8% (29/600)
Grade 3	0.2% (1/602)	0.2% (1/600)
Headache:	--	--
Any†	11.6% (70/602)	13.0% (78/600)
Grade 1	8.1% (49/602)	9.7% (58/600)
Grade 2	3.3% (20/602)	3.0% (18/600)
Grade 3	0.2% (1/602)	0.3% (2/600)
Arthralgia:	--	--
Any†	5.3% (32/602)	5.5% (33/600)
Grade 1	3.7% (22/602)	4.3% (26/600)
Grade 2	1.7% (10/602)	1.2% (7/600)
Grade 3	0.0% (0/602)	0.0% (0/600)

Solicited Adverse Reaction*	**PCV15 (N=602) % (n participants/N)**	**PCV13 (N=600) % (n participants/N)**
Fever‡:	--	--
≥38.0°C	0.5% (3/600)	1.3% (8/598)
38.0 to <38.5°C	0.2% (1/600)	1.2% (7/598)
38.5 to <39.0°C	0.2% (1/600)	0.2% (1/598)
39.0 to <40.0°C	0.0% (0/600)	0.0% (0/598)
≥40.0°C	0.2% (1/600)	0.0% (0/598)

Source: Adapted from STN 125741.0, Study P019V114 Clinical Study Report, Table 12-6, Table 12-7, Table 14.5-2.
APaT: All Participants as Treated Population was used as the analysis set for safety; n: #participants who experienced the relevant type of AE; N: #participants in APaT.
* Local (injection site) reactions were solicited on Days 1-5 postvaccination. Systemic reactions were solicited on Days 1-14 postvaccination. The following toxicity grade definitions apply to the solicited reactions of injection site pain, myalgia, fatigue, headache and arthralgia: Grade 1 - Did not interfere with activity; Grade 2 - Interfered with activity (criteria for injection site pain and headache also included repeated use of non-narcotic pain reliever >24 hours; criteria for arthralgia also excluded medical intervention); Grade 3 - Prevented daily activity (criteria for injection site pain and headache also included any use of narcotic pain reliever; criteria for arthralgia also required medical intervention). No Grade 4 events were reported.
ł Includes participants with "unknown" toxicity grade or size.
‡ Percentages are calculated based on the number of participants with temperature data. The temperature value ≥40.0 C reported by a participant in the PCV15 group was considered erroneous by the investigator based on clinical review. The temperature value ≥40.0 C reported by a participant in the PCV15 group was considered erroneous by the investigator based on clinical review.

Injection site pain was the most frequently reported local reaction (PCV15: 54% vs PCV13: 42.3%). The majority of events were reported as Grade 1, with 8% of PCV15 recipients and 4.5% of PCV13 recipients reporting Grade 2 events. Local swelling and erythema were reported in <12% of participants across groups, and the majority of events reported were Grade 1 (0 to ≤2.4cm). The majority of local injection site ARs had a duration of ≤3 days, with 4 participants reporting local pain for >5 days, 2 participants reporting erythema for >5 days, and 2 participants reporting swelling for >5 days.

The most frequently reported systemic reactions were fatigue (~17% across groups) and myalgia (PCV15: ~15% vs PCV13:12%). The majority of these events were reported as Grade 1. Headache was reported by ~11-13% of all participants, the majority of which were also reported as Grade 1. Across groups, the majority of systemic reactions lasted ≤3 days. Among PCV15 recipients, 9 reported fatigue for >5 days, 6 reported myalgia for >5 days, and 4 reported arthralgia for >5 days.

The rates of fever were low across groups, with 3 PCV15 recipients reporting temperature ≥38.0C, including one with temperature ≥40.0C, and 8 PCV13 participants reporting fever, including one with temperature ≥38.5C.

> ***Reviewer Comment:*** *The rates of solicited reactions were generally higher in PCV15 recipients compared to PCV13 recipients, but within an acceptable range when compared to other licensed vaccines for adults. The most frequently reported reactions were local injection site pain, fatigue, and myalgia. The proportion of PCV15 recipients reporting Grade 2 or higher severity events was <5% for each adverse reaction, except for injection site pain, that had 8% of PCV15 recipients reporting Grade 2 pain (0.3% Grade 3 pain) compared to 4.5% of PCV13 recipients (0.3% Grade 3 pain).*

Unsolicited AEs (Non-Serious): 14 days Postvaccination
Rates of unsolicited AEs within 14 days postvaccination were similar between study groups (PCV15: 67.0% vs PCV13: 58.2%). The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) included *General disorders and administration site conditions* (PCV15: 63.3% vs PCV13: 52.3%); *Musculoskeletal and connective tissue disorders* (PCV15: 20.4% vs PCV13: 16.2%), and *Nervous system disorders* (PCV15: 12.0% vs PCV13: 13.5%).

Reviewer Comment: *The reported rates and types of unsolicited adverse events are comparable across study groups and represent common medical conditions in the general population for the evaluated age cohort (adults ≥50 years).*

6.1.12.3 Deaths

There were 2 deaths reported in the study, one in each study group. In the PCV15 group, a 74-year-old White male with a history of atrial fibrillation died of unknown causes on Day 55 postvaccination. The participant's relatives declined to provide additional details and there were no other AEs reported for this participant. The PCV13 recipient was an 82-year-old White male with a history of cardiac disease who died on Day 87 postvaccination due to arrhythmia and associated acute myocardial infarction. Both deaths were not considered related to study vaccination by the investigator.

Reviewer Comment: *The clinical reviewer agrees with the investigator's assessment that none of the reported deaths were related to study vaccination.*

6.1.12.4 Nonfatal Serious Adverse Events

There were 9 SAEs (1.5%) reported in PCV15 recipients and 13 SAEs (2.2%) reported in the PCV13 recipients. The most frequently reported SAEs were classified under the SOC *Cardiac disorders* (PCV15: 2 vs PCV13: 2) which included one event of atrial fibrillation and another event of myocardial infarction in PCV15 recipients. Within 30 days of study vaccination, there were no reported SAEs in the PCV15 study group. None of the SAEs were considered related to study vaccination.

Reviewer Comment: *The clinical reviewer agrees with the investigator's assessment that none of the reported SAEs were related to study vaccination.*

6.1.12.7 Dropouts and/or Discontinuations

Of the 1205 participants randomized, 1202 (99.8%) were vaccinated and 1190 (98.8%) completed the study. The study intervention included a single vaccination dose administered on Day 1, therefore discontinuation from study intervention due to an AE could not occur. There were 15 participants who withdrew from the study, including 10 participants lost-to-follow-up (PCV15: 5 vs PCV13: 5). There were 2 deaths, none of which were considered related to study vaccination, and 1 recipient of PCV15 voluntarily withdrew from the study. Protocol deviations are discussed above in Section 6.1.10.2.1.

Table 7. Discontinuations, Study V114-019

Disposition	**PCV15 (N=604) n (%)**	**PCV13 (N=601) n (%)**
Enrolled	604	601
Vaccinated	602 (99.7%)	600 (99.8%)
Completed Study	596 (98.7%)	594 (98.8%)
Withdrawal due to:	--	--
Voluntary W/d	1 (0.2%)	0
Lost to F/up	5 (0.8%)	5 (0.8%)
Protocol Deviation	0	1 (0.2%)
Death	1 (0.2%)	1

Source: Adapted from STN 125741.0, Study P019V114, Table 10-1. *Participants were unable to complete the Month 6 follow-up telephone contact due to COVID-19.

6.1.13 Study Summary and Conclusions

Study V114-019 was designed to demonstrate the immunogenicity and safety of PCV15 compared to PCV13, a licensed pneumococcal conjugate vaccine for use in adults ≥50 years of age. The primary

objectives evaluated the immunologic non-inferiority of PCV15 to PCV13 for the 13 shared serotypes and the statistical superiority of PCV15 to PCV13 for the two unique serotypes in PCV15 based on OPA responses. The secondary objectives also evaluated the statistical superiority of PCV15 to PCV13 for serotype 3, which is included in both vaccines. The study met all the predefined statistical criteria for success for the respective non-inferiority and statistical superiority tests. The data from this study support the safety and effectiveness of PCV15 for use as a single dose in adults ≥50 years and OPA GMT comparative data will be included in the USPI to support PCV15 effectiveness.

6.2 Trial #2 (Study V114-020)

NCT03950856
"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"

Study Overview: The purpose of this study was to evaluate the safety of PCV15 in adults ≥50 years of age (N=2340) and to demonstrate clinical lot consistency of PCV15. The study was conducted in the US, Australia, Chile, Denmark, Finland, and Great Britain.

6.2.1 Objectives

Primary Objectives
1. To evaluate the safety and tolerability of PCV15.
    - *Endpoints:* % of participants with solicited injection site ARs (redness, swelling, pain), solicited systemic ARs (muscle pain/myalgia, joint pain/arthralgia, headache, fatigue), fever, unsolicited non-serious AEs, serious adverse events (SAEs)

2. To compare serotype-specific OPA geometric mean titers (GMTs) at 30 days postvaccination (Day 30) across 3 different lots of PCV15.
    - *Endpoint:* Serotype-specific OPA GMTs for the 15 serotypes in PCV15
        - 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

Secondary Objectives
1. To evaluate serotype-specific IgG GMCs at Day 30 compared across the 3 different lots of PCV15 and combined lots of PCV15 compared to PCV13.
    - *Endpoint:* Serotype-specific IgG GMCs for the 15 serotypes in PCV15 at Day 30

2. To evaluate the serotype-specific GMFRs and proportions of participants with a ≥4-fold increase from pre-vaccination (Day 1) to 30 days postvaccination for OPA and IgG responses separately for each of the 3 vaccine lots of PCV15
    - *Endpoint:* Serotype-specific OPA and IgG responses for the 15 serotypes in PCV15

6.2.2 Design Overview

A total of 2340 pneumococcal vaccine-naïve adults ≥50 years of age were randomized 3:3:3:1 to one of three PCV15 lots (667 participants/vaccine lot) or PCV13 (220 participants). Enrollment was stratified by age group as follows: 50 to 64 years, 65 to 74 years, and ≥75 years, with at least 50% participants ≥65 years.

***Reviewer Comment*:** *CBER viewed the stratification plans acceptable in order to ensure adequate sample size of participants ≥65 years of age early phase development. OPA GMT responses among participants ≥65 years were lower than responses among younger adults.*

In countries with recommendations for sequential administration of PCV13 followed at least 12 months later by PPV23 (Merck and Co, Inc; PPV23), PPV23 was administered outside the study protocol.

6.2.3 Population

Eligibility criteria were the same as Study V114-019 (see Section 6.1.3 above).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Table 8. Vaccinations Administered in Study V114-020

Study Group	Vaccination Schedule (Day 1)
PCV15 Lot 1	Single dose
PCV15 Lot 2	Single dose
PCV15 Lot 3	Single dose
PCV13	Single dose

PCV15: 15-valent pneumococcal conjugate vaccine

- Lot 1; Lot 2; Lot 3
- Dose: single 0.5mL intramuscular (IM)
- Composition: Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F
- Presentation: Sterile suspension in a prefilled syringe
- Manufacturing
  - Lot 1: #WL00068940
  - Lot 2: #WL00068989
  - Lot 3: #0000957291

Prevnar 13: 13-valent pneumococcal conjugate vaccine (diphtheria CRM_{197} protein)

- Dose: single 0.5mL intramuscular
- Composition: Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Presentation: Sterile suspension in a prefilled syringe
- Lot #0000947747 (PCV13 used in US)
- Lot #0000956034 (PCV13 used in Australia, Chile, Denmark, Finland, United Kingdom)

6.2.5 Directions for Use

A single dose (0.5mL) was administered IM.

6.2.6 Sites and Centers

55 sites in US, Australia, Chile, Denmark, Finland, and Great Britain.
US sites enrolled 1056 participants (45% of all participants).

6.2.7 Surveillance/Monitoring

Safety monitoring and immunogenicity assays were the same as those in Study V114-019 (See Section 6.1.7 above).

6.2.8 Endpoints and Criteria for Study Success

See Section 6.2.1 above.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Primary Hypothesis

- H_0: GMT_x/GMT_y <0.5 or GMT_x/GMT_y >2.0 vs. H_1: 0.5<GMT_x/GMT_y <2.0
  - GMT_x is serotype-specific OPA GMT for one of the PCV15 lots and GMT_y is serotype-specific OPA GMT for another PCV15 lot.
  - Rejecting the null hypothesis at the 1-sided α =0.025 level corresponds to the bounds of the 95% CI on the GMT ratios between each PCV15 lot being between 0.5 and 2.0 and would lead to the conclusion that the OPA responses across the PCV15 lots are equivalent.
  - Estimation of the GMT ratios and 95% CIs, and the hypothesis test was conducted using the cLDA method utilizing data from the participants randomized to PCV15.
  - For the primary hypothesis, the sample size provided >90% power to demonstrate equivalent immunogenicity across the three PCV15 lots. The power and sample size were based on the following assumptions: 90% evaluable participants, underlying serotype-specific OPA GMT ratios for each of the 15 pneumococcal serotypes was 1.0, variabilities for OPA titers in the PCV15 vaccination groups are the same as those observed in V114-006, statistical criterion for equivalence required that the bounds of the 2-sided 95% CI of the OPA GMT ratios were between 0.50 and 2.0.

*Secondary Immunogenicity Endpoints (*descriptive, 30 days postvaccination): pneumococcal serotype-specific IgG GMCs, OPA and IgG: Reverse cumulative distribution curve, GMFR, % of participants with ≥4-fold increase compared to baseline

Safety Endpoints: % of participants with

- Solicited injection site ARs (redness, swelling, pain) during Days 1-5 postvaccination
- Solicited systemic ARs (muscle pain/myalgia, joint pain/arthralgia, headache, fatigue) during Days 1-14 postvaccination
- Maximum temperature measurement
- Any AE, any vaccine-related AE during Days 1-14 postvaccination
- Any SAE, any vaccine-related SAE, and death from Day 1 through Month 6 postvaccination

Analyses: p-values (Tier 1 events [solicited local reactions and systemic AEs] and 95% CIs [any AE, any SAE] were provided for between-treatment differences in the percentage of participants with events; these analyses were performed using the Miettinen and Nurminen (M&N) method.

Interim Analysis: Performed to support the periodic review of safety and tolerability data across the adult PCV15 Phase 3 program. An external unblinded statistician provided unblinded interim safety summaries to an eDMC for their review.

Multiplicity: No multiplicity adjustments were applied for immunogenicity or safety comparisons.

Protocol Amendments

- The protocol was not amended from the original protocol (version January 9, 2019)

Significant Changes in the Conduct of the Study and Planned Analyses:

- There were no changes in the conduct of the study implemented by protocol amendment

- COVID-19 Pandemic: see Section 6.1.9

6.2.10 Study Population and Disposition

A total of 2340 participants were enrolled in the study during June 12, 2019 (first participant, first visit) to October 3, 2020 (last participant, last visit).

6.2.10.1 Populations Enrolled/Analyzed

Same as Study V114-019.

6.2.10.1.1 Demographic and Baseline Characteristics

Table 9. Demographic Characteristics, by Study Group, All Vaccinated Participants, Study V114-020

Demographic Characteristic	PCV15 Lot 1 (N=698)	PCV15 Lot 2 (N=704)	PCV15 Lot 3 (N =700)	PCV13 (N=231)
Sex ratio M:F (%)	312:386 (44.7%:55.3%)	282:422 (40.1%:59.9%)	297:403 (42.4%:57.6%)	99:132 (42.9%:57.1%)
Age, years:				
Mean age (SD)	64.4 (7.5)	64.4 (7.8)	64.3 (7.4)	64.3 (7.9)
Median age	65.0	65.0	65.0	65.0
Age range	50, 88	50, 91	50, 92	50, 89
Age group (years), n (%):				
50-64	310 (44.4%)	312 (44.3%)	311 (44.4%)	101 (43.7%)
65-74	320 (45.8%)	323 (45.9%)	321 (45.9%)	107 (46.3%)
≥75	68 (9.7%)	69 (9.8%)	68 (9.7%)	23 (10.0%)
Racial origin, n (%):				
Am. Indian/A.N.	1 (0.1%)	4 (0.6%)	0 (0.0%)	0 (0.0%)
Asian	18 (2.6%)	34(4.8%)	36 (5.1%)	10 (4.3%)
Black/A.A.	35 (5.0%)	41 (5.8%)	34 (4.9%)	20 (8.7%)
White	640 (91.7%)	621 (88.2%)	627 (89.6%)	201 (87.0%)
N. Hawaiian/P.I.	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple	3 (0.4%)	4 (0.6%)	3 (0.4%)	0 (0.0%)
Not reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity, n (%):				
Hispanic/Latino	130 (18.6%)	154 (21.9%)	138 (19.7%)	41 (17.7%)
Not H/L	557 (79.8%)	540 (76.7%)	557 (79.6%)	188 (81.4%)
Not reported	10 (1.4%)	9 (1.3%)	5 (0.7%)	2 (0.9%)
Unknown	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)

Source: Adapted from STN 125741.0, P020V114 Clinical Study Report, Table 10-5. All Vaccinated Participants Analyses Set.
PCV13: Prevnar 13; SD: standard deviation.
For Sex, Racial Origin, and Ethnicity: X indicates number of participants fulfilling the item followed by (%).
N: total number of participants for the Safety Analyses Set (participants who received 1 dose and had any safety data available).
Sex Ratio M:F indicates Male:Female.
Racial origin: Black/A.A.: Black/African American; Am. Indian/A.N: American Indian/Alaska Native; N. Hawaiian/P.I.: Native Hawaiian/Pacific Islander. Ethnicity: Hispanic/Latino; Not H/L: Not Hispanic/Latino. Not reported ethnicity accounted for 26 participants (1.1%) across all groups.

Among all vaccinated participants, there were more females (58%) than males, the median age for the study was 65 years, and the proportion of participants 50 to 64 years was ~44%, 65 to 74 years was 46%, and ≥75 years was ~10%. Overall, the majority of participants were White (~90%), followed by Black/African American (5.6%) and Asian (4.2%); 20% had Hispanic/Latin ethnicity. Table 9 above shows that the demographic characteristics of participants were similar between study groups.

6.1.10.1.3 Participant Disposition

Table 10. Participant Disposition, by Study Group, All Randomized Participants, Study V114-020

Population	PCV15 Lot 1 (N=702) n (%)	PCV15 Lot 2 (N=704) n (%)	PCV15 Lot 3 (N=701) n (%)	PCV13 (N=233) n (%)
Enrolled	702 (100%)	704 (100%)	701 (100%)	233 (100%)
Vaccinated	698 (99.4%)	704 (100%)	700 (99.9%)	231 (99.1%)
Completed study	683 (97.3%)	689 (97.9%)	683 (97.4%)	227 (97.4%)
Safety Analysis*	699 (99.6%)	704 (100%)	700 (99.9%)	230 (98.7%)
FAS Set**	698 (99.4%)	704 (100%)	700 (99.9%)	231(99.1%)
Per-Protocol OPA***	693 (98.7%)	693 (98.4%)	688 (98.1%)	225 (96.6%)
Per-Protocol IgG***	693 (98.7%)	693 (98.4%)	688 (98.1%)	225 (96.6%)
≥1 Important Protocol Deviation	19 (2.7%)	28 (4.0%)	36 (5.1%)	11 (4.7%)

Source: Adapted from STN 125741.0, P020V114 Clinical Study Report and Module 2.7.3: Table 10-1, Table 11-1, Table 11-2, Table 11-3, Table 12-1, 12-2, Table 14.1-3, Table 14.2-2, Table 2.7.3-adultpneumo: 12.
X indicates number of participants fulfilling the item followed by (%).
N: total number of participants enrolled.
≥1 Important Protocol Deviation: participants with one or more important protocol deviations. Important protocol deviation is a deviation that may significantly impact the quality (i.e. completeness, accuracy, and reliability) or integrity of key trial data; or that may significantly affect a participant's rights, safety, or well-being.
*Safety analyses using the APaT population included all randomized participants who received the study intervention. For this study safety analyses was conducted on 2333 randomized participant, however 3 participants received the wrong vaccine: PCV15 Lot 1 group: one participant received Lot 3; PCV15 Lots 3 group: one participant received Lot 1; and PCV13 group: one participant received Lot 1.
**FAS: Full Analysis Set: All randomized participants who received the intervention and had at least 1 serology result. Maximum "n" across all serotypes from the primary (OPA) immunogenicity analysis table in the FAS population.
***Maximum "n" across all serotypes from the primary (OPA) and secondary (IgG) immunogenicity analysis tables in the Per-Protocol Population.

A list of pre-specified protocol deviations is provided in Section 6.2.10.1 (above). Overall, 94 participants (4.0%) experienced at least 1 protocol deviation that the Applicant considered to be important,[7] of whom 24 participants (1%) had clinically important protocol deviations. The number of participants by group who had a protocol deviation included the following:

- Lot 1: 4 participants (0.6%)
- Lot 2: 4 participants (0.6%)
- Lot 3: 11 participants (1.6%)
- PCV13: 5 participants (2.1%)

Of the 24 participants who reported clinically important protocol deviations, 17 participants (71%) were administered improperly stored study intervention that was deemed unacceptable for use (8 participants in the Lot 3 Group and 5 participants in the PCV13 Group). Other reported protocol deviations that occurred infrequently (~1-2 participants/group) included administration of a study intervention that was not assigned, failure to report safety event and/or follow-up safety event information within the timelines outlined in the protocol, and study vaccine administered to a female participant prior to pregnancy testing.

> ***Reviewer Comment:*** *The reported rates of clinically important protocol deviations were low across groups and do not raise concerns about study conduct or Good Clinical Practice. Although there were higher proportions of (blinded) participants reporting events in the PCV15 Lot 3 Group and PCV13 Group than in the other PCV15 lot groups, the observed protocol deviations do not*

[7] Protocol deviations were classified as per the International Conference on Harmonisation E3 classification of protocol deviations as important (those that may significantly impact the quality or integrity of key trial data or that may significantly affect a participant's rights, safety, or well-being) or not important. Important protocol deviations were further classified as either clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) or not clinically important.

undermine the interpretability of the study results. The non-important protocol deviations were associated with COVID-19 Pandemic (see Section 6.2.9, Significant Changes in Planned Analyses) and unlikely impacted study results.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoints

Primary Analyses: Lot-to-Lot Equivalence

The primary objective evaluated serotype OPA GMTs at 30 days postvaccination across the three PCV15 lot groups of adults ≥50 years of age following a single dose. The 3 lots were considered equivalent if for each pairwise comparison of PCV15 vaccine lots, the 2-sided 95% CI of the ratio of GMTs was contained within pre-specified equivalence margin [95% CI: 0.5, 2.0] for each of the 15 PCV15 serotypes. The primary objective was met for all 15 serotypes. Table 11 below provides 30-day postvaccination OPA GMTs [95% CI] for each PCV15 serotype by lot group. Table 12 shows the ratio of GMTs [95% CI] for each pairwise comparison of lot groups.

Table 11. Serotype-Specific OPA GMTs at 30 Days Postvaccination, by PCV15 Lot Group, Per-Protocol Analysis Set, Study V114-020

Pneumococcal Serotype	Lot 1 (N=649-663) GMT [95% CI]	Lot 2 (N=646-665) GMT [95% CI]	Lot 3 (N=636-653) GMT [95% CI]
1	246.5 [215.1, 282.5]	243.7 [213.2, 278.4]	237.8 [208.6, 271.1]
3	194.3 [176.6, 213.8]	227.8 [207.0, 250.8]	213.3 [193.5, 235.0]
4	1046.3 [919.4, 1190.7]	1280.5 [1142.1, 1435.7]	1059.0 [936.4, 1197.6]
5	371.1 [321.7, 428.0]	457.1 [397.1, 526.2]	383.6 [331.1, 444.4]
6A	5644.9 [5041.7, 6320.3]	5969.8 [5308.2, 6713.8]	6002.4 [5357.8, 6724.5]
6B	5009.1 [4476.3, 5605.5]	5377.5 [4794.0, 6032.2]	4950.1 [4392.2, 5578.8]
7F	3710.1 [3350.3, 4108.4]	4564.6 [4187.4, 4975.7]	4144.2 [3784.0, 4538.7]
9V	1685.6 [1517.7, 1872.1]	1680.4 [1514.4, 1864.6]	1729.0 [1557.7, 1919.1]
14	2285.2 [2023.9, 2580.3]	2526.9 [2255.1, 2831.6]	2057.2 [1837.4, 2303.3]
18C	3786.4 [3429.0, 4181.0]	3500.6 [3173.9, 3860.8]	3361.8 [3047.5, 3708.4]
19A	3312.3 [3023.3, 3629.0]	3744.4 [3419.4, 4100.2]	3404.9 [3095.6, 3745.1]
19F	1837.3 [1673.5, 2017.2]	2038.2 [1851.3, 2243.9]	1958.9 [1773.7, 2163.5]
23F	2203.1 [1931.7, 2512.7]	2382.8 [2101.6, 2701.7]	2110.3 [1860.7, 2393.4]
22F	2559.0 [2276.6, 2876.5]	2744.0 [2460.2, 3060.4]	2652.0 [2366.3, 2972.1]
33F	7614.2 [6812.1, 8510.7]	7697.8 [6916.2, 8567.7]	7400.6 [6606.9, 8289.6]

Source: Adapted from STN 125741.0, V114-020, module 5.3.5.4 (b)(4) Statistical Report (Sensitivity Analyses), Table 15.
Pn Serotypes: Pneumococcal Serotypes included in V114; OPA: Opsonophagocytic activity; PPAS: Per-Protocol Analyses Set; CI: confidence interval; N: # participants in PPAS; GMT: Geometric Mean Titer (1/dil); GMTs: calculated by exponentiating the estimates of the mean of the natural logarithm values; Within-group 95% CIs: calculated by exponentiating the bounds of the CIs of the mean of the natural logarithm values based on the t-distribution. Lot 1: lot# WL00068940; Lot 2: lot# WL00068989; Lot 3: lot# 0000957291.

Table 12: Geometric Mean Titer Ratios for PCV15 Pneumococcal Serotypes, by Each Pairwise Lot-to-Lot Comparison, Per-Protocol Analysis Set, Study V114-020

Pneumococcal Serotype	Lot 1/Lot 2 GMTR [95% CI]	Lot 2/Lot 3 GMTR [95% CI]	Lot 1/Lot 3 GMTR [95% CI]
1	0.99 [0.83, 1.18]	1.05 [0.88, 1.25]	1.03 [0.86, 1.23]
3	0.84 [0.74, 0.96]	1.08 [0.95, 1.23]	0.91 [0.80, 1.04]
4	0.82 [0.70, 0.97]	1.22 [1.03, 1.43]	1.00 [0.85, 1.18]
5	0.83 [0.68, 1.00]	1.20 [1.00, 1.45]	0.99 [0.82, 1.20]
6A	0.96 [0.82, 1.12]	0.99 [0.84, 1.16]	0.94 [0.81, 1.11]
6B	0.96 [0.82, 1.12]	1.04 [0.89, 1.22]	1.00 [0.86, 1.17]
7F	0.82 [0.72, 0.93]	1.10 [0.97, 1.25]	0.90 [0.79, 1.02]
9V	0.99 [0.87, 1.14]	0.96 [0.84, 1.10]	0.95 [0.83, 1.09]
14	0.93 [0.80, 1.09]	1.23 [1.05, 1.43]	1.14 [0.98, 1.34]
18C	1.08 [0.95, 1.24]	1.05 [0.91, 1.20]	1.14 [0.99, 1.30]
19A	0.89 [0.79, 1.01]	1.07 [0.94, 1.21]	0.95 [0.84, 1.08]
19F	0.92 [0.81, 1.05]	1.00 [0.88, 1.14]	0.92 [0.81, 1.05]
23F	0.93 [0.79, 1.11]	1.11 [0.94, 1.32]	1.04 [0.88, 1.24]
22F	0.93 [0.79, 1.09]	1.04 [0.89, 1.22]	0.96 [0.82, 1.13]
33F	1.01 [0.87, 1.17]	1.04 [0.89, 1.20]	1.05 [0.90, 1.22]

Source: Adapted from STN 125741.0, module 5.3.5.4 (b)(4) Statistical Report (Sensitivity Analyses), P020V114 Table 11.
Pn Serotypes: Pneumococcal Serotypes included in PCV15. PPAS: Per-Protocol Analyses Set, GMTR: Geometric Mean Titer Ratio; CI: confidence interval. GMTRs and 95% CI are estimated from a cLDA model.

The non-inferiority criteria were met for all serotypes, demonstrating lot-to-lot equivalency.

6.2.11.2 Analyses of Secondary Endpoints

Secondary Objectives: OPA GMTs and IgG GMCs

The serotype-specific OPA GMFRs and the proportion of participants with a ≥4-fold increase from baseline (pre-vaccination) were comparable across the PCV15 lot groups for OPA responses with overlapping 95% CIs. The OPA GMTs for the PCV15 Combined Lot group were comparable to those of the PCV13 group; GMT ratios (PCV15 Combined Lot/PCV13) were between 0.7 and 1.69 [95% CI: 0.57, 2.01] for the 13 shared serotypes. OPA GMT ratios were 32.27 [95% CI: 25.59, 40.69] for serotype 22F and 9.12 [7.46, 11.15] for serotype 33F.

The secondary immunogenicity objective also included the descriptive evaluations of IgG GMCs 30 days postvaccination. Lot-to-lot comparisons based on IgG GMCs were consistent with the primary analyses of OPA GMTs. The IgG GMCs for the PCV15 Combined Lot group were comparable to the those of the PCV13 group; GMC ratios (PCV15 Combined Lot/PCV13) were between 0.75 and 1.55 [95% CI: 0.62 to 1.86] for the 13 shared serotypes, 12.2 [95% CI: 10.11, 14.74] and 9.42 [95% CI: 7.96, 11.13] for serotypes 22F and 33F, respectively.

6.2.11.3 Subpopulation Analyses

Subpopulation Analyses by Age:

The serotype-specific OPA GMT ratios between lots groups were descriptively evaluated in participants aged 50 to 64 years, 65 to 74 years, and ≥75 years. The equivalence margins for pairwise lot-to-lot comparisons (Lots 1, 2, 3) for the 50 to 64-year-old and 65 to 74-year-old age cohorts were similar to those of the primary analyses. However, in adults ≥75 years, the GMT ratios across lots groups had greater variability when considering all PCV15 serotypes, [95% CI: 0.36 to 2.12], though the majority of serotypes were within the pre-specified equivalence margin for the primary analyses [95% CI: 0.5, 2.0].

Subpopulation Analyses by Sex:

OPA GMT responses to the three lots of PCV15 observed in male and female participants separately were similar to those observed in all participants in the primary analysis.

Subpopulation Analyses by Racial/Ethnic Origin:
As noted above in Section 6.2.10.1.1, the number of participants of non-White races were small and included 4.2% Asian, 5.6% Black, 0.4% Multiple, 0.2% American Indian/Alaska Native 0.2%, and only 1 participant identified as Native Hawaiian/Other Pacific Islander. Results of subgroup analyses of lot-to-lot equivalence for Asian, Black, and White participants yielded findings generally comparable to those among participants overall. The majority of vaccinated participants were not Hispanic/Latino (79%); subgroup analyses by ethnicity were also comparable to the results for participants overall.

6.2.11.4 Dropouts and/or Discontinuations
Approximately 97.5% of randomized participants completed the study (Table 10, above). Missing immunogenicity data was not imputed and no test or search for outliers was performed.

6.2.11.5 Exploratory and Post Hoc Analyses
As discussed in Section 6.2.10.1 above, the Applicant conducted post hoc analyses of OPA GMT results based on a modified (b) (4) test for several studies included in this application. For the primary and secondary analyses of Study V114-020, the Applicant submitted a sensitivity analysis of OPA testing results that excluded (b) (4)-positive samples.

6.2.12 Safety Analyses

6.2.12.1 Methods
See Section 6.2.2.

6.2.12.2 Overview of Adverse Events
Safety data were presented for each of the three PCV15 lot groups and the PCV13 group. The table below summarizes rates of adverse events during the study period.

Table 13. Proportion of Participants Reporting at Least One Adverse Event Following Pneumococcal Conjugate Vaccination, All Participants as Treated, Study V114-020

AE Type: Monitoring Period*	PCV15 Combined Lots (N=2103) % (n /N)	PCV13 (N=230) % (n /N)
Immediate AEs: 30 minutes	2.6% (55/2103)	0.9% (2/230)
Solicited injection site ARs: 5 days	70.0% (1473/2103)	57.0% (131/230)
Solicited systemic ARs: 14 days	46.4% (976/2103)	43.0% (99/230)
Temperature ≥38.0°C: 5 days[1]	0.8% (16/2100)	0.4% (1/230)
Unsolicited AEs: 14 days	18.4% (386/2103)	18.3% (42/230)
SAEs: 6 months	1.8% (38/2103)	2.2% (5/230)
Deaths: 6 months	0.1% (3/2103)	0.0% (0/230)

Source: Adapted from STN 125741.0, Study P020V114 Clinical Study Report including Table 12-2, Table 12-3, Table 12-11.
APaT: All Participants as Treated Population was used as the analysis set for safety; n: #participants who experienced the relevant type of AE; N: #participants in APaT; AEs: adverse events; SAEs: serious adverse events.
* Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.
[1] Percentages are calculated based on the number of participants with temperature data.

Across PCV15 lot groups, rates of reported adverse events were comparable. Rates of any reported adverse event were higher in the PCV15 combined lot group than in the PCV13 group (69% and 79%, respectively). Most PCV15 recipients reported at least one AE, with rates of solicited injection site reactions and solicited systemic events of 70% and 46%, respectively. Among PCV15 recipients, the rate of SAEs was low (1.8%) and deaths were few (n=3); no deaths or SAEs were considered related to treatment.

Subpopulation Analyses
Vaccine recipients in older age groups (65 to 70 years and >75 years) had lower rates of AEs than those in younger age groups (50 to 64 years). For example, 63.9% of PCV15 recipients and 52.2% of PCV13 recipients older than ≥75 years reported ≥1 AE, compared to 85.5% of PCV15 recipients and 73.3% of PCV13 recipients 50 to 64 years of age. By sex, rates of AEs were generally comparable to rates among participants overall, though females consistently reported higher rates of AEs than males. By racial group (White, Black, and Asian), rates of AEs were comparable to the overall rates, with minor differences observed in racial cohorts with small numbers of participants.

Solicited Reactions
The table below shows proportions of participants who reported solicited reactions on their VRC during the 5 days postvaccination for local reactions and fever, and the 14 days postvaccination for systemic reactions. As mentioned in Section 6.2.7, solicited AR data reflect VRC information as assessed and revised by the investigators.

Table 14. Proportions of Participants With Solicited Reactions (Local, Systemic, Fever) Postvaccination, All Participants as Treated, Study V114-020

Solicited Adverse Reaction*	**PCV15 Combined Lots (N=2103) % (n participants/N)**	**PCV13 (N=230) % (n participants/N)**
Local (injection site)	--	--
Pain:	--	--
Any†	66.8% (1405/2103)	52.2% (120/230)
Grade 1	52.6% (1106/2103)	43.5% (100/230)
Grade 2	13.4% (281/2103)	8.7% (20/230)
Grade 3	0.9% (18/2103)	0.0% (0/230)
Swelling	--	--
Any†	15.4% (323/2103)	14.3% (33/230)
0 to ≤2.4 cm	8.6% (181/2103)	9.6% (22/230)
>2.4 to ≤5.0 cm	3.9% (83/2103)	1.7% (4/230)
>5.0 to ≤10.0 cm	2.6% (55/2103)	3.0% (7/230)
>10.0 cm	0.2% (4/2103)	0.0% (0/230)
Erythema:	--	--
Any†	10.9% (229/2103)	9.6% (22/230)
0 to ≤2.4 cm	6.0% (126/2103)	6.1% (14/230)
>2.4 to ≤5.0 cm	2.2% (47/2103)	0.9% (2/230)
>5.0 to ≤10.0 cm	2.0% (42/2103)	2.2% (5/230)
>10.0 cm	0.6% (13/2103)	0.4% (1/230)
Systemic	--	--
Myalgia:	--	--
Any†	26.9% (566/2103)	21.7% (50/230)
Grade 1	19.6% (412/2103)	17.4% (40/230)
Grade 2	6.9% (146/2103)	4.3% (10/230)
Grade 3	0.4% (8/2103)	0.0% (0/230)
Fatigue:	--	--
Any†	21.5% (452/2103)	22.2% (51/230)
Grade 1	14.6% (307/2103)	10.9% (25/230)
Grade 2	6.1% (128/2103)	10.0% (23/230)
Grade 3	0.7% (15/2103)	0.9% (2/230)

Solicited Adverse Reaction*	**PCV15 Combined Lots (N=2103) % (n participants/N)**	**PCV13 (N=230) % (n participants/N)**
Headache:	--	--
Any [†]	18.9% (397/2103)	18.7% (43/230)
Grade 1	12.7% (268/2103)	13.0% (30/230)
Grade 2	5.2% (110/2103)	5.2% (12/230)
Grade 3	0.8% (17/2103)	0.0% (0/230)
Arthralgia:	--	--
Any [†]	7.7% (161/2103)	5.7% (13/230)
Grade 1	5.0% (105/2103)	4.3% (10/230)
Grade 2	2.5% (52/2103)	1.3% (3/230)
Grade 3	0.2% (4/2103)	0.0% (0/230)
Fever [‡]:	--	--
≥38.0°C	0.8% (16/2100)	0.4% (1/230)
38.0 to <38.5°C	0.6% (12/2100)	0.4% (1/230)
38.5 to <39.0°C	0.1% (3/2100)	0.0% (0/230)
39.0 to <40.0°C	0.0% (1/2100)	0.0% (0/230)
≥40.0°C	0.0% (0/2100)	0.0% (0/230)

Source: Adapted from STN 125741.0, Study P020V114 Clinical Study Report, Table 12-7, Table 12-8, Table 14.5-2.
APaT: All Participants as Treated Population was used as the analysis set for safety; n: #participants who experienced the relevant type of AE; N: #participants in APaT.
[*] Local (injection site) reactions were solicited on Days 1-5 postvaccination. Systemic reactions were solicited on Days 1-14 postvaccination. The following toxicity grade definitions apply to the solicited reactions of injection site pain, myalgia, fatigue, headache and arthralgia: Grade 1 - Did not interfere with activity; Grade 2 - Interfered with activity (criteria for injection site pain and headache also included repeated use of non-narcotic pain reliever >24 hours; criteria for arthralgia also excluded medical intervention); Grade 3 - Prevented daily activity (criteria for injection site pain and headache also included any use of narcotic pain reliever; criteria for arthralgia also required medical intervention). No Grade 4 events were reported.
[†] Includes participants with "unknown" toxicity grade or size.
[‡] Percentages are calculated based on the number of participants with temperature data.

In both study groups, injection site pain was the most frequently reported local reaction (PCV15 Combined Lots 66.8% vs. PCV13 52.2%), of which the vast majority was Grade 1 pain (no interference with daily activities). The proportion reporting Grade 3 pain (use of narcotic pain reliever) was low across groups (PCV15: 0.8% vs PCV13: 0). The majority of reported solicited local reactions lasted for ≤3 days across study groups, though ~7% of PCV15 recipients reported pain that lasted 3 to 5 days compared to 5.7% of PCV13 recipients for the same time period.

For both study groups, myalgia was the most frequently reported systemic reaction (PCV15 Combined Lots 26.9% vs PCV13: 21.7%), the majority of which was Grade 1. Fatigue (~22%) and headache (~19%) were reported at equal rates across groups, the majority of which were Grade 1 or 2. Solicited systemic reactions lasted for ≤3 days, with few events reported of longer duration.

The rates of fever were low across groups; the numbers of participants reporting fever were 16 and 1 in the PCV15 and 1 PCV13 groups, respectively. The majority of PCV15 recipients with fever reported temperatures between 38.0°C and 38.5°C, though three PCV15 recipients reported temperatures between 38.5°C and 39.0°C.

> ***Reviewer Comment:*** *The rates of solicited adverse reactions after PCV15 across each of the 3 combined lot groups were similar, however the overall rates of solicited reactions for the PCV15 Combined Lot groups were higher than those observed following PCV13 groups, and the majority of PCV15 recipients reported myalgia, fatigue, and headache, in addition to injection site pain.*

Unsolicited AEs (Non-Serious): 14 Days Postvaccination
The rates of unsolicited AEs within 14 days postvaccination across study groups were similar; 78.8% and 60.1% of participants reported one or more adverse events in the PCV15 combined and PCV13 groups, respectively. The most frequently reported events by SOC included *General disorders and administration site conditions* (PCV15: 73.9% vs PCV13: 61.7%); *Nervous system disorders* (PCV15: 19.7% vs PCV13: 19.1%); and *Musculoskeletal and connective tissue disorders* (PCV15: 30.7% vs PCV13: 24.8%).

> ***Reviewer Comment***: *The reported rates and types of unsolicited adverse events are comparable across groups and represent common medical conditions in the general population for the evaluated age cohort (adults ≥50 years).*

6.2.12.3 Deaths
There were 3 deaths reported in the study, two in the PCV15 Lot 2 group and one in the PCV15 Lot 1 group. A 69-year-old white male with a history of Type 2 diabetes mellitus and hypertension died of unknown cases on Day (b) (6), though the primary care physician stated that the participant likely died of pre-existing conditions. A 66-year-old white male died on Day (b) (6) due to worsening chronic obstructive pulmonary disease (COPD), congestive heart failure, and acute respiratory failure. The third death was in a 69-year-old white male who was diagnosed with and subsequently died of pancreatic cancer on Days 84 and (b) (6), respectively. None of the reported deaths were considered related to study vaccination by the investigator.

> ***Reviewer Comment:*** *The clinical reviewer agrees with the investigator's assessment that none of the reported deaths were related to study vaccinations.*

6.2.12.4 Nonfatal Serious Adverse Events
There were 38 SAEs (1.8%) reported in PCV15 recipients and 5 SAEs (2.2%) reported in PCV13 recipients. The most frequently reported events were classified under the SOCs *Cardiac disorders*; *Infections and infestations*; *Neoplasms benign, malignant, and unspecified*; and *Nervous system disorders*. Within 30 days of study vaccination, there were 10 SAEs reported in the PCV15 groups; these are described in the case narratives below. Of note, none of the SAEs reported in this study were considered related to study vaccination by the investigator.

(b) (6) *; PCV15-Lot 2:* Cholelithiasis
60-year-old white female with past medical history significant for cholelithiasis was hospitalized for cholelithiasis/possible cholecystitis on Day 17 with subsequent cholecystectomy on Day 18. After two days of in-hospital management, the participant was discharged home and the event was considered resolved.

(b) (6) *; PCV15-Lot 2:* Migraine
57-year-old white female with past medical history significant for obesity was admitted to the hospital on Day 27 for new onset migraines and was treated accordingly and then discharge on Day 30 after the event resolved.

(b) (6) *; PCV15-Lot 2:* Cholelithiasis
69-year-old white male with past medical history significant for type 2 diabetes mellitus, hyperlipidemia, and COPD was admitted to the hospital on Day 12 for cholelithiasis/potential cholecystitis with gallstone pancreatitis, and bacteremia. The events resolved on Day 15 and the participant was discharge on Day 18.

(b) (6) *; PCV15-Lot 2:* Cerebrovascular Accident
72-year-old white female with past medical history significant for hypertension, hyperlipidemia, and type 2 diabetes mellitus was admitted to the hospital due to cerebrovascular accident on Day 6 following onset

of severe headache, muscle weakness, and blurred vision. The participant was treated and discharged on Day 9 to an inpatient rehabilitation center and the event was considered resolved by Day 30.

(b) (6) *PCV15-Lot 2:* Gastric Cancer
69-year-old white male with past medical history significant for benign prostatic hyperplasia developed dyspepsia on Day 8 and was subsequently diagnosed with gastric adenocarcinoma. By Day 151 the participant was continuing chemotherapy and the event was considered not resolved and by Day 171 the participant has completed the study.

(b) (6) *; PCV15-Lot 1:* Diverticulitis
55-year-old white male with past medical history significant for asthma was admitted to the hospital for diverticulitis on Day 23 and treated accordingly. He was discharged on Day 29 and the event resolved on Day 34.

(b) (6) *PCV15-Lot 3:* Invasive Breast Carcinoma
73-year-old white female with past medical history significant reflux discovered a small lump in her breast on Day 22 and was subsequently diagnosed with invasive breast carcinoma. She was hospitalized on Day 52 for surgical resection and was receiving treatment through Day 111. The event was not recovered at the time of study completion on Day 187.

(b) (6) *; PCV15-Lot 1:* Pneumonia
64-year-old white male with past medical history significant for hypercholesterolemia, essential hypertension, and aortic aneurysm reported onset of cough, sputum production on fever on Day 30 that subsequently worsened resulting in hospitalization on Day 41. The participant was treated accordingly and discharged on Day 45, and the event was considered resolved by Day 48.

(b) (6) *; PCV15-Lot 2*: Acute Kidney Injury
59-year-old female with past medical history significant for type 2 diabetes mellitus, hypertension, and diabetic neuropathy presented on Day 18 with bilateral flank pain with nausea and lethargy. The participant was treated accordingly and discharged on Day 23 and the event was considered resolved.

(b) (6) *; PCV15-Lot 3:* Pulmonary Embolism
69-year-old with past medical history of hypercholesterolemia, hypertension, and Type 2 diabetes mellitus developed chest tightness and right thig deep muscle ache at the time of pulmonary embolism that was evaluated on Day 24. The participant was hospitalized on day 27 (participant has departed following initial medical evaluation) and was treated accordingly and then was continued on therapy from Day 31 to Day 61. As of Day 169, the participant had completed the study and the event was considered resolved with sequelae.

Among PCV13 recipients, there were 2 SAEs reported within 30 days of vaccination: a 62-year-old female with cholecystitis, and a 74-year-old with cystitis. Neither event was considered related to study vaccination by the investigator.

> ***Reviewer Comment:*** *This reviewer agrees with the study investigator's assessment that none of the reported SAEs during the study were considered related to vaccination.*

6.2.12.5 Adverse Events of Special Interest (AESI)
There were no protocol specified AESI that were assessed in any of the clinical studies included for review in this application.

6.2.12.7 Dropouts and/or Discontinuations

Of the 2340 participants randomized, 2333 (99.7%) were vaccinated and 2282 (97.5%) completed the study. As the study intervention involved a single vaccination dose administered on Day 1, discontinuation from study intervention due to an AE could not occur. Withdrawals from the study are summarized in the table below. A total of 21 participants were lost to follow-up and the statuses of 22 participants could not be recorded at the Month 6 telephone contact due to COVID-19. There were 3 deaths, none of which were considered related to study vaccination, and 9 participants voluntarily withdrew from the study. Protocol deviations are discussed above in Section 6.2.10.1.

Table 15. Discontinuations, Study V114-020

	Lot 1 (N=702) n (%)	**Lot 2 (N=704) n (%)**	**Lot 3 (N=701) n (%)**	**PCV13 (N=233) n (%)**
Enrolled	702	704	701	233
Vaccinated	698 (99.4%)	704 (100%)	700 (99.9%)	231 (99.1%)
Completed Study	683 (97.3%)	689 (97.9%)	683 (97.4%)	227 (97.4%)
Withdrawal due to:	--	--	--	--
Voluntary W/d	4 (0.6%)	1 (0.1%)	3 (0.4)	1 (0.4%)
Lost to F/up	5 (0.7%)	6 (0.9%)	8 (1.1%)	2 (0.9%)
Protocol Deviation	2 (0.3%)	0	0	1 (0.4%)
Death	1 (0.1%)	2 (0.3%)	0	0
*Status Not Recorded**	7 (1.0%)	6 (0.9%)	7 (1.0%)	2 (0.2%)

Source: Adapted from STN 125741.0, Study P020V114, Table 10-1. *Participants were unable to complete the Month 6 follow-up telephone contact due to COVID-19.

6.2.13 Study Summary and Conclusions

Study V114-020 was designed as a lot consistency, immunogenicity, and safety study conducted in 6 countries, with ~45% of participants enrolled at US sites. Pneumococcal vaccine-naïve adults (≥50 years) received one of three PCV15 lots or PCV13. The non-inferiority criteria were met for all 15 serotypes in PCV15, demonstrating lot-to-lot equivalency. The safety profile of PCV15 was generally comparable to the safety profile of the US-licensed PCV13, with slightly higher rates of reactogenicity. The solicited adverse reaction comparative safety data from this study are included appropriate for inclusion in the USPI to support the safety of PCV15.

6.3 Trial #3 (Study V114-017)

NCT03547167
"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."

Study Overview: This study was designed to descriptively (without hypothesis testing) assess the safety and immunogenicity of PCV15 compared to PCV13 in pneumococcal vaccine-naïve adults 18-49 years of age with an underlying medical condition and/or behavioral risk factor for which ACIP recommends pneumococcal vaccination, and/or a Native American living at or near a tribal reservation, a community with increased risk of pneumococcal disease transmission.

6.3.1 Objectives

Primary Objectives

- To evaluate the safety of PCV15 and PCV13

  - *Endpoints:* Same as Study V114-016.
- Duration of SAE monitoring: Day 1 through Month 6
- To evaluate serotype-specific OPA GMTs at 30 days postvaccination (Day 30) with PCV15 and after PCV13 separately
  - *Endpoint:* OPA GMTs for the 15 serotypes in PCV15 at Day 30

Secondary Objectives

- To evaluate the safety of PPV23 administered 6 months following PCV15 and following PCV13
  - *Endpoints:* Same as Study V114-016.
- Duration of SAE monitoring: Month 6 through Month 7
- To evaluate serotype-specific IgG GMCs at 30 days after PCV15 and after PCV13 separately
  - *Endpoint (PCV15):* IgG GMCs for 15 serotypes in PCV15 (Day 30)
  - *Endpoint (PCV13):* IgG GMCs for 13 serotypes, and IgG GMCs for serotypes 22F and 33F (Day 30)
- To evaluate serotype-specific OPA GMTs and IgG GMCs at 30 days after PPV23 vaccination
  - *Endpoint*: OPA GMTs and IgG GMCs for 15 serotypes in PCV15 (Month 7)
- To evaluate serotype-specific OPA and IgG response (GMFRs and proportions of participants with a ≥4-fold increase) at Day 30 compared to Day 1, Month 7 compared to Day 1, Month 7 compared to Month 6

Exploratory Objectives

- To evaluate serotype-specific OPA GMTs and IgG GMCs at Day 30 after PCV15 vaccination compared with PCV13
  - *Endpoints:* OPA and IgG responses for the 15 serotypes in PCV15 (Day 30)
- To evaluate serotype-specific OPA GMTs and IgG GMCs at 30 days after PPV23 vaccination in participants who initially received PCV15 compared to participants who initially received PCV13
  - *Endpoints:* OPA and IgG responses for the 15 serotypes in PCV15 (Month 7)

6.3.2 Design Overview

Study V114-017 is a randomized, double-blind, active-controlled, multi-center study to evaluate the safety and immunogenicity of PCV15 in pneumococcal vaccine-naïve adults 18-49 years of age who are at increased risk for pneumococcal disease due to an underlying medical condition (e.g., diabetes mellitus, chronic heart disease, chronic liver disease, chronic lung disease including asthma), behavioral risk factor (e.g., smoking, increased alcohol use), and/or a Native American enrolled through clinical sites of the Johns Hopkins Center for American Indian Health (CAIH).

A total of 1515 adults were randomized in a 3:1 ratio (PCV15: PCV13) to receive either PCV15 (n=1135) or PCV13 (n=380), followed by PPV23 6 months later. A total of 600 Native Americans living at or near a reservation in the southwestern US were recruited and enrolled at CAIH sites. Randomization was stratified based on (1) if a participant was enrolled at CAIH or not and (2) the type/number of risk factors for pneumococcal disease a participant had at the time of randomization. Risk factors for pneumococcal disease included chronic lung disease, tobacco use, diabetes mellitus, chronic liver disease, chronic heart disease, or alcohol consumption defined as AUDIT-C score ≥5. Alcohol Use Disorders Identification Test-Concise (AUDIT-C) is a 3-item alcohol screening instrument that can help identify patients who are hazardous drinkers or who have active alcohol use disorders (including alcohol abuse or dependence).

Blinding: PCV15 and PCV13 differ in appearance; therefore, the study vaccine preparer/administrator was unblinded to the treatment assignment. PPV23 was administered open-label. The vaccine preparer/administrator was not involved in collecting safety information.

6.3.3 Population

Inclusion criteria

- Male or female
- Age 18 to 49 inclusive
- Native American from clinical sites of the CAIH site in good health (i.e., without any of the risk conditions for pneumococcal disease listed below)
  or
  Native American from clinical sites of the CAIH-or-participants from study sites other than the CAIH with ≥1 of the following risk conditions for pneumococcal disease:
  - Type 1 or type 2 diabetes mellitus, receiving treatment with at least 1 approved anti-diabetic medication, and hemoglobin A1c <10% at screening visit (Visit 1)
  - Chronic liver disease with compensated cirrhosis due to non-alcoholic fatty liver disease, chronic hepatitis B, chronic hepatitis C, or alcoholic liver disease, diagnosed by clinician's assessment, with at least 1 liver staging assessment
  - Chronic Obstructive Pulmonary Disease (COPD) confirmed by spirometric data in the preceding 5 years showing post-bronchodilator FEV_1/FVC <0.7, and $FEV_1 \geq 30\%$ predicted
  - Mild or moderate persistent asthma confirmed by documented reversible airflow obstruction on spirometry within 5 years prior to Visit 1
  - Chronic heart disease confirmed within the last 5 years to be due to heart failure or non-cyanotic congenital heart disease
  - History of smoking at least 100 cigarettes during lifetime, currently smoking every day or most days of the week, and not receiving smoking cessation therapy at Visit 1
- Receiving stable medical management for the conditions listed above for at least 3 months with no anticipated major change expected for the duration of the study
- Females: see criteria for Study V114-020 in Section 6.2.3.

Exclusion criteria:

Same Exclusion Criteria for Study V114-019 and the following additional criteria:

- Prior administration of any pneumococcal vaccine or expected to receive any pneumococcal vaccine during the study outside of the protocol.
- History of the following medical conditions within 3 months of Visit 1 (screening)
  - active hepatitis with elevation in pretreatment aspartate transaminase or alanine transaminase >5x upper limit of normal (ULN) active hepatitis with elevation in pretreatment aspartate transaminase or alanine transaminase >5x ULN
  - diabetic ketoacidosis or >1 episode of severe, symptomatic hypoglycemia
  - myocardial infarction, acute coronary syndrome, transient ischemic attack, or ischemic or hemorrhagic stroke
  - history of hospitalization
- At Visit 1: diabetes mellitus with HgA1c ≥10%, chronic liver disease with Child-Pugh Class B or C cirrhosis, chronic lung disease with COPD Global Initiative for Chronic Obstructive Lung Disease Stage 4 or severe persistent asthma, chronic heart disease with New York Heart Association heart failure Class 4
- Any history of severe pulmonary hypertension with World Health Organization functional class ≥3 or history of Eisenmenger syndrome, Stage 4 or 5 Chronic Kidney Disease (Glomerular Filtration Rate below 30 mL/min/1.73 m2) or nephrotic syndrome, alcohol withdrawal or alcohol withdrawal seizure in the past 12 months
- Planned organ transplantation (heart, liver, lung, kidney, or pancreas) or other planned major surgery during the duration of this study
- Expected survival for less than 1 year according to the investigator's judgment

- Receiving immunomodulatory therapy with biological agents such as monoclonal antibodies directed against interleukin or cytokine pathways which could potentially interfere with immunogenicity assessment
- Receiving chronic home oxygen therapy

Reviewer Comment: *The study included Native Americans without identified risk factors and individuals (Native Americans or not) with identifiable risk factors. Individuals with severe and/or unstable underlying medical conditions were excluded from study participation.*

6.3.4 Study Treatments or Agents Mandated by the Protocol

Table 16. Vaccinations Administered in Study V114-017

Study Group	Vaccine	Vaccination Regimen
PCV15	PCV15	Single dose at Visit 2 (Day 1)
	PPV23	Single dose at Visit 4 (Month 6)
PCV13	PCV13	Single dose at Visit 2 (Day 1)
	PPV23	Single dose at Visit 4 (Month 6)

PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine (Prevnar 13).
PPV23: 23-valent pneumococcal polysaccharide vaccine (Pneumovax23).

Vaccine Composition
PCV15: same as Study V114-020. Lot #WL00068290
PCV13: same as Study V114-020. Lot #0000793304, #0000921112, and #0000814723
PPV23: same as Study V114-016. Lot #0000794346

6.3.5 Directions for Use

PCV15, PCV13, and PPV23: single dose (0.5mL) administered IM

6.3.6 Sites and Centers

77 centers: US (51.3%), Canada (7.5%), Australia (3.7%), New Zealand (11.7%), Poland (18.5%), Russia (1.0%%), Chile (6.3%)

6.3.7 Surveillance/Monitoring

Safety Monitoring
Same as Study V114-016, with the following exceptions: duration of SAE monitoring after PCV15 and after PCV13 was 6 months (from Day 1 through Month 7), and participants enrolled at CAIH sites used paper VRCs, rather than electronic VRCs, based on community preference within the CAIH sites.

Immunogenicity Monitoring
- Blood samples for immunogenicity assessments were drawn prior to PCV15 or PCV13 vaccination (Day1), 30 days after pneumococcal conjugate vaccination (Day 30), and before PPV23 vaccination (Month 6), and 30 days after PPV23 vaccination (Month 7).
- MOPA and pneumococcal ECL assays: same as Study V114-020. See Section 6.2.7.

6.3.8 Endpoints and Criteria for Study Success

See Section 6.3.1 above.

6.3.9 Statistical Considerations & Statistical Analysis Plan

All analyses were descriptive.

Sample size calculations: Planned enrollment: total of 1500 participants (PCV15, n=1125; PCV13, n=375 PCV13 participants was estimated to result in 1013 and 337 evaluable PCV15 and PCV13 participants, respectively.

Immunogenicity Analyses

- Immunogenicity analyses were performed for each of the 15 pneumococcal serotypes in PCV15
- OPA GMTs at 30 days postvaccination with PCV15 or PCV13 (Day 30): Point estimates for the OPA GMTs 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 IgG GMCs at 30 days post-vaccination with PCV15 or PCV13 (Day 30) and the OPA GMTs and IgG GMCs at 30 days post-vaccination with PPV23 (Month 7).

Safety Analyses
Except for the duration of SAE monitoring after PCV15 and after PCV13 vaccination (Day 1-Month 7), the analyses were the same as Study V114-019

Interim Analyses: same as Study V114-019

6.3.10 Study Population and Disposition

A total of 1515 participants were enrolled in the study (1135 in the PCV15 group; 380 in the PCV13 group). Study period: July 16, 2018 (first participant, first visit) to October 26, 2020 (last participant, last visit).

6.3.10.1 Populations Enrolled/Analyzed

PPAS and FAS: Same as Study V114-016. See Section 6.5.10.1
APaT (safety): all randomized participants who received the relevant study vaccination for the timepoint of interest (i.e., single-dose of PCV15/PCV13 at Day 1 to be included in the analyses following PCV23; a single-dose of PPV23 at Month 6 to be included in the analyses following PPV23). Analyses were performed according to vaccine received.

6.3.10.1.1 Demographics

Table 17. Demographic and Baseline Characteristics, Study V114-017

Demographic Characteristic	**PCV15 N=1133 n (%)**	**PCV13 N=379 n (%)**	**Total N=1512 n (%)**
Sex	-	-	-
Male	552 (48.7)	179 (47.2)	731 (48.3)
Female	581 (51.3)	200 (52.8)	781 (51.7)
Age (Years)	-	-	-
18-29	329 (29.0)	105 (27.7)	434 (28.7)
30-39	351 (31.0)	112 (29.6)	463 (30.6)
40-49	453 (40.0)	162 (42.7)	615 (40.7)
Mean Age (SD)	35.8y (8.9)	35.8y (8.9)	35.8 (8.9)
Median Age	36.0	36.0	36.0

Demographic Characteristic	**PCV15 N=1133 n (%)**	**PCV13 N=379 n (%)**	**Total N=1512 n (%)**
Age Range	18y to 49	18y to 49	18y to 49
Race	-	-	-
American Indian or Alaska Native	445 (39.3)	148 (39.1)	593 (39.2)
Asian	15 (1.3)	8 (2.1)	23 (1.5)
Black or African American	43 (3.8)	18 (4.7)	61 (4.0)
Multiple	17 (1.5)	3 (0.8)	20 (1.3)
Native Hawaiian or Other Pacific Islander	33 (2.9)	11 (2.9)	44 (2.9)
White	580 (51.2)	191 (50.4)	771 (51.0)
Ethnicity	-	-	-
Hispanic or Latino	135 (11.9)	39 (10.3)	174 (11.5)
Not Hispanic or Latino	982 (86.7)	337 (88.9)	1319 (87.2)
Not reported	8 (0.7)	1 (0.3)	9 (0.6)
Unknown	8 (0.7)	2 (0.5)	10 (0.7)
Risk Factors	-	-	-
CAIH participant, no risk factors	280 (24.7)	93 (24.5)	373 (24.7)
CAIH participant with diabetes mellitus	26 (2.3)	9 (2.4)	35 (2.3)
CAIH participant with chronic heart disease	1 (0.1)	1 (0.3)	2 (0.1)
CAIH participant, current smoker	53 (4.7)	18 (4.7)	71 (4.7)
CAIH participant with AUDIT-C score greater than or equal to 5	58 (5.1)	19 (5.0)	77 (5.1)
CAIH participant with 2 risk factors	20 (1.8)	7 (1.8)	27 (1.8)
CAIH participant with 3 or more risks	1 (0.1)	1 (0.3)	2 (0.1)
Non-CAIH participant, diabetes mellitus and AUDIT-C <5	120 (10.6)	40 (10.6)	160 (10.6)
Non-CAIH participant with chronic liver disease and AUDIT-C <5	26 (2.3)	9 (2.4)	35 (2.3)
Non-CAIH participant with chronic lung disease and AUDIT-C <5	161 (14.2)	53 (14.0)	214 (14.2)
Non-CAIH participant with chronic heart disease and AUDIT-C <5	55 (4.9)	19 (5.0)	74 (4.9)
Non-CAIH participant, current smoker and with AUDIT-C <5	111 (9.8)	37 (9.8)	148 (9.8)
Non-CAIH participant with 2 risk factors	200 (17.7)	66 (17.4)	266 (17.6)
Non CAIH participant with 3 or more risk factors	21 (1.9)	7 (1.8)	28 (1.9)

Source: Adapted from STN 125741.0, P017V114 Table 10-5 Participant Characteristics (All Vaccinated Participants).
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine.
%: n/N: #participants with available data for relevant endpoint. N = All vaccinated participants (PCV15, N=1135; PCV13, N=380). SD = standard deviation. AUDIT-C: Alcohol Use Disorders Identification Test-Consumption. CAIH: Center for American Indian Health. Risk factors for pneumococcal disease included chronic lung disease, tobacco use, diabetes mellitus, chronic liver disease, chronic heart disease, or alcohol consumption (defined as the AUDIT-C score ≥5).

Overall, 593 of 1515 (~40%) of participants were American Indian or Alaska Native, of which 99% were enrolled at CAIH sites; 87.5% of participants were non-Hispanic/Latino.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The 5 most commonly reported baseline medical history conditions and concurrent illnesses were asthma (26.0%), obesity (17.9%), hypertension (15.6%), back pain (15.3%), and upper respiratory tract infection (14.0%).

6.3.10.1.3 Participant Disposition

Table 18. Participant Disposition, Study V114-017

Population	PCV15 N=1135 n (%)	PCV13 N=380 n (%)
Enrolled	1135 (100.0)	380 (100.0)
Vaccinated with PCV (Day 1)	1133 (99.8)	379 (99.7)
Vaccinated with PPV23 (Month 6)	1035 (91.2)	346 (91.1)
Completed study*	1038 (91.5)	350 (98.8)
APaT (safety)**	1134 (99.7)	378 (92.1)
FAS Set***	1101 (97.0)	368 (96.8)
Per-Protocol OPA****	1019 (89.8)	343 (90.3)
Per-Protocol IgG****	1020 (89.9)	343 (90.3)
≥1 Important Protocol Deviation	313 (27.6)	104 (27.4)

Source: Adapted from STN 125741.0, P017V114 Clinical Study Report: Table 10-1, Table 12-1, Table 11-1, Table 14.1-3, Table 14.2-2, Table 14.2-4
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine.
%: n/N N: total number of participants enrolled.
≥1 Important Protocol Deviation: participants with one or more important protocol deviations.
* Participants could have been considered to complete the study without receipt of PPV23.
** All participants as treated (APaT) population: all randomized participants who received the study intervention.
*** Full Analysis Set (FAS): all randomized participants who received the intervention and had at least 1 serology result. Maximum "n" across all serotypes from the primary (OPA) immunogenicity summary table at Day 30 in the FAS population.
**** Maximum "n" across all serotypes from the primary (OPA) and secondary (IgG) immunogenicity summary tables at Day 30 in the Per-Protocol Population.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Primary Objective #1: Pneumococcal OPA GMTs at 30 days after PCV15 and after PCV13 vaccination

PCV15 group: post-vaccination OPA GMTs for all of the 15 vaccine serotypes in PCV15 were higher than baseline (Day 1), particularly for serotypes 6A, 6B and 33F.

> ***Reviewer Comment:*** *For serotypes 4 and 7F, OPA GMTs following PCV15 vaccination were lower than those observed after PCV13 vaccination, with 95% CI that do not overlap. However, the OPA GMTs following PCV15 for these two serotypes were actually higher than those observed following PCV15 in the main study demonstrating effectiveness (V114-019) in participants ≥50 years.*

PCV13 group: postvaccination OPA GMTs for the 13 vaccine serotypes in PCV13 were higher than baseline (Day 1), particularly for serotypes 6A.

The table below summaries the serotype-specific OPA GMTs at 30 days following vaccination with PCV15 and following vaccination with PCV13.

Table 19. Pneumococcal OPA GMTs at 30 Days After PCV15 or PCV13 in Pneumococcal Vaccine-Naïve Adults 18-49 Years of Age, Study V114-017

Pneumococcal Serotype	PCV15 N=1133 Observed GMT	PCV15 N=1133 95% CI	PCV13 N=379 Observed GMT	PCV13 N=379 95% CI
1	267	[242, 295]	267	[220, 324]
3	198	[184, 214]	150	[129, 173]
4	1401	[1294, 1517]	2568	[2268, 2908]
5	560	[508, 618]	731	[613, 873]
6A	12763	[11772, 13838]	11313	[9739, 13141]

Pneumococcal Serotype	PCV15 N=1133 Observed GMT	PCV15 N=1133 95% CI	PCV13 N=379 Observed GMT	PCV13 N=379 95% CI
6B	10164	[9486, 10891]	6958	[5987, 8086]
7F	5725	[5382, 6091]	7583	[6762, 8503]
9V	3354	[3132, 3590]	3969	[3541, 4450]
14	5245	[4860, 5660]	5863	[5191, 6622]
18C	5695	[5314, 6103]	3050	[2685, 3465]
19A	5335	[4985, 5710]	5884	[5221, 6632]
19F	3253	[3051, 3468]	3272	[2949, 3631]
23F	4829	[4443, 5247]	3876	[3323, 4521]
22F	3939	[3654, 4246]	291	[221, 383]
33F	11734	[10917, 12612]	2181	[1826, 2606]

Source: Adapted from STN 125741.0, P017V114 module 5.3.5.4 (b) (4) Statistical Report (Sensitivity Analyses), Table 13.
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine.
N: # participants in the Per-Protocol Analyses Set (PPAS) [based on (b) (4) negative samples]. GMT: Geometric Mean Titer.

6.3.11.2 Analyses of Secondary Endpoints

Pneumococcal OPA GMTs at Day 30 (after conjugate vaccination) and Month 7 (after PPV23 vaccination), adults 18-49 years of age

PCV15 study group

- At Month 7 (30 days after PPV23 vaccination): For 10 of the 14 serotypes in common with PPV23, serotype-specific OPA GMTs were similar after PPV23 vaccination compared to OPA GMTs for the corresponding serotype measured 30 days after PCV15 vaccination (Day 30), including serotype 33F. For serotypes 6B, 18C, and 22F, the OPA GMTs 30 days after PPV23 vaccination were half the numerical values for the observed OPA GMTs 30 days after PCV15 vaccination given . As expected, for serotype 6A (contained in PCV15 but not PPV23), the GMT was lower when measured 7 months after PCV15 vaccination, compared to 30 days after PCV15 vaccination.

PCV13 study group

- At Month 7 (30 days after PPV23 vaccination): For 10 of the 12 serotypes in common with PPV23, serotype-specific OPA GMTs were similar after PPV23 vaccination compared to OPA GMTs for the corresponding serotype measured 30 days after PCV13 vaccination (Day 30). The OPA GMT for serotype 6B was lower (~0.6x lower OPA GMT) 30 days after PPV23 vaccination than 30 days after PCV15 vaccination. As expected, for serotype 6A (contained in PCV13 but not PPV23), the OPA GMT was lower when measured 7 months after PCV13 vaccination as compared to 30 days after PCV13 vaccination.

Table 20. Pneumococcal OPA GMTs at 30 Days After PPV23 (Month 7) in Pneumococcal Vaccine-Naïve Adults 18-49 Years of Age, Study V114-017

Serotype	PCV15 N=820-834 Observed GMT	PCV15 N=820-834 95% CI	PCV13 N=270-277 Observed GMT	PCV13 N=270-277 95% CI
1	266	[243, 291]	213	[179, 254]
3	210	[194, 227]	207	[178, 239]
4	1725	[1611, 1847]	1972	[1761, 2208]
5	590	[540, 646]	623	[527, 736]
6A	5760	[5318, 6239]	5737	[4988, 6599]
6B	5210	[4856, 5590]	4460	[3937, 5052]
7F	6097	[5722, 6496]	6261	[5618, 6976]
9V	3144	[2927, 3377]	3387	[2988, 3841]
14	5648	[5263, 6061]	5241	[4616, 5950]

Serotype	PCV15 N=820-834 Observed GMT	PCV15 N=820-834 95% CI	PCV13 N=270-277 Observed GMT	PCV13 N=270-277 95% CI
18C	3262	[3058, 3480]	2313	[2067, 2589]
19A	4318	[4019, 4639]	4302	[3856, 4800]
19F	3202	[3013, 3403]	3124	[2801, 3484]
23F	3053	[2817, 3309]	2938	[2532, 3410]
22F	3627	[3385, 3885]	4094	[3373, 4969]
33F	11333	[10463, 12275]	16045	[13656, 18852]

Source: Module 5.3.5.4 (b) (4) Statistical Report (Sensitivity Analyses), Table 13.
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine. PPV23: 23-valent pneumococcal polysaccharide vaccine.
N: # participants in the Per-Protocol Analyses Set (PPAS) [based on (b) (4)) negative samples]. CI = confidence interval. GMT: Geometric Mean Titer.

Pneumococcal OPA GMTs at Day 1 (baseline), Month 6 and Month 7 (pre- and post-PPV23 vaccination), adults 18-49 years of age

PCV15 study group

- At Month 6 (prior to PPV23 vaccination): For all 15 serotypes, OPA GMTs continued to be higher at Month 6 than at baseline (Day 1). At Month 6, GMTs were between 3 times higher (serotype 33F) and 19 times higher (serotype 6B), depending on the serotype, than at Day 1.

- At Month 7 (30 days after vaccination with PPV23), OPA GMTs for all 15 serotypes were higher than OPA GMTs for the corresponding serotype at Month 6.

PCV13 study group

- At Month 6 (prior to PPV23 vaccination): For all 13 serotypes, OPA GMTs continued to be higher at Month 6 than at baseline (Day 1); GMTs were between 4 times higher (serotype 9V) and 21 times higher (serotype 4) at Month 6, depending on the serotype, than at baseline (Day 1).

- At Month 7 (30 days after vaccination with PPV23): OPA GMTs for all 13 serotypes were higher than OPA GMTs for the corresponding serotype at Month 6.

Pneumococcal IgG GMCs at Day 30, adults 18-49 years of age

At Day 30 (30 days after pneumococcal conjugate vaccination), IgG GMCs after PCV15 vaccination were numerically higher than corresponding IgG GMCs at baseline (Day 1) for all 15 serotypes contained in PCV15. A similar pattern was observed after PCV13 vaccination, for the 13 serotypes contained in PCV13.

6.3.11.3 Subpopulation Analyses

Within each study group, OPA GMTs were lower in the older age group (40 to 49 years) than the younger age group (18 to 29 years). Analyses of immunogenicity by gender, race, and ethnicity were generally consistent with those in the overall study population.

6.3.11.4 Dropouts and/or Discontinuations

See Section 6.3.10.1.3.

6.3.11.5 Exploratory Analyses

At 30 days after pneumococcal conjugate vaccination, OPA GMTs were numerically lower in the PCV15 group than in the PCV13 group for serotypes 4 and 7F, similar between groups for the other 11 serotypes in common with PCV13, and numerically higher in the PCV15 group than the PCV13 group for serotypes 22F and 33F. PCV15 and PCV13 both contain serotypes 4 and 7F. PCV15, but not PCV13, contains

serotypes 22F and 33F. However, after PPV23 was administered 6 months later, OPA GMTs for serotypes 22F and 33F did not differ based on the initial pneumococcal conjugate vaccine administered.

6.3.12 Safety Analyses

6.3.12.1 Methods
See Section 6.3.2.

6.3.12.2 Overview of Adverse Events
The following table provides an overview of AE rates in the PCV15 group compared to the PCV13 group.

Table 21. Proportion of Participants Reporting an Adverse Event Following Pneumococcal Conjugate Vaccination, All Participants as Treated, Study V114-017

AE Type: Monitoring Period[*]	PCV15 N=1134 n (%)	PCV13 N=378 n (%)
Immediate AEs: 30 minutes	45 (4.0)	18 (4.8)
Solicited injection site AEs: 5 days	889 (78.4)	272 (72.0)
Solicited systemic AEs: 14 days	627 (55.3)	208 (55.0)
Temperature ≥38.0°C: 5 days[1]	16 (1.5)	1 (0.3)
Unsolicited AEs: 14 days	300 (26.5)	105 (27.8)
SAEs: 6 months	49 (4.3)	12 (3.2)
Deaths: 6 months	3 (0.3%)	2 (0.5)

Source: Adapted from STN 125741.0, Study P017V114 Clinical Study Report including Table 12-1, Table 12-2, Table 12- 10.
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine.
%: n/N. n= #participants who experienced the relevant type of AE; N: #participants in All Participants as Treated Population (APaT)
[*] Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.
[1] Percentages are calculated based on the number of participants with temperature data.

Solicited Adverse Reactions
The solicited local AR and systemic AE data presented below reflect VRC information as assessed and revised by the investigators (see Section 6.2.7 for further details).

Table 22. Percentage of Participants Reporting Solicited Local Reactions (Days 1-5) and Systemic (Days 1-14) Following Pneumococcal Conjugate Vaccination, Study V114-017

--	PCV15 N=1134 (% = n/N)	PCV13 Group N=378 (% = n/N)
Local (injection site)	--	--
Injection site pain	--	--
Total	75.8%	68.8%
Mild	56.6%	54.5%
Moderate	18.3%	12.7%
Severe	1.1%	1.6%
Injection site erythema	--	--
Total	15.1%	14.0%
NA (0 to ≤2.4cm)	7.3%	6.6%
Grade 1 (>2.4 to ≤5.0cm)	3.6%	5.6%
Grade 2 (>5.0 to ≤7.4cm)	2.3%	0.8%
Grade 2 (>7.4 to ≤10.0cm)	0.9%	0.5%
Grade 3 (>10.0cm)	0.5%	0.3%
Unknown	0.4%	0.3%

--	PCV15 N=1134 (% = n/N)	PCV13 Group N=378 (% = n/N)
Injection site swelling	--	--
Total	21.7%	22.2%
NA (0 to ≤2.4cm)	10.0%	12.4%
Grade 1 (>2.4 to ≤5.0cm)	6.6%	6.3%
Grade 2 (>5.0 to ≤7.4cm)	3.1%	1.6%
Grade 2 (>7.4 to ≤10.0cm)	1.4%	0.8%
Grade 3 (>10.0cm)	0.4%	0.5%
Unknown	0.3%	0.5%
Systemic	--	--
Arthralgia	--	--
Total	12.7%	11.6%
Mild	9.0%	10.1%
Moderate	3.4%	1.6%
Severe	0.3%	0.0%
Fatigue	--	--
Total	34.3%	36.8%
Mild	23.9%	27.2%
Moderate	9.5%	8.7%
Severe	0.9%	0.8%
Headache	--	--
Total	26.5%	24.9%
Mild	18.4%	16.4%
Moderate	7.3%	7.9%
Severe	0.9%	0.8%
Myalgia	--	--
Total	28.8%	26.5%
Mild	20.5%	19.3%
Moderate	8.1%	6.6%
Severe	0.3%	0.5%
Fever	--	--
<100.4 °F	98.5%	99.7%
≥100.4 °F and <101.3 °F	1.0%	0.3%
≥101.3 °F and <102.2 °F	0.3%	0.0%
≥103.1 °F and <104.0 °F	0.2%	0.0%

Source: Adapted from STN 125741.0, P017V114 report. Participants With Select Solicited Adverse Reactions by Maximum Intensity (Incidence >0% in One or More Vaccination Groups). #n: #participants with available data for relevant endpoint, N= #participants in SafAS. *Grade 3 (pain, myalgia, headache, malaise): significant, prevents daily activity.

The percentages of participants who reported at least 1 AE in each study group were similar (84.7% PCV15 and 82.5% PCV13).

Subpopulation Analyses
Within each study group, males had lower proportions of AEs than females. Safety results observed within each age, race, ethnicity, and risk factor subgroup were generally consistent with those of the overall population.

6.3.12.3 Deaths
Five deaths (PCV15, n=4, PCV13, n=1) were reported during the study and one additional death (PCV13 group) occurred outside of the protocol-specified reporting period:

PCV15 study group

- 21-year-old male with a history of suicidal ideation/attempt died on Day (b) (6) postvaccination 1 due to completed suicide at home.
- 49-year-old female was hit by a motor vehicle on Day (b) (6) postvaccination 1 and died the next day.
- 49-year-old male with a history of hypertension/cirrhosis who was hospitalized on Day 156 due to worsening chronic liver disease and died on Day (b) (6) due to hepatic encephalopathy.
- 46-year-old male with a history of hypertension, type 2 diabetes mellitus, acute myocardial infarction and chronic left ventricular failure developed acute pulmonary embolism on Day 183 and subsequently died on Day (b) (6) following an apparent syncopal episode due to cardiac arrest.

PCV13 study group: Two death reported, including a 25 year old a history of alcoholism who developed severe bronchopneumonia with subsequent cardiac failure and sepsis on Day (b) (6) and died the next day; and a 48-year-old female with a history of mitral valve replacement who died of a hemorrhagic stroke on Day (b) (6).

All deaths in the study were considered unrelated to vaccination by the study investigator and the clinical reviewer.

6.3.12.4 Nonfatal Serious Adverse Events

The percentages of participants reporting as least one SAE after pneumococcal conjugate vaccination was 4.3% in the PCV15 group and 3.2% in the PCV13 group. The most common non-fatal SAEs in both study groups were infections and infestations (1.1% and 0.8%), nervous system disorders (0.5% and 0.3%), GI disorders (0.4% and 0.5%). No SAEs were assessed by the study investigator or clinical reviewer to be related to vaccination.

The proportion of participants reporting at least one SAE following vaccination with PPV23 was 0.3% in the PCV15 group and 0.9% in the PCV13 group.

6.3.12.7 Dropouts and/or Discontinuations

Three PCV15 participants discontinued from the study due to serious non-vaccine-related AEs of colon cancer, nephrotic syndrome, and rheumatoid arthritis, respectively. All of the events occurred >65 days after vaccination. None of the AEs were assessed by the study investigator and the clinical reviewer as related to vaccination.

6.3.13 Study Summary and Conclusions

In pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age (inclusive) with or without risk factors for pneumococcal disease, the safety profile of PCV15 was similar to PCV13. In descriptive analyses, OPA GMTs for most common serotypes were similar 30 days following PCV15 and PCV13. For serotypes 4 and 7F, OPA GMTs following PCV15 vaccination were notably lower than those observed after PCV13 vaccination in this age cohort 18-49 years; however, OPA GMTs following PCV15 for these two serotypes were actually higher than those observed following PCV15 in the main study demonstrating effectiveness (V114-019) in participants ≥50 years. When PPV23 was administered to all participants at Month 6, OPA GMTs one month later were similar between participants who had received PCV15 on Day 1 and those who had received PCV13 on Day 1 for all shared serotypes, including 4 and 7F in participants 18-49 years of age, including individuals with conditions that increase their risk for invasive pneumococcal disease. The data generated from Study V114-017 support the safety and effectiveness of PCV15 in 18-49 years of age participants and will be included in Section 6 (Adverse Reactions) and Section 14 (Clinical Studies).

6.4 Trial #4 (Study V114-021)

NCT03615482
"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"

Study Overview: This study was designed to evaluate the safety and immunogenicity of PCV15 and a quadrivalent influenza vaccine (Fluarix Quadrivalent, GlaxoSmithKline Biologicals) [QIV] administered concomitantly, compared to sequential administration of QIV followed by PCV15 one month later (nonconcomitant study group).

6.4.1 Objectives

Primary Objectives

- To evaluate the safety of PCV15 and QIV when administered concomitantly compared with PCV15 and QIV when administered sequentially.
  - *Endpoints:* After PCV15 vaccination: same as Study V114-020. Solicited local and systemic ARs, unsolicited non-serious AEs, and SAEs were also assessed after QIV vaccination.
- To compare OPA GMTs at 30 days postvaccination when PCV15 is administered concomitantly with QIV vs. PCV15 administered sequentially with QIV.
  - *Endpoint:* Serotype-specific OPA GMTs for 15 serotypes in PCV15
  - *Hypothesis:* Pneumococcal OPA responses when PCV15 is administered concomitantly with QIV are noninferior to corresponding antibody responses when PCV15 is administered nonconcomitantly with QIV, as measured by serotype-specific OPA GMTs at 30 days after PCV15 vaccination.
    - The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio [concomitant/nonconcomitant] to be greater than 0.50.
- To compare the strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination when QIV is administered concomitantly with PCV15 vs. QIV administered nonconcomitantly with PCV15.
  - *Endpoint:* Strain-specific HAI responses for the 4 strains in QIV
  - *Hypothesis:* HAI GMTs when QIV is administered concomitantly with PCV15 are noninferior to corresponding antibody responses when QIV is administered nonconcomitantly with PCV15, as measured by strain-specific HAI GMTs at 30 days postvaccination with QIV.
    - The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the HAI GMT ratio [concomitant/nonconcomitant] to be greater than 0.50.

Secondary Objectives

- To evaluate pneumococcal serotype-specific IgG GMCs at 30 days postvaccination when PCV15 is administered concomitantly with QIV vs. PCV15 administered nonconcomitantly with QIV.
  - *Endpoint:* Serotype-specific IgG responses for 15 serotypes in PCV15
- Within each vaccination group, to evaluate pneumococcal serotype-specific GMFRs and proportions of participants with a ≥4-fold increase from baseline (pre-vaccination with PCV15) to 30 days postvaccination with PCV15 for both OPA and IgG responses in participants who received PCV15 concomitantly with QIV and participants who received PCV15 nonconcomitantly with QIV.
  - *Endpoints:* Serotype-specific OPA and IgG responses for 15 serotypes in PCV15 at pre-vaccination with PCV15 and 30 days postvaccination with PCV15

- 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 ≥1:40 at 30 days postvaccination with QIV, and (3) proportions of subjects who seroconvert (defined as achieving a 4-fold rise from baseline to postvaccination among participants who are seropositive at baseline) at 30 days postvaccination with QIV for participants who received QIV concomitantly with PCV15 and participants who received QIV nonconcomitantly with PCV15.
    - *Endpoints:* Strain-specific HAI responses for the 4 strains in QIV at pre-vaccination with QIV and 30 days postvaccination with QIV

6.4.2 Design Overview

Study V114-021 was a phase 3 randomized, double-blind, placebo-controlled, multi-center study. A total of 1200 healthy adults ≥50 years of age were randomized 1:1 to the concomitant group (PCV15 + QIV, followed 30 days later by placebo [saline]) or the nonconcomitant group (saline + QIV, followed 30 days later by PCV15). Randomized participants were stratified by age in years (50 to 64, 65 to 74, and ≥75 years) and history of PPV23 vaccination (yes/no) at the time of randomization.

Blinding
PCV15 and QIV differ in appearance; therefore, the study vaccine preparer/administrator was unblinded to the treatment assignment. QIV was administered open-label. The vaccine preparer/administrator was not involved in collecting safety information.

The participants and study investigators involved in the clinical evaluation of the participants were blinded to the group assignments.

6.4.3 Population

Inclusion criteria: same as Study V114-019. See Section 6.1.3.

Exclusion criteria: Except for the criteria listed below, the exclusion criteria are the same as V114-020: History of IPD or known history of other culture-positive pneumococcal disease within 3 years before Day 1; known hypersensitivity to any component of influenza vaccines, including egg protein, or following a previous dose of influenza vaccine; a WOCBP who has a positive urine or serum pregnancy test before the first vaccination at Day 1; prior administration of any PCV or is expected to receive any pneumococcal vaccine during the study outside of the protocol; prior administration of PPV23≤12 months before Visit 1; previous receipt of influenza vaccine during the 2018/2019 flu season or expected to receive any influenza vaccine during the study outside of the protocol.

Temporary exclusion criteria: Except for the following criterion, the temporary exclusion criteria are the same as Study V114-020: received any non-live vaccine within the 14 days before receipt of any study vaccine or is scheduled to receive any non-live vaccine within 30 days following receipt of any study vaccine (no exception for inactivated influenza vaccination).

6.4.4 Study Treatments or Agents Mandated by the Protocol

Table 23. Vaccinations Administered in Study V114-021

Study Group	Study Intervention	Injection Site Location	Vaccination Regimen
Concomitant	PCV15	Left arm	Single dose at Visit 1 (Day 1)
	QIV[a]	Right arm	Single dose at Visit 1 (Day 1)
	Placebo (Saline)	Left arm	Single dose at Visit 2 (Day 30)
Nonconcomitant	Placebo (Saline)	Left arm	Single dose at Visit 1 (Day 1)
	QIV[a]	Right arm	Single dose at Visit 1 (Day 1)
	PCV15	Left arm	Single dose at Visit 2 (Day 30)

Source: Adapted from STN 125741.0, P021V114 Clinical Study Report, page 26, Table 9-1 Study Interventions Administered.
PCV15: 15-valent pneumococcal conjugate vaccine.
[a] Fluarix Quadrivalent (GlaxoSmithKline Biologicals). QIV: quadrivalent influenza vaccine (seasonal inactivated).

Vaccine Composition
PCV15: same as Study V114-020. See Section 6.2.4.
Lot# WL00068290

Fluarix Quadrivalent:

- Composition: each 0.5mL dose contains 60 mcg hemagglutinin in the recommended ratio of 15 mcg hemagglutinin of the 4 influenza virus strains:
  - A/Singapore/GP1908/2015 (H1N1) IVR-180 (an A/Michigan/45/2015 [H1N1] pdm09-like virus)
  - A/Singapore/INFIMH-16-0019/2016 (H3N2) NIB-104
  - B/Maryland/15/2016 NYMC BX-69A (a B/Colorado/06/2017-like virus),
  - B/Phuket/3073/2013.
- Each dose may also contain residual amounts of hydrocortisone, ≤0.0015 mcg, gentamicin sulfate, ≤0.15 mcg, ovalbumin, ≤0.050 mcg, formaldehyde, ≤5 mcg, and sodium deoxycholate, ≤65 mcg from the manufacturing process.
- Appearance: colorless and slightly opalescent suspension
- Packaged in single dose prefilled syringe. Lot #0000877231

Saline (placebo): 0.5mL, supplied in an ampule. Lot #0000841511

6.4.5 Directions for Use

- PCV15 and QIV: 0.5 mL administered IM
- Saline: 0.5mL injection administered IM

6.4.6 Sites and Centers

45 sites in the US

6.4.7 Surveillance/Monitoring

Safety Monitoring
Except for the duration of SAE monitoring in the concomitant group (Day 1 through Month 7), the safety parameters and monitoring after PCV15 vaccination were the same as Study V114-020.

QIV vaccination: parameters assessed and duration of monitoring for solicited local/systemic ARs and unsolicited non-serious AEs were the same as for PCV15. The duration of SAE monitoring after QIV vaccination was from Day 1 through Month 7 for the concomitant and nonconcomitant study groups.

Immunogenicity Monitoring

- Pneumococcal MOPA: same as Study V114-020 (see Section 6.2.7 of this memo)
- Hemagglutination inhibition (HAI) assay: The HAI assay is based on the WHO established method as described in the WHO Manual for Laboratory Diagnosis and Virological Surveillance 13 of Influenza (WHO Global Influenza Surveillance Network 2011). The HAI titers are the inverse of the highest dilution of serum exhibiting complete inhibition of hemagglutination.

6.4.8 Endpoints and Criteria for Study Success

See Section 6.4.1.

6.4.9 Statistical Considerations & Statistical Analysis Plan

Primary Endpoints/Hypotheses

- The primary objective to compare the serotype-specific OPA GMTs at 30 days postvaccination with PCV15 between participants administered PCV15 concomitantly with QIV vs. participants administered PCV15 nonconcomitantly with QIV was assessed via the following noninferiority hypothesis:
  - H_0: $GMT_1/GMT_2 \leq 0.50$ vs. H_1: $GMT_1/GMT_2 > 0.50$
    - GMT_1 is serotype-specific OPA GMT for the concomitant group, and GMT2 is serotype-specific OPA GMT for the nonconcomitant group.
    - A ratio of 0.50 corresponds to a 2.0-fold decrease of OPA GMT in the concomitant group as compared with the nonconcomitant 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 being >0.50 and would lead to the conclusion that the OPA responses in the concomitant group are noninferior to the nonconcomitant group for the 15 pneumococcal serotypes.
- The primary objective to compare the strain-specific HAI GMTs at 30 days postvaccination with QIV between participants administered QIV concomitantly with PCV15 vs. participants administered QIV nonconcomitantly was assessed via the following noninferiority hypothesis:
  - H_0: $GMT_1/GMT_2 \leq 0.50$ vs. H_1: $GMT_1/GMT_2 > 0.50$
    - GMT1 is strain-specific HAI GMT for the concomitant group, and GMT2 is strain-specific HAI GMT for the nonconcomitant group.
    - A ratio of 0.50 corresponds to a 2.0-fold decrease of HAI GMT in the concomitant group as compared with the nonconcomitant 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 being >0.50 and would lead to the conclusion that the HAI responses in the concomitant group are noninferior to the nonconcomitant group for the 4 influenza strains.

Estimation of the GMT was calculated using a cLDA method proposed by Liang and Zeger. The Kenward-Roger adjustment was used with restricted maximum likelihood to make the proper statistical inference.

Overall, the sample size provides 87% power to achieve the primary objectives, using a 1-sided 2.5% alpha-level.

Secondary Immunogenicity Analyses: descriptive

Safety Analyses
Except for SAEs (Day 1 through Month 7 in the concomitant group), the analyses after PCV15 vaccination were the same as Study V114-020.

Analyses of solicited ARs and unsolicited non-serious AEs after QIV vaccination were the same as for PCV15. The duration of SAE monitoring after QIV vaccination was from Day 1 through Month 7 for the concomitant and nonconcomitant study groups.

Interim Analyses: same as Study V114-019. See Section 6.1.9.
Multiplicity: No multiplicity adjustments were needed.

Protocol Amendments
Amendment 1 (01-June-2018) removed the collection of medical device incidents from the protocol because FDA guidance for reporting events related to combination products was not implemented until January 2020.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

Analysis Populations

- PPAS: primary population for the immunogenicity analyses
  - Except for the potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses, the criteria for the PP analysis population is the same as for Study V114-019
    - Failure to receive any study vaccination at Visit 2
    - Failure to receive correct clinical material as per randomization schedule at Visit 2
- Full Analysis Set (FAS) for immunogenicity and All Participants as Treated (APaT) dataset for safety: same as Study V114-019.
- Safety Analyses Set (APaT): same as Study V114-019. See Section 6.1.10.1.

6.4.10.1.1 Demographics

Table 24. Demographic and Baseline Characteristics, Study V114-021

Demographic Characteristic	Concomitant Group N=599 n (%)	Nonconcomitant Group N=598 n (%)	Total N=1197 n (%)
Sex	-	-	-
Male	269 (44.9)	256 (42.8)	525 (43.9)
Female	330 (55.1)	342 (57.2)	672 (56.1)
Age (Years)	-	-	-
50-64	299 (49.9)	298 (49.8)	597 (49.9)
65-74	236 (39.4)	236 (39.5)	472 (39.4)
≥75	64 (10.7)	64 (10.7)	128 (10.7)
Mean	64.2	64.2	64.2
SD	8.3	8.1	8.2
Median	65.0	65.0	65.0
Range	50 to 98	50 to 88	50 to 98

Demographic Characteristic	Concomitant Group N=599 n (%)	Nonconcomitant Group N=598 n (%)	Total N=1197 n (%)
Race	-	-	-
American Indian or Alaska Native	1 (0.2)	3 (0.5)	4 (0.3)
Asian	25 (4.2)	30 (5.0)	55 (4.6)
Black or African American	73 (12.2)	63 (10.5)	136 (11.4)
Multiple	5 (0.8)	3 (0.5)	8 (0.7)
Native Hawaiian or Other Pacific Islander	2 (0.3)	1 (0.2)	3 (0.3)
White	493 (82.3)	495 (82.8)	988 (82.5)
Missing	0 (0.0)	3 (0.5)	3 (0.3)
Ethnicity	-	-	-
Hispanic or Latino	120 (20.0)	119 (19.9)	239 (20.0)
Not Hispanic or Latino	471 (78.6)	472 (78.9)	943 (78.8)
Not Reported	6 (1.0)	5 (0.8)	11 (0.9)
Unknown	2 (0.3)	2 (0.3)	4 (0.3)
History of Prior PPV23	-	-	-
With prior PPV23	124 (20.7)	126 (21.1)	250 (20.9)
Without prior PPV23	475 (79.3)	472 (78.9)	947 (79.1)

Source: STN 125741.0, P021V114 Clinical Study Report, Table 10-6. Participant Characteristics (All Vaccinated Participants)
Concomitant group: PCV15+QIV (Day 1), then saline at Day 30. Nonconcomitant group: QIV+saline (Day 1), then PCV15 at Day 30.
PCV15: 15-valent pneumococcal conjugate vaccine. QIV: quadrivalent influenza vaccine (seasonal inactivated).
SD: standard deviation, n: #participants.

6.3.10.1.3 Participant Disposition

Table 25. Participant Disposition, Study V114-021

Population	Concomitant Group n (%)	Nonconcomitant Group n (%)	Total n (%)
Enrolled	600 (100.0)	600 (100.0)	1200 (100.0)
Vaccinated at Vaccination 1	-	-	-
QIV	599 (99.8)	598 (99.7)	1197 (99.)
PCV15	599 (99.8)	2 (0.3)	601 (50.1)
Placebo (saline)	0 (0.0)	596 (99.3)	596 (49.7)
Vaccinated at Vaccination 2	-	-	-
PCV15	0 (0.0)	586 (97.7)	586 (48.8)
Placebo	583 (97.2)	1 (0.2)	584 (48.7)
Completed Study	583 (97.2)	583 (97.2)	1166 (97.2)
≥1 Protocol Deviation	36 (6.0)	42 (7.0)	78 (6.5)

Source: Adapted from STN 125741.0, P021V114 Clinical Study Report, Table 10-1 Disposition of Participants.
Concomitant group: PCV15+QIV (Day 1), then saline at Day 30. Nonconcomitant group: QIV+saline (Day 1), then PCV15 at Day 30.
PCV15: 15-valent pneumococcal conjugate vaccine. QIV: quadrivalent influenza vaccine (seasonal inactivated).
#n: #participants with available data for relevant endpoint.

Of the 1200 participants, 78 (6.5%) had at least 1 protocol deviation, most frequently due to blood sample drawn outside of the protocol-defined window (3.5% overall; range 3.0% to 4.0%). In the Nonconcomitant Group, 1 participant incorrectly received PCV15 at Visit 1 resulting administration of 2 doses of PCV15 and another participant incorrectly received the concomitant group intervention schedule. Therefore, the APaT study population for the evaluation of safety included 600 PCV15 concomitant recipients and 585 PCV15 nonconcomitant recipients.

6.4.11 Immunogenicity Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

Primary Objective #1: Pneumococcal OPA antibody responses

The first primary immunogenicity objective evaluated the OPA GMTs 30 days following a single-dose vaccination with PCV15 administered concomitantly with QIV compared to PCV15 administered nonconcomitantly. The NI criteria for all pneumococcal serotypes were met, since the lower bound of the 2-sided 95% CI of the OPA GMT ratio was >0.50 for the 15 serotypes.

Table 26 below summarizes the 30-day postvaccination GMTs for the 15 pneumococcal serotypes in PCV15, by study group.

Table 26. Pneumococcal OPA GMTs at 30 Days After PCV15 Vaccination, Per-Protocol Analysis Set, Study V114-021

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

Source: Adapted from STN 125741.0, P021V114 Clinical Study Report, Table 11-1: Analysis of Postvaccination OPA GMTs.
Concomitant group: PCV15+QIV (Day 1), then saline at Day 30. Nonconcomitant group: QIV+saline (Day 1), then PCV15 at Day 30.
PCV15: 15-valent pneumococcal conjugate vaccine. QIV: quadrivalent influenza vaccine (seasonal inactivated).
N: #participants in Per-Protocol Analysis Set (PPAS). GMT: Geometric Mean Titer.

Primary Objective #2: Influenza HAI antibody responses

The second primary immunogenicity objective evaluated the HAI GMTs 30 days following a single-dose vaccination with QIV administered concomitantly with PCV15 compared to QIV administered nonconcomitantly. The NI criteria for all influenza vaccine strains were met, since the lower bound of the 2-sided 95% CI of the HAI GMT ratio was >0.5 for the 4 influenza strains.

Table 27 below provides the 30-day postvaccination HAI GMTs against each strain for the concomitant group and nonconcomitant groups.

Table 27. Influenza HAI GMTs at 30 Days After QIV Vaccination, Study V114-021

Influenza Strain	Concomitant Group N=599 GMT	Nonconcomitant Group N=598 GMT	GMT Ratio [Concomitant Group/ Nonconcomitant Group] [95% CI]
H1N1	124.82	115.00	1.09 [**0.94**, 1.25]
H3N2	87.85	85.62	1.03 [**0.90,** 1.117]
B-Victoria	35.53	36.88	0.96 [**0.86**, 1.08]
B-Yamagata	33.47	33.13	1.01 [**0.90,** 1.13]

Source: STN 125741.0, P021V114 Clinical Study Report, Table 11-2 Analysis of Postvaccination HAI GMTs (Per-Protocol Population).
Concomitant group: PCV15+QIV (Day 1), then saline at Day 30. Nonconcomitant group: QIV+saline (Day 1), then PCV15 at Day 30.
PCV15: 15-valent pneumococcal conjugate vaccine. QIV: quadrivalent influenza vaccine (seasonal inactivated).
N: #participants in Per-Protocol Analysis Set. HAI: hemagglutination inhibition. GMT: Geometric Mean Titer. NI was met if the LB of the 2-sided 95% CI of the HAI GMTR was >0.5 for each of the 4 influenza strains.

Reviewer Comment: *If the study design had included a more stringent NI margin (lower bound of the 95% CI of the GMTR of >0.67) often used when evaluating the NI of HAI GMTs for influenza vaccines, then study success criteria would have also been met for each of the 4 influenza strains.*

6.4.11.2 Analyses of Secondary Endpoints

Pneumococcal antibody responses

For each serotype, IgG GMCs at 30 days postvaccination and the proportion of participants with ≥4-fold increase in IgG concentration from baseline to 30 days postvaccination were similar in both study groups.

The proportions of participants with ≥4-fold rise in OPA GMT and IgG responses from baseline to 30 days postvaccination were generally comparable in both groups.

Influenza HAI responses

In both study groups, HAI responses were generally comparable, as measured by HAI GMTs, percentages of participants with HAI titers ≥1:40, and seroconversion rates at 30 days after QIV vaccination.

6.4.11.3 Subpopulation Analyses

OPA GMTs and H1N1 HAI GMTs in older age groups (65 to 74 and ≥75 years of age) were generally lower than those in younger age groups (50 to 64 years of age). OPA GMTs and HAI GMTs between the two groups were generally consistent in analyses by sex, race, ethnicity, and history of PPV23.

6.4.11.4 Dropouts and/or Discontinuations

See Section 6.4.10.1.3.

6.4.12 Safety Analyses

6.4.12.1 Methods

See Section 6.4.2.

6.4.12.2 Overview of Adverse Events

Safety Overview

Table 28 below summarizes rates of adverse events during the study period.

Table 28. Proportions of Participants Reporting at Least One Adverse Event, All Participants as Treated, Study V114-021

AE Type: Monitoring Period[‡]	Concomitant Group[*] N=600 n (%)	Nonconcomitant Group[†] N=585 n (%)
Immediate AEs: 30 minutes	15 (2.5)	21 (3.6)
Solicited injection site AEs: 5 days	403 (67.2)	408 (69.7)
Solicited systemic AEs: 14 days	246 (41.0)	202 (34.5)
Temperature ≥38.0°C: 5 days [§]	6 (1.0)	5 (0.9)
Unsolicited AEs: 14 days	109 (18.2)	88 (15.0)
SAEs: 1 month	6 (1.0)	2 (0.3)
Deaths: 1 month	0 (0.0)	0 (0.0)

Source: Study V114-021 Clinical Study Report including Table 14.3-11, Table 14.3-14, Table 14.5-3, Listing 16.2.7.1.2, Listing 16 2.7.1.3.
PCV15: 15-valent pneumococcal conjugate vaccine.
%: n/N. n: #participants who experienced the relevant type of AE; N: #participants in All Participants as Treated Population (APaT).
AE: Adverse event. SAE: Serious adverse event.
[*] Following vaccination 1 (PCV15 + QIV); solicited injection site AEs are based on data collected for the PCV15 injection site only.
[†] Following vaccination 2 (PCV15).
[‡] Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.
[§] Percentages are calculated based on the number of participants with temperature data (N=596 in the concomitant group and N=584 in the nonconcomitant group).

Solicited Local and Systemic Adverse Reactions

The data presented in the Table 29 below reflect VRC information as assessed and revised by the investigators (see Section 6.2.7 above for further details).

Table 29. Percentage of Participants Reporting Solicited Local Reactions (Days 1-5) and Systemic AEs (Days 1-14) After Concomitant and Nonconcomitant PCV15 Vaccination, All Participants as Treated, Study V114-021

Solicited Adverse Reaction[‡]	Concomitant Group[*] N=600 n (%)	Nonconcomitant Group[†] N=585 n (%)
Local (PCV15 injection site)	--	--
Pain:	--	--
Any[§]	390 (65.0)	398 (68.0)
Grade 1	288 (48.0)	288 (49.2)
Grade 2	96 (16.0)	101 (17.3)
Grade 3	5 (0.8)	8 (1.4)
Swelling:	--	--
Any[§]	73 (12.2)	74 (12.6)
0 to ≤2.4 cm	34 (5.7)	37 (6.3)
>2.4 to ≤5.0 cm	20 (3.3)	18 (3.1)
>5.0 to ≤10.0 cm	17 (2.8)	16 (2.7)
>10.0 cm	2 (0.3)	3 (0.5)
Erythema:	--	--
Any[§]	45 (7.5)	48 (8.2)
0 to ≤2.4 cm	0 (0.0)	21 (3.6)
>2.4 to ≤5.0 cm	1 (0.2)	11 (1.9)
>5.0 to ≤10.0 cm	0 (0.0)	11 (1.9)
>10.0 cm	0 (0.0)	3 (0.5)
Systemic	--	--
Myalgia:	--	--
Any[§]	122 (20.3)	86 (14.7)
Grade 1	85 (14.2)	51 (8.7)
Grade 2	34 (5.7)	28 (4.8)
Grade 3	2 (0.3)	7 (1.2)

Solicited Adverse Reaction[‡]	**Concomitant Group[*] N=600 n (%)**	**Nonconcomitant Group[I] N=585 n (%)**
Fatigue:	--	--
Any[§]	136 (22.7)	107 (18.3)
Grade 1	96 (16.0)	76 (13.0)
Grade 2	37 (6.2)	23 (3.9)
Grade 3	3 (0.5)	8 (1.4)
Headache:	--	--
Any[§]	105 (17.5)	81 (13.8)
Grade 1	74 (12.3)	52 (8.9)
Grade 2	28 (4.7)	27 (4.6)
Grade 3	3 (0.5)	2 (0.3)
Arthralgia:	--	--
Any[§]	44 (7.3)	46 (7.9)
Grade 1	26 (4.3)	26 (4.4)
Grade 2	17 (2.8)	15 (2.6)
Grade 3	1 (0.2)	5 (0.9)
Fever[‖]:	--	--
≥38.0°C	6 (1.0)	5 (0.9)
38.0 to <38.5°C	6 (1.0)	3 (0.5)
38.5 to <39.0°C	0 (0.0)	1 (0.2)
39.0 to <40.0°C	0 (0.0)	1 (0.2)
≥40.0°C	0 (0.0)	0 (0.0)

Source: Study V114-021 Clinical Study Report including Table 14.3-11, Table 14.2-27, Table 14.3-14, Table 14.5-3.
%: n/N. n: #participants who experienced the relevant type of AE; N: #participants in All Participants as Treated (APaT) population.
[*] Following vaccination 1 (PCV15 + QIV); solicited local (injection site) adverse reactions are based on data collected for the PCV15 injection site only.
[I] Following vaccination 2 (PCV15).
[‡] Local (injection site) reactions were solicited on Days 1-5 postvaccination. Systemic reactions were solicited on Days 1-14 postvaccination. The following toxicity grade definitions apply to the solicited reactions of injection site pain, myalgia, fatigue, headache and arthralgia: Grade 1 - Did not interfere with activity; Grade 2 - Interfered with activity (criteria for injection site pain and headache also included repeated use of non-narcotic pain reliever >24 hours; criteria for arthralgia also excluded medical intervention); Grade 3 - Prevented daily activity (criteria for injection site pain and headache also included any use of narcotic pain reliever; criteria for arthralgia also required medical intervention). No Grade 4 events were reported.
[§] Includes participants with "unknown" toxicity grade or size; maximum size of solicited injection site erythema in the concomitant group following vaccination 1 with PCV15 was reported as "unknown" for most participants due to a programming error.
[‖] Percentages are calculated based on the number of participants with temperature data (N=596 in the concomitant group and N=584 in the nonconcomitant group).

> ***Reviewer Comment:*** *During the study, a programming error was identified that impacted data acquisition related to the eVRC when used to collect solicited injection site complaints from participants. Due to this error, solicited ARs of injection site erythema for the following groups were reported with an unknown maximum size: 44 participants in the concomitant group following administration of PCV15 at Visit 1, 2 participants in the nonconcomitant group following administration of PCV15 at Visit 2, 8 participants following administration of QIV at Visit 1 (4 in each group), and 15 participants in the nonconcomitant group following administration of placebo at Visit 1.*

For both study groups, injection site pain was the most frequently reported adverse reaction (concomitant 65.0% vs. nonconcomitant 68.0%) and grade 3 local reaction (defined as injection site pain that prevents daily activity) (concomitant 0.7% vs nonconcomitant 2.1%).

For both study groups, the most frequently reported systemic AE after was fatigue (concomitant 22.7% vs. nonconcomitant 19.3%). Rates of arthralgia, headache, and myalgia were similar between the two

study groups. Severe adverse reactions of each type were reported in <2.5% of participants in both groups.

Reactogenicity among males and females and by race were generally comparable in the two study groups. Proportions of participants with any AEs in the older age groups (65 to 74 and ≥75 years of age) were generally lower than those in the younger age group (50 to 64 years of age).

Non-serious Unsolicited AEs
After PCV15 vaccination for the study duration of 7 months, 65.2% and 68.0% of participants in the concomitant group and nonconcomitant groups, respectively, reported at least 1 AE, most frequently in the SOC *General disorders and administration site conditions*, of which injection site pain was most common in both study groups.

6.4.12.3 Deaths
One death due to myocardial infarction was reported for an 81-year-old participant in the concomitant group with a medical history of type 2 diabetes mellitus, hypertension, hypothyroidism and obesity who presented to the emergency department in pulseless cardiac arrest (b) (6) days following PCV15 and QIV vaccinations (b) (6) days following vaccination with placebo). The participant was diagnosed with a myocardial infarction (severe). The investigator considered that death not related to study vaccine.

> ***Reviewer Comment:*** *This reviewer agrees with the study investigator's assessment that the reported death was not related to vaccination.*

6.4.12.4 Nonfatal Serious Adverse Events
Overall, the proportion of participants with non-fatal SAEs after any vaccination from Day 1-Month 7 was 3.7% in the concomitant group and 2.3% in the nonconcomitant group. The events were consistent with common medical conditions in the population studied. AEs in the SOCs *Cardiac disorders* (1.3% concomitant group vs. 0.2% nonconcomitant group) and *Infections and infestations* (0.7% concomitant group vs 0.7% nonconcomitant group) were the most frequently reported non-fatal SAEs. None of the SAEs were considered by the investigator or this reviewer to be related to study vaccine.

6.4.12.7 Dropouts and/or Discontinuations
Three participants discontinued study intervention due to AEs that occurred within the reporting period. Two participants in the concomitant group discontinued study vaccine following vaccination 1 due to sinusitis (non-serious AE) and cerebrovascular accident (SAE), respectively. A participant in the nonconcomitant group discontinued study vaccine following vaccination 1 due to nonserious, vaccine-related AEs of abdominal pain upper, fatigue, nausea, arthralgia, rhinorrhea, and myalgia.

Subpopulation Analyses
The safety profile was generally comparable across study groups within each age subgroup. Proportions of participants with AEs were generally lower in the older age groups (65 to 74 and ≥75 years of age) than the younger age group (50 to 64 years of age). Lower proportions of participants with solicited AEs were observed among participants who were Hispanic or Latino compared with those who were not. The safety profile was generally comparable across study groups for sex and race.

6.4.13 Study Summary and Conclusions

PCV15 administered concomitantly with QIV (Fluarix) was noninferior to PCV15 administered nonconcomitantly with QIV (based on a 2-fold noninferiority margin), as assessed by pneumococcal OPA GMTs at 30 days postvaccination with PCV15 for all 15 serotypes contained in the vaccine. The influenza strain-specific HAI GMTs postvaccination when QIV was administered concomitantly with

PCV15 was noninferior to QIV when administered nonconcomitantly 30 days prior to PCV15, based on 2-fold noninferiority margin for all 4 influenza strains. If the study design had included a more stringent NI margin (lower bound of the 95% CI of the GMTR of >0.67) often used when evaluating the NI of HAI GMTs for influenza vaccines, then study success criteria would have also been met for each of the 4 influenza strains. There was no notable increase in frequency or severity of reported AEs in the concomitant group compared to the nonconcomitant group. The pneumococcal serotype-specific OPA GMTs and influenza vaccine strain specific HAI GMTs data from this study support concomitant vaccine administration of PCV15 with QIV and inclusion of summary results in Section 14.2 (Concomitant Vaccination) of the USPI.

6.5 Trial #5 (Study V114-016)

NCT03480763
"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."

Study Overview: This study was designed to descriptively (without hypothesis testing) evaluate the safety and immunogenicity of a single dose of PCV15 compared with PCV13 when administered to pneumococcal vaccine-naïve adults ≥50 years of age, and to describe serotype-specific pneumococcal immune responses to the 15 serotypes contained in PCV15 when PPV23 was given approximately 12 months after PCV15 or PCV13.

6.5.1 Objectives

Primary Objectives

- To evaluate the safety of PCV15 compared with PCV13
  - *Endpoints:* same as Study V114-020
- To evaluate the safety of PPV23 when administered 12 months after PCV15, compared to PPV23 administered 12 months after PCV13
  - Endpoints:
    - Following vaccination with PPV23:
      - Solicited injection site reactions (Days 1-5 postvaccination)
      - Solicited systemic AEs (Days 1-14 postvaccination)
      - Fever (Days 1-14 postvaccination; recorded on eVRC Days 1-5 postvaccination)
      - Any other unsolicited injection site or systemic AEs (Days 1-14 postvaccination)
      - SAEs (Month 12-Month 13)
- To evaluate the serotype-specific OPA GMTs at 30 days postvaccination with PPV23 (Month 13), when PPV23 is administered 12 months after PCV15 or PCV13
  - *Endpoint:* OPA GMTs for the 15 serotypes in PCV15

Secondary Objectives

- To evaluate the serotype-specific IgG GMCs at 30 days postvaccination with PPV23 (Month 13), when PPV23 was administered 12 months after PCV15, and separately for participants administered PCV13
  - *Endpoint:* IgG GMCs for the 15 serotypes in PCV15 (Month 13)
- To evaluate serotype-specific OPA GMTs and IgG GMCs prior to PPV23 and at 30 days after PPV23 vaccination for each study group separately
  - *Endpoints*: OPA GMTs and IgG GMCs for the 15 serotypes in PCV15 (Month 12, Month 13)

- To evaluate serotype-specific OPA and IgG response (GMFRs and proportions of participants with a ≥4-fold increase) at Day 30 compared to Day 1, Month 12 compared to Day 1, Month 13 compared to Day 1, and Month 13 compared to Month 12

6.5.2 Design Overview

Study V114-016 is a randomized, double-blind (participant and study investigator), active-controlled, multi-center study in a total of 600 pneumococcal vaccine-naïve adults 50 years and older. Participants received PCV15 (n=300) or PCV13 (n=300), followed by PPV23 12 months later. Participants were stratified by age cohorts: 50 to 64 years; 65 to 74 years, and 75 years and older. At least 50% of the participants were older than 65 years of age.

Blinding: PCV15 and PCV13 differ in appearance; therefore, the study vaccine preparer/administrator was unblinded to the treatment assignment. PPV23 was administered open-label to all participants at Month 12. The vaccine preparer/administrator was not involved in collecting safety information at any visit.

6.5.3 Population

Eligibility criteria are the same as Study V114-019. See Section 6.1.3.

6.5.4 Study Treatments or Agents Mandated by the Protocol

Table 30. Vaccinations Administered in Study V114-016

Study Group	Vaccines	Vaccination Regimen
PCV15	PCV15	Single dose at Visit 1 (Day 1)
	PPV23	Single dose at Visit 3 (Month 12)
PCV13	PCV13	Single dose at Visit 1 (Day 1)
	PPV23	Single dose at Visit 3 (Month 12)

PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine (Prevnar 13).
PPV23: 23-valent pneumococcal polysaccharide vaccine (Pneumovax23).

Vaccine Composition
PCV15: same as Study V114-020. Lot # WL00068290
PCV13: same as Study V114-020. Lot #0000793304 and #0000814723

PPV23:

- Composition: each 0.5mL dose contains 25µg capsular polysaccharides from each of the following *S. pneumoniae* types: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F.
- Appearance: clear, colorless solution
- Presentation: liquid in prefilled syringe. Lot #0000794346 and #0000883498

6.5.5 Directions for Use

PCV15, PCV13, and PPV23: single dose (0.5mL) administered IM

6.5.6 Sites and Centers

Total of 22 centers; US (PCV15 n=164, PCV13 n=167), Spain (PCV15 n=62, PCV13 n=58), Taiwan (PCV15 n=52, PCV13 n=49), Korea (PCV15 n=49, PCV13 n=51)

6.5.7 Surveillance/Monitoring

Safety Monitoring
The parameters monitored after pneumococcal conjugate vaccination were the same as Study V114-020; except for SAE monitoring (from Day 1 to Month 12), the duration of monitoring was the same as Study V114-020.

The parameters monitored after PPV23 were the same as after pneumococcal conjugate vaccination; except for SAE monitoring (from Month 12 to Month 13), the duration of monitoring was the same as the duration of monitoring after pneumococcal conjugate vaccination.

Immunogenicity Monitoring

- Blood samples collected at baseline (Day 1), 30 days postvaccination with PCV15 or PCV13 (Day 30), prior to PPV23 vaccination (Month 12), and 30 days after PPV23 vaccination (Month 13).
- MOPA and pneumococcal ECL assays: same as Study V114-020.

6.5.8 Endpoints and Criteria for Study Success

Same as Study V114-020. See Section 6.2.1.

6.5.9 Statistical Considerations & Statistical Analysis Plan

All analyses were descriptive.

Sample size calculations: Planned enrollment of 300 participants per study group was estimated to result in 240 evaluable participants.

Immunogenicity Analyses

- OPA GMTs at Month 13 (primary endpoint), and at Day 30 and Month 12 (secondary endpoints) for each of the 15 serotypes in PCV15 were calculated using a cLDA method.
- IgG GMCs at Month 13, Day 30, and Month 12 (secondary endpoints) for each of the 15 serotypes in PCV15 were calculated using a cLDA method.

Safety Analyses: same as Study V114-019
Interim Analyses: same as Study V114-019

6.5.10 Study Population and Disposition

6.5.10.1 Populations Enrolled/Analyzed

Analysis Populations

- Per-Protocol Analysis Set: population for the primary immunogenicity analyses
  - Consisted of all randomized participants without deviations from the protocol that substantially affected the results of the immunogenicity endpoint.
  - Potential deviations that resulted in the exclusion of a participant from the PP population for all immunogenicity analyses, for example, included:
    - Failure to receive any study vaccine at Visit 1 (Day 1).
    - Failure to receive correct clinical materials as per randomization schedule
    - Receipt of a prohibited medication or prohibited vaccine prior to study vaccination.
    - Failure to receive PPV23.
    - Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection.

- Collection of a blood sample outside of the pre-specified window (Day 1, Day 30, Month 12, Month 13).

- Final determination of all protocol deviations, i.e., composition of the PP population was made prior to the final unblinding of the database. Participants were included in the vaccination group to which they were randomized.

- FAS: same as Study V114-020
- APaT (safety): all randomized participants who received the relevant study vaccination for the timepoint of interest (i.e., a single dose of PCV15/PCV13 at Visit 1 [Day 1] to be included in the analyses following PCV; a single dose of PPV23 at Visit 3 [Month 12] to be included in the analyses following PPV23). Analyses were performed according to vaccine received.

6.5.10.1.1 Demographics

Table 31. Demographic and Baseline Characteristics, Study V114-016

- **Demographic Characteristic**	**PCV15 N=326 n (%)**	**PCV13 N=325 n (%)**	**Total N=651 n (%)**
Sex	-	-	-
Male	137 (42.0)	144 (44.3)	281 (43.2)
Female	189 (58.0)	181 (55.7)	370 (56.8)
Age (Years)	-	-	-
50-64	163 (50.0)	162 (49.8)	325 (49.9)
65-74	123 (37.7)	124 (38.2)	247 (37.9)
≥75	40 (12.3)	39 (12.0)	79 (12.1)
Mean	64.0	64.1	64.1
SD	8.0	8.4	8.2
Median	64.5	65.0	65.0
Range	50 to 89	50 to 90	50 to 90
Race	-	-	-
Asian	102 (31.3)	103 (31.7)	205 (31.5)
Black or African American	18 (5.5)	22 (6.8)	40 (6.1)
Multiple	2 (0.6)	2 (0.6)	4 (0.6)
White	203 (62.3)	198 (60.9)	401 (61.6)
Missing	1 (0.3)	0 (0.0)	1 (0.2)
Ethnicity	-	-	-
Hispanic or Latino	42 (12.9)	37 (11.4)	79 (12.1)
Not Reported	2 (0.6)	1 (0.3)	3 (0.5)

Source: STN 125741.0, P016V114 Clinical Study Report, Table 10-5 Participant Characteristics.
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine.
#n: #participants with available data for relevant endpoint.

6.5.10.1.3 Participant Disposition

In the PCV15 group, 327 participants were randomized, 326 (99.6%) were vaccinated with PCV15, and 298 (91.1%) were vaccinated with PPV23; 303 (92.7%) completed the study, and 24 discontinued from the study. In the PCV13 group, 325 participants were randomized, 325 (100%) were vaccinated with PCV13, and 302 (92.9%) were vaccinated with PPV23; 306 (94.2%) completed the study, and 19 discontinued from the study.

6.5.11 Immunogenicity Analyses

6.5.11.1 Analyses of Primary Endpoint(s)

Primary Objective #1: Pneumococcal OPA GMTs at 30 days after PPV23 (Month 13)

Following sequential vaccination with PPV23, OPA GMTs for 15 pneumococcal serotypes were measured at 30 days after PPV23 vaccination. PPV23 contains 14 and 12 serotypes in common with PCV15 and PCV13, respectively. PCV15 and PCV13 (but not PPV23) contain serotype 6A. PCV15 contains serotypes 22F and 33F, which are not contained in PCV13.

For 14 serotypes, OPA GMTs at 30 days after PPV23 vaccination (Month 13) were similar between participants who initially received PCV15 or PCV13 (on Day 1); serotype 22F OPA GMT was 1.6 times higher in participants who initially received PCV15, compared to participants who initially received PCV13, then PPV23 12 months later.

Table 32. Pneumococcal OPA GMTs at 30 Days After PPV23 (Month 13), Study V114-016

Serotype	PCV15→PPV23 N=326 Observed GMT	PCV13→PPV23 N=325 Observed GMT	GMT Ratio [PCV15/PCV13] [95% CI]
1	387.2	278.0	1.39 [1.11, 1.75]
3	277.6	259.2	1.07 [0.90, 1.28]
4	1670.1	1559.6	1.07 [0.86, 1.34]
5	693.0	577.2	1.20 [0.93, 1.55]
6A	3221.7	2791.4	1.15 [0.94, 1.42]
6B	3194.1	2859.7	1.12 [0.93, 1.35]
7F	5100.9	4830.9	1.06 [0.90, 1.25]
9V	2027.1	1864.6	1.09 [0.90, 1.31]
14	3370.6	2641.0	1.28 [1.06, 1.54]
18C	2356.8	2086.7	1.13 [0.95, 1.34]
19A	3651.6	3132.7	1.17 [0.97, 1.40]
19F	2236.1	2151.9	1.04 [0.89, 1.21]
23F	1897.6	1478.2	1.28 [1.01, 1.62]
22F	3114.2	1903.3	1.64 [1.29, 2.07]
33F	7932.7	8225.9	0.96 [0.78, 1.19]

Source: STN 125741.0, P016V114 Statistical Report, Table 4 Analysis of OPA GMTs at Month 13 (Sensitivity Analysis Based Only on Samples Testing (b)(4) Negative) (Per-Protocol Population)
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine.
PPV23: 23-valent pneumococcal polysaccharide vaccine (Pneumovax23).
#n: #participants with available data for relevant endpoint. N= #participants in Per-Protocol Analysis Set. GMT: Geometric Mean Titer.

6.5.11.2 Analyses of Secondary Endpoints

Pneumococcal OPA GMTs at Day 30 (after conjugate vaccination) and Month 13 (after PPV23 vaccination), adults 50 years and older

In both study groups (PCV15 and PCV13), OPA GMTs 30 days after conjugate vaccination and 30 days after sequential PPV23 vaccination were comparable for the 13 shared serotypes and for the serotypes contained in PCV15 but not in PCV13 (22F and 33F).

Pneumococcal OPA GMTs at Day 1 (baseline), Month 12 and Month 13 (pre- and post-PPV23 vaccination), adults 50 years and older

At Month 12 (pre-PPV23 vaccination), OPA GMTs were higher than at baseline (Day 1) for both study groups. Immune responses after PCV15 were comparable to immune responses after PCV13 at 30 days and at 12 months following vaccination for the 13 shared serotypes, and higher for serotypes 22F and 33F.

One month after vaccination with PPV23 (Month 13), OPA GMTs for all 15 serotypes were comparable between study groups and higher than those observed at Month 12.

Pneumococcal IgG GMCs at Month 13, adults 50 years and older
IgG GMCs at 30 days following vaccination with PPV23 (Month 13) were comparable between the PCV15 and PCV13 study groups.

6.5.11.3 Subpopulation Analyses
PCV15 study group: There were lower OPA GMTs at Month 13 in older adults (65 to 74 and ≥75 years of age) compared with younger adults (50 to 64 years of age). Immune responses were similar by sex, race, and ethnicity.

6.5.11.4 Dropouts and/or Discontinuations
See Section 6.5.10.1.3.

6.5.12 Safety Analyses

6.5.12.1 Methods
See Section 6.5.2.

6.5.12.2 Overview of Adverse Events
Safety Overview
Table 33 below provides an overview of AE rates in the PCV15 group compared to the PCV13 group.

Table 33. Proportion of Participants Reporting at Least One Adverse Event, All Participants as Treated, Study V114-016

AE Type: Monitoring Period*	PCV15 N=327 n (%)	PCV13 N=324 n (%)
Immediate AEs: 30 minutes	5 (1.5)	2 (0.6)
Solicited injection site AEs: 5 days	195 (59.6)	146 (45.1)
Solicited systemic AEs: 14 days	129 (39.4)	88 (27.2)
Temperature ≥38.0°C: 5 days[1]	4 (1.2)	4 (1.2)
Unsolicited AEs: 14 days	71 (21.7)	66 (20.4)
SAEs: 12 months	17 (5.2)	19 (5.9)
Deaths: 12 months	0 (0.0)	0 (0.0)

Source: Study V114-016 Clinical Study Report including Table 12-1, Table 12-3, Table 12-19.
PCV15: 15-valent pneumococcal conjugate vaccine.
%: n/N. n: #participants who experienced the relevant type of AE; N: #participants in All Participants as Treated Population (APaT).
AE: Adverse event. SAE: Serious adverse event.
* Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.
[1] Percentages are calculated based on the number of participants with temperature data (N=325 in the PCV15 group and N=323 in the PCV13 group).

Solicited Adverse Reactions
The solicited local AR and systemic AE data presented below reflect VRC information as assessed and revised by the investigators (see Section 6.2.7 for further details).

Table 34. Proportions of Participants Reporting Solicited Local Reactions (Days 1-5) and Systemic AEs (Days 1-14) After Pneumococcal Conjugate Vaccination, All Participants as Treated, Study V114-016

--	PCV15 N=327 (% = n/N)	PCV13 N=324 (% = n/N)
Local (PCV15 injection site)	--	--
Injection site pain	--	--
Total	55.0%	41.4%
Grade 1	41.0%	34.6%
Grade 2	13.5%	6.5%
Grade 3	0.6%	0.3%
Injection site erythema	--	--
Total	9.8%	5.6%
NA (0 to ≤2.4cm)	4.0%	2.8%
Grade 1 (0 to ≤2.4cm)	1.5%	1.2%
Grade 2 (>2.4 to ≤7.4cm)	1.5%	0.6%
Grade 2 (>7.4 to ≤10.0)	1.5%	0.0%
Grade 3 (>10.0cm)	0.6%	0.3%
Unknown	0.6%	0.6%
Injection site swelling	--	--
Total	16.2%	11.4%
NA (0 to ≤2.4cm)	7.6%	7.4%
Grade 1 (0 to ≤2.4cm)	5.5%	3.4%
Grade 2 (>2.4 to ≤7.4cm)	1.8%	0.3%
Grade 2 (>7.4 to ≤10.0)	0.6%	0.3%
Grade 3 (>10.0cm)	0.6%	0.3%
Systemic	--	--
Arthralgia	--	--
Total	6.4%	5.2%
Grade 1	4.0%	4.0%
Grade 2	2.1%	1.2%
Grade 3	0.3%	0.0%
Fatigue	--	--
Total	23.5%	13.9%
Grade 1	16.2%	10.0%
Grade 2	6.4%	3.4%
Grade 3	0.9%	0.3%
Headache	--	--
Total	14.1%	12.7%
Grade 1	8.9%	8.0%
Grade 2	4.6%	4.0%
Grade 3	0.6%	0.6%
Myalgia	--	--
Total	17.7%	11.1%
Grade 1	14.4%	8.3%
Grade 2	3.4%	1.9%
Grade 3	0.0%	0.9%

--	PCV15 N=327 (% = n/N)	PCV13 N=324 (% = n/N)
Fever	--	--
<100.4 °F	98.8%	98.8%
≥100.4 °F and <101.3 °F	0.3%	0.6%
≥101.3 °F and <102.2 °F	0.3%	0.0%
≥102.2 °F and <103.1 °F	0.0%	0.3%
≥105.8 °F	0.6%	0.3%

Source: Adapted from STN 125741.0, P016V114 Clinical Study Report, Table 12-9 and 12-10 Participants With Solicited Adverse Reactions by Maximum Intensity; Participants With Solicited Injection Site Erythema and Injection Site Swelling by Maximum size.
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine.
#n: #participants with available data for relevant endpoint, N= #participants in All Participants as Treated Population.
Injection site pain, myalgia, headache, malaise: Grade 1 - Did not interfere with activity; Grade 2 - Interfered with activity (criteria for injection site pain and headache also included repeated use of non-narcotic pain reliever >24 hours; criteria for arthralgia also excluded medical intervention); Grade 3 - Prevented daily activity (criteria for injection site pain and headache also included any use of narcotic pain reliever; criteria for arthralgia also required medical intervention).

After PPV23 vaccination, frequencies of solicited systemic AEs were similar between study groups. Within each study group, frequencies of solicited systemic AEs after PPV23 and after conjugate vaccine were similar.

Unsolicited Adverse Reactions
The proportions of unsolicited adverse events were similar between the two groups (70.6% in the PCV15 group and 60.8% in the PCV13 group) for the study duration of 13 months. In both study groups, unsolicited AEs in the SOCs *Musculoskeletal and connective tissue disorders* and *General disorders and administration site conditions* were most commonly reported of the unsolicited adverse reactions with myalgia (17.7% for PCV15 and 11.1% for PCV13) and injection site pain (55.4% for PCV15 and 42.3% for PCV13) being the most frequently occurring reaction in each category respectively.

Subpopulation Analyses
Within each study group, lower proportions of participants with AEs were observed in older age groups (65 to 74, and ≥75 years of age) compared with the younger age group (50 to 64 years of age). Within each study group, the proportion of female participants who experienced AEs was higher compared with male participants. Safety results observed within each race and ethnicity subgroup were generally consistent with those of the overall population.

6.5.12.3 Deaths
There were no deaths reported in this study.

6.5.12.4 Nonfatal Serious Adverse Events
During the time period from Day 0 through 12 months following administration of pneumococcal conjugate vaccine, 5.2% (17 participants) of PCV15 participants and 5.9% (19 participants) of PCV13 participants reported a non-fatal SAE. AEs in the SOC *Infections and infestations* were most frequently reported of non-fatal SAEs in the PCV15 and PCV13 groups, of which osteomyelitis (0.6% PCV15, 0% PCV13) was most common.

Three participants reported a non-fatal SAE within the 30 days after PPV23 vaccination:

- PCV15: 84-year-old participant with medical history of COPD and hypertension was hospitalized for COPD exacerbation 128 days (Day 164) after PCV15 vaccination, recovered 6 days later after medical intervention, then was re-hospitalized 67 days later (Day 226) for cardiac failure and recovered 1 day later after medical intervention. The participant was again hospitalized 32 days after receiving PPV23 (on Day 380) and diagnosed with acute pulmonary edema, respiratory tract

infection, and worsening cardiac failure; symptoms resolved 4 days later after medical intervention and the participant completed the study.

- PCV13: 2 participants were hospitalized for rib fracture and syncope, respectively. The participant hospitalized for syncope was 70 years old and had a medical history of congestive heart failure, pulmonary hypertension, and sleep apnea. The participant was hospitalized 160 days after PCV13 for exacerbation of pulmonary hypertension, after experiencing lightheadedness, recovered 2 days later after medical intervention, and continued to require oxygen via nasal cannula. The second participant was hospitalized for syncope 13 days after PPV23 (Day 353) and had been wearing an oxygen nasal cannula improperly. Treatment included oxygen, antibiotics and change in diuretic medications for symptoms of pulmonary congestion, which was confirmed by x-ray. All symptoms resolved 2 days later.

None of the SAEs were considered by the study investigator or this reviewer to be related to study vaccination.

6.5.12.7 Dropouts and/or Discontinuations
Two participants discontinued the study intervention due to an AE.

- PCV15: 64-year-old male with medical history of headache and hypermetropia developed severe vertigo and associated vomiting, mild bradycardia, somnolence, and hypothermia on Day 1 after PCV15 vaccination. Symptoms resolved after 5.5 hours without medical intervention.

- PCV13: 57-year-old male with a medical history of hypertension, hypercholesterolemia, COPD, and myocardial infarction was diagnosed with squamous cell carcinoma of the hypopharynx on Day 29 after PCV13 vaccination after experiencing pharyngitis with cough and odynophagia.

6.5.13 Study Summary and Conclusions

In adults 50 years of age and older, the safety profile after PCV15 vaccination was similar to the safety profile after PCV13 vaccination; the safety profiles in both study groups were similar after PPV23 vaccination given 12 months later. For the 13 common pneumococcal serotypes, OPA GMTs at 30 days and 12 months after PCV15 or PCV13 vaccination were similar. Serotypes 22F and 33F OPA GMTs, which are contained in PCV15 but not PCV13, were higher after PCV15 vaccination (Day 30).

At 30 days following administration of PPV23 (Month 13), which contains 22F and 33F, OPA GMTs to the 15 serotypes in PCV15 were comparable across the study groups. The study results support the added clinical benefit of PCV15 vaccination, when administered one year before PPV23, with an increase observed in OPA GMTs for all PCV15 serotypes one month following PPV23.

6.6 Trial #6 (Study V114-007)

NCT02573181
A Multicenter, Double-Blind Study of the Safety, Tolerability, and Immunogenicity of V114 Compared to Prevnar 13™ in Healthy Adults 65 Years of Age or Older Previously Vaccinated with 23-Valent Pneumococcal Polysaccharide Vaccine

Study Overview: This Phase 2 study was designed to descriptively (without hypothesis testing) evaluate the potential impact of prior receipt of PPV23 on the safety and immunogenicity of a single dose of PCV15 compared to PCV13 in adults ≥65 years of age. The study was conducted in the United States only.

6.6.1 Objectives

Primary Objectives

- To describe the safety and tolerability profiles of PCV15 and PCV13 when administered as a single dose in adults ≥65 years of age with a prior history of PPV23.
- To summarize the serotype-specific IgG responses measured at Day 1 and Day 30 postvaccination in recipients of PCV15 and PCV13 for the 13 shared pneumococcal serotypes contained in both vaccines and the 2 serotypes unique to PCV15.

Secondary Objective

- To summarize the serotype-specific OPA responses measured at Day 1 and Day 30 postvaccination in recipients of PCV15 and PCV13 for the 13 shared pneumococcal serotypes contained in both vaccines and the 2 serotypes unique to PCV15.

Exploratory Objectives

- To summarize the safety and immunogenicity (as measured by the pneumococcal electrochemiluminescence (ECL) assay and the multiplexed OPA [MOPA-4] assay) of PCV15 and Prevnar 13 by time since receipt of PPV23 (1 to 3 years vs. >3 years) for each age cohort (65 to 74 years of age vs. ≥75 years of age).
- To compare the immunogenicity (as measured by the MOPA-4 and pneumococcal ECL assays) at Day 30 postvaccination in recipients of PCV15 and PCV13 for the 13 shared pneumococcal serotypes contained in both vaccines and the 2 serotypes unique to PCV15.

6.6.2 Design Overview

Study 007 is a multicenter, randomized, double-blind study to evaluate the safety, tolerability, and immunogenicity of a single dose of PCV15 compared to PCV13 in 250 healthy adults 65 years of age or older in good health or with stable underlying chronic conditions who were vaccinated previously with PPV23.

Participants was randomized 1:1 by IVRS/IWRS, with ~125 participants per group. Treatment allocation was stratified by age at randomization (65-74 years and ≥75 years) and time since vaccination with PPV23 (1-3 years and >3 years). Approximately 30% of participants was ≥75 years of age

6.6.3 Population

Participants were eligible to be included in the study only if all of the following criteria apply: adults ≥65 years and in good health, may have underlying chronic illness that is documented to be in stable condition, able to comply with study procedures, and had documented receipt of PPV23 one year or longer prior to study entry, male, or if female then postmenopausal.

Participants were excluded from the study if any of the following criteria applied: prior receipt of a pneumococcal vaccine other than PPV23; history of invasive pneumococcal disease, hypersensitivity to any component of a pneumococcal polysaccharide, conjugate or any diphtheria toxoid (DT)-containing vaccine, known/suspected immune impairment, including receipt of corticosteroids (≥2 mg/kg total dose of prednisone or equivalent) or systemic steroids for ≥14 days and had not completed treatment prior to study entry; receipt of immunosuppressive medications, receipt of non-live vaccines within 14 days of study vaccine, inactivated influenza vaccine may be administered but at least 7 days prior to study vaccine, receipt of live virus vaccine within 30 days of study participation, febrile illness (≥38.0°C) or on antibiotics within 72 hours; participation in another clinical trial within 2 months; user of

recreational/illicit drugs, or history of substance abuse; cannot comply with study procedures, or another reason that the principal investigator might believe would interfere with evaluations required by study.

6.6.4 Study Treatments or Agents Mandated by the Protocol

Table 35. Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Admin	Vaccination Regimen	IMP/ NIMP	Sourcing
PCV15	Experimental	PCV15	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to IB	0.5 mL	IM	Single dose at Visit 1 (Day 1)	IMP	Central
PCV13	Active Comparator	PCV13	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to IB	0.5 mL	IM	Single dose at Visit 1 (Day 1)	IMP	Central

6.6.5 Directions for Use

See Section 6.2.5.
PCV15 Lots #: WL00061714
PCV13 Lot#: L87117/WL00062729

6.6.6 Sites and Centers

There were 17 sites in the United States that enrolled 253 participants.

6.6.7 Surveillance/Monitoring

Safety Monitoring: Similar to those outlined in Section 6.1.7 for V114-019, except that for V114-007, SAEs were monitored for 30 days post vaccination, rather than 6 months.

Immunogenicity Monitoring: See Section 6.1.7 for description of immunogenicity monitoring assays. Time of Immunogenicity Measurements on Day 1 and Day 30

6.6.8 Endpoints and Criteria for Study Success

- Primary immunogenicity endpoints for the 15 serotypes in the PCV15 based on the serotype-specific IgG responses as measured by pneumococcal ECL:
  - GMCs at Day 1 and Day 30
  - GMFR from baseline
  - Proportion of participants with ≥4-fold-increase from baseline
- Secondary immunogenicity endpoints for the 15 serotypes in PCV15 based on the OPA responses as measured by the MOPA-4 assay:
  - GMTs at Day 1 and Day 30
  - GMFR from baseline
  - Proportion of participants with ≥4-fold-increase from baseline
- Safety endpoints:
  - Safety and tolerability was assessed by clinical review of all relevant parameters including AEs.
  - Events for this study will consist of the solicited injection site and solicited systemic ARs.

6.6.9 Statistical Considerations & Statistical Analysis Plan

All analyses were descriptive.

6.6.10 Study Population and Disposition

A total of 253 participants were enrolled in the study. Study period: November 2, 2015 (first participant, first visit) to January 28, 2016 (last participant, last visit).

6.6.10.1 Populations Enrolled/Analyzed

Per-Protocol (PPAS) and Full Analysis Set (FAS) for immunogenicity, and All Participants as Treated (APaT) dataset for safety (same as Study V114-020).

6.6.10.1.1 Demographics

Table 36. Demographic Characteristics, All Vaccinated Participants, Study V114-007

Demographic Characteristic	PCV15 (N=127) n (%)	PCV13 (N=126) n (%)
Sex ratio M:F (%)	51:76 (40.2%:59.8%)	51:75 (40.5%:59.5%)
Age, years:		
Mean age (SD)	72.7 (5.8)	72.7 (5.7)
Median age	72.0	72.0
Age range	65, 89	65, 96
Age group, years:		
50-64	N/A	N/A
65-74	88 (69.3%)	89 (70.6%)
≥75	39 (30.7%)	37 (29.4%)

Source: Adapted from STN 125741.0, P007V114 Clinical Study Report Table 10-6. All Vaccinated Participants Analyses Set.
PCV13: Prevnar 13; SD: standard deviation. N: total number of participants for the Safety Analyses Set (participants who received 1 dose and had any safety data available). Sex Ratio M:F indicates Male:Female.

Among all vaccinated participants, there were more females (~60%) than males, the median age was 72 years, and the proportion of participants 65 to 74 years was 70% and ≥75 years was 30%. Most participants were White (94%) and some were Black/African American (6%). Though not shown, the demographic and ethnicity characteristics of participants were similar between study groups.

6.6.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Participants included adults ≥65 years and in good health who had documented receipt of PPV23 one year or longer prior to study entry.

6.6.10.1.3 Participant Disposition

All randomized participants had completed the study (100%), and were included in the Safety and FAS populations, while ~95096% of participants were included in the PP for OPA analyses. Across study groups, there were 20 participants who were excluded from the postvaccination OPA Per-Protocol Population, including 9 PCV15 recipients and 11 PCV13 recipients. The most common reasons for exclusion were that the participant had a history of autoimmune diseases (PCV15: 4 vs PCV13: 3) and missing postvaccination serology (PCV15: 1 vs PCV13: 4).

***Reviewer Comment*:** *The reported number and types of protocol deviations were low and do not raise concerns about study conduct.*

6.6.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints, rather OPA serologic endpoints were used to assess the response to vaccination.

6.6.11.2 Analyses of Secondary Endpoints

Secondary Analyses of OPA Results

The secondary objective descriptively evaluated the serotype specific OPA responses measured at Day 30 postvaccination in recipients of PCV15 compared to PCV13, shown in the table below. For the 13 shared serotypes, the OPA GMTR point estimates were 0.71 to 1.62 and the lower bound of the 95% CI for the OPA GMTR was between 0.49 and 1.12. Though the study was not powered to demonstrate the NI of PCV15 to PCV13 based on a LB of the 95% CI of OPA GMTR >0.5, the data for the shared serotypes align with those of pivotal studies in which formal hypothesis testing was conducted. For the two unique serotypes, the LB of the 95% CI of the OPA GMTR were ~8.3 (22F) and 2.5 (33F), and the LB of the 95% CI of the proportion of participants with 4-fold rise was ~30% (22F) and 22% (33F). Therefore, the OPA data for the two unique serotypes support the overall findings from the pivotal studies as well.

Table 37. Serotype-Specific OPA GMTs in Adult Participants ≥65 years With Previous Pneumococcal Vaccination, and Proportions of Participants With ≥4-Fold Rise in OPA Responses at Day 30, Per-Protocol Analysis Set, Study V114-007

Pneumococcal Serotype	PCV15 (N=117-118) GMTs [95% CI] % 4-Fold Rise [95% CI]	PCV13 (N=112-115) GMTs [95% CI] % 4-Fold Rise [95% CI]	GMTRs [95% CI] % Difference [95% CI]
1	109.3 [79.5, 150.2] 40.7% [48/118] [31.7, 50.1]	91.5 [65.8, 127.4] 33.6% [38/113] [25.0, 43.1]	1.3 [0.9, 1.9] 7.2 [-5.0, 19.4]
3	145.2 [114.9, 183.6] 53.8% [63/117] [44.4, 63.1]	103.8 [81.9, 131.4] 39.3% [44/112] [30.2, 49.0]	1.5 [1.1, 2.0] 15.0 [2.2, 27.1]
4	881.9 [662.1, 1174.8] 44.1% [52/118] [34.9, 53.5]	924.8 [706.7, 1210.2] 54.9% [62/113] [45.2, 64.2]	0.9 [0.6, 1.3] -10.1 [-22.3, 2.3]
5	183.1 [128.2, 261.4] 44.9% [53/118] [35.7, 54.3]	222.2 [154.8, 318.8] 50.4% [57/113] [40.9, 60.0]	0.8 [0.6, 1.2] -5.2 [-17.7, 7.5]
6A	2321.1 [1632.4, 3300.2] 71.8% [84/117] [62.7, 79.7]	2798.1 [2064.2, 3792.9] 77.0% [87/113] [68.1, 84.4]	0.8 [0.5, 1.2] -4.5 [-15.7, 6.6]
6B	2389.2 [1747.7, 3266.2] 62.7% [74/118] [53.3, 71.4]	2423.3 [1731.3, 3391.1] 67.0% [75/112] [57.4, 75.6]	0.9 [0.6, 1.4] -3.7 [-15.9, 8.5]
7F	1232.9 [905.9, 1677.9] 41.0% [48/117] [32.0, 50.5]	1664.9 [1328.8, 2085.9] 50.0% [56/112] [40.4, 59.6]	0.7 [0.5, 1.0] -8.6 [-21.2, 4.1]
9V	1962.5 [1450.3, 2655.6] 47.9% [56/117] [38.5, 57.3]	1387.5 [1008.5, 1908.8] 44.6% [50/112] [35.2, 54.3]	1.2 [0.8, 1.8] 3.3 [-9.4, 16.0]
14	1228.8 [964.7, 1565.2] 18.6% [22/118] [12.1, 26.9]	899.7 [683.7, 1183.8] 15.9% [18/113] [9.7, 24.0]	1.4 [1.0, 1.9] 2.9 [-7.1, 12.8]
18C	1550.7 [1172.3, 2051.1] 54.2% [64/118] [44.8, 63.4]	1009.2 [728.6, 1397.8] 43.4% [49/113] [34.1, 53.0]	1.6 [1.1, 2.3] 11.4 [-1.4, 23.8]

Pneumococcal Serotype	PCV15 (N=117-118) GMTs [95% CI] % 4-Fold Rise [95% CI]	PCV13 (N=112-115) GMTs [95% CI] % 4-Fold Rise [95% CI]	GMTRs [95% CI] % Difference [95% CI]
19A	2078.6 [1650.0, 2618.5] 37.3% [44/118] [28.6, 46.7]	1861.8 [1480.2, 2341.8] 37.2% [42/113] [28.3, 46.8]	1.1 [0.9, 1.5] 0.6 [-11.8, 13.0]
19F	919.3 [690.6, 1223.8] 40.2% [47/117] [31.2, 49.6]	961.7 [747.2, 1237.8] 38.1% [43/113] [29.1, 47.7]	1.1 [0.8, 1.6] 2.3 [-10.1, 14.7]
23F	846.3 [617.6, 1159.9] 61.0% [72/118] [51.6, 69.9]	572.8 [382.8, 857.2] 52.2% [59/113] [42.6, 61.7]	1.3 [0.8, 2.1] 9.0 [-3.9, 21.5]
22F	1761.3 [1255.4, 2471.0] 50.4% [59/117] [41.0, 59.8]	107.8 [64.7, 179.8] 9.8% [11/112] [5.0, 16.9]	13.9 [8.3, 23.4] 40.8 [29.7, 51.1]
33F	7856.8 [5750.0, 10735.5] 38.1% [45/118] [29.4, 47.5]	2572.8 [1800.3, 3676.7] 6.3% [7/112] [2.5, 12.5]	3.5 [2.5, 5.0] 31.7 [21.7, 41.6]

Source: Adapted from STN 125741.0, P007V114 Clinical Study Report Table 11-2, Table 11-6.
PPAS: Per-Protocol Analyses Set; N: # participants in PPAS; GMTs: Geometric Mean Titers; GMTRs: estimated from cLDA model; % Difference: estimated from Miettinen & Nurminen method stratified by age group (65 to 74 years, and ≥75 years).

6.6.11.3 Subpopulation Analyses

The small number of participants in Study 007 did not allow for subpopulation analyses.

6.6.11.4 Dropouts and/or Discontinuations

All enrolled participants completed the study. Missing immunogenicity data were not imputed and no test or search for outliers was performed.

6.6.11.5 Exploratory Analyses

Exploratory objective #1 for this study summarized the OPA immune responses to PCV15 and PCV13 stratified by time since receipt of PPV23, either 1 to 3 years or >3 years following PPV23 vaccination. An overview of the proportion with ≥4-fold rise from Day 1 to Day 30 are provided below for participants 65 to 74 years. The sample size for participants over 75 years was <10 participants, therefore data for this age cohort are not presented.

Table 38. Proportion of Participants 65 to 74 years With ≥4-Fold Rise in OPA Titer From Day 1 to Day 30, by Time Since Prior PPV23, Exploratory Analyses, PPAS, Study V114-007

Pneumococcal Serotype	PCV15 (%) [95% CI] N=29-48 1-3 years after PPV23 >3 years after PPV23	PCV13 (%) [95% CI] N=27-50 1-3 years after PPV23 >3 years after PPV23
1	20.6% [8.7, 37.9] 43.8% [29.5, 58.8]	25.8% [11.9, 44.6] 34.0% [21.2, 48.8]
3	44.1% [27.2, 62.1] 48.9% [34.1, 63.9]	33.3% [17.3, 52.8] 42.0% [28.2, 56.8]
4	17.6% [6.8, 34.5] 52.1% [37.2, 66.7]	35.5% [19.2, 54.6] 64.0% [49.2, 77.1]
5	23.5% [10.7, 41.2] 50.0% [35.2, 64.8]	54.8% [36.0, 72.7] 46.0% [31.8, 60.7]
6A	55.9% [37.9, 72.8] 77.1% [62.7, 88.0]	67.7% [48.6, 83.3] 84.0% [70.9, 92.8]
6B	38.2% [22.2, 56.4] 66.7% [51.6, 79.6]	67.7% [48.6, 83.3] 74.0% [59.7, 85.4]
7F	26.5% [12.9, 44.4] 42.6% [28.3, 57.8]	38.7% [21.8, 57.8] 55.1% [40.2, 69.3]

Pneumococcal Serotype	PCV15 (%) [95% CI] N=29-48 1-3 years after PPV23 >3 years after PPV23	PCV13 (%) [95% CI] N=27-50 1-3 years after PPV23 >3 years after PPV23
9V	35.3% [19.7, 53.5] 43.8% [29.5, 58.8]	32.3% [16.7, 51.4] 52.0% [37.4, 66.3]
14	11.8% [3.3, 27.5] 18.8% [8.9, 32.6]	16.1% [5.5, 33.7] 16.0% [7.2, 29.1]
18C	41.2% [24.6, 59.3] 50.0% [35.2, 64.8]	32.3% [16.7, 51.4] 56.0% [41.3, 70.0]
19A	23.5% [10.7, 41.2] 39.6% [25.8, 54.7]	41.9% [24.5, 60.9] 42.0% [28.2, 56.8]
19F	24.2% [11.1, 42.3] 39.6% [25.8, 54.7]	32.3% [16.7, 51.4] 40.0% [26.4, 54.8]
23F	44.1% [27.2, 62.1] 60.4% [45.3, 74.2]	61.3% [42.2, 78.2] 54.0% [39.3, 68.2]
22F	35.3% [19.7, 53.5] 44.7% [30.2, 59.9]	10.0% [2.1, 26.5] 14.0% [5.8, 26.7]
33F	26.5% [12.9, 44.4] 37.5% [24.0, 52.6]	9.7% [2.0, 25.8] 4.1% [0.5, 14.0]

Source: Adapted from STN 125741.0, V114-007 Clinical Study Report Table 11.4.
N: range of total number of subjects in PPAS with OPA results at both the Day 1 and Day 30 timepoints across all serotypes within the "Time Since Prior PPV23" categories.
CI = confidence interval; OPA: opsonophagocytic activity; PCV13: Prevnar 13; PPV23: PNEUMOVAX™23; PPAS: Per-Protocol Analysis Set.

In exploratory analyses evaluating the impact of prior PPV23 vaccination on OPA responses to PCV (PCV15 or PCV13) numerical differences were observed in the proportions of participants achieving ≥4-fold rise in OPA titers based on time since receipt of PPV23. In general, a greater proportion of participants 65 to 74 years achieved ≥4-fold rise in OPA titers from baseline when there was a longer duration of time between PPV23 and pneumococcal conjugate vaccination (>3 years).

6.6.12 Safety Analyses

6.6.12.1 Methods
See Section 6.6.2.

6.6.12.2 Overview of Adverse Events
Safety data were presented for the PCV15 group and PCV13 group. The following table provides an overview of the rates of adverse events during the study period.

Table 39. Proportion of Participants Reporting an Adverse Event Following Pneumococcal Conjugate Vaccination, All Participants as Treated, Study V114-007

AE Type: Monitoring Period*	PCV15 (N=127) % (n participants/N)	PCV13 (N=126) % (n participants/N)
Immediate AEs: 30 minutes	0% (0/127)	0% (0/126)
Solicited injection site AEs: 5 days	59.8% (76/127)	46.8% (59/126)
Solicited systemic AEs: 14 days	33.9% (43/127)	31.7 (40/126)
Temperature ≥38.0°C: 5 days [1]	1.6% (2/127)	0% (0/126)
Unsolicited AEs: 14 days	22.0% (28/127)	18.3% (23/126)
AEs leading to study w/d: 1 month	0% (0/127)	0% (0/126)

AE Type: Monitoring Period*	PCV15 (N=127) % (n participants/N)	PCV13 (N=126) % (n participants/N)
SAEs: 1 month	0% (0/127)	1.6% (2/126)
Deaths: 1 month	0% (0/127)	0% (0/126)

Source: Adapted from STN 125741.0, Study P007V114 Clinical Study Report including Table 10-2, Table 12-1, Table 12-5, Table 12-10, Table 12-14.
APaT: All Participants as Treated Population was used as the analysis set for safety; n: #participants who experienced the relevant type of AE; N: #participants in APaT; AEs: adverse events; SAEs: serious adverse events
* Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.
[1] Percentages are calculated based on the number of participants with temperature data.

Rates of AEs were comparable across study groups, except for injection site ARs which were reported at a higher rate in the PCV15 group than the PCV13 group. All other types of AEs were comparable across groups. There were no deaths during the study.

Solicited Reactions

The table below shows proportions of participants who reported solicited reactions on their VRC during the 5 days postvaccination for local reactions and fever, and the 14 days postvaccination for systemic reactions. As mentioned in Section 6.2.7, solicited AR data reflect VRC information as assessed and revised by the investigators.

Table 40. Proportion of Participants With Solicited Reactions (Local, Systemic, Fever) Postvaccination, All Participants as Treated, Study V114-007

Solicited Adverse Reaction*	PCV15 (N=127) % (n participants/N)	PCV13 (N=126) % (n participants/N)
Local (injection site)	--	--
Pain:	--	--
Any[1]	55.1% (70/127)	44.4% (56/126)
Grade 1	41.7% (53/127)	38.9% (49/126)
Grade 2	12.6% (16/127)	5.6% (7/126)
Grade 3	0.8% (1/127)	0.0% (0/126)
Swelling:	--	--
Any[1]	14.2% (18/127)	6.3% (8/126)
0 to <2.5 cm	10.2% (13/127)	2.4% (3/126)
≥2.5 to <5.1 cm	2.4% (3/127)	3.2% (4/126)
≥5.1 to ≤10 cm	0.8% (1/127)	0.8% (1/126)
>10.0 cm	0.0% (0/127)	0.0% (0/126)
Erythema:	--	--
Any [1]	7.9% (10/127)	7.1% (9/126)
0 to <2.5 cm	3.1% (4/127)	4.0% (5/126)
≥2.5 to <5.1 cm	0.0% (0/127)	1.6% (2/126)
≥5.1 to ≤10 cm	3.1% (4/127)	0.8% (1/126)
>10.0 cm	0.8% (1/127)	0.0% (0/126)
Systemic	--	--
Myalgia:	--	--
Any [1]	15.7% (20/127)	11.1% (14/126)
Grade 1	7.9% (10/127)	9.5% (12/126)
Grade 2	7.1% (9/127)	1.6% (2/126)
Grade 3	0.8% (1/127)	0.0% (0/126)
Fatigue:	--	--
Any[1]	18.1% (23/127)	19.0% (24/126)
Grade 1	11.8% (15/127)	14.3% (18/126)
Grade 2	6.3% (8/127)	4.8% (6/126)
Grade 3	0.0% (0/127)	0.0% (0/126)

Solicited Adverse Reaction*	**PCV15 (N=127) % (n participants/N)**	**PCV13 (N=126) % (n participants/N)**
Headache:	--	--
Any [†]	13.4% (17/127)	15.9% (20/126)
Grade 1	9.4% (12/127)	11.1% (14/126)
Grade 2	3.9% (5/127)	4.8% (6/126)
Grade 3	0.0% (0/127)	0.0% (0/126)
Arthralgia:	--	--
Any[†]	5.5% (7/127)	8.7% (11/126)
Grade 1	2.4% (3/127)	7.1% (9/126)
Grade 2	3.1% (4/127)	1.6% (2/126)
Grade 3	0.0% (0/127)	0.0% (0/126)
Fever[‡]:	--	--)
≥38.0°C	1.6% (2/127)	0% (0/126)
38.0 to <38.5°C	1.6% (2/127)	0% (0/126)
38.5 to <39.0°C	0% (0/127)	0% (0/126)
39.0 to <40.0°C	0% (0/127)	0% (0/126)
≥40.0°C	0% (0/127)	0% (0/126)

Source: Adapted from STN 125741.0, Study P007V114 Clinical Study Report including Table 12-13, Table 12-14.
APaT: All Participants as Treated Population was used as the analysis set for safety; n: #participants who experienced the relevant type of AE; N: #participants in APaT.
[*] Local (injection site) reactions were solicited on Days 1-5 postvaccination. Systemic reactions were solicited on Days 1-14 postvaccination. The following toxicity grade definitions apply to the solicited reactions of injection site pain, myalgia, fatigue, headache and arthralgia: Grade 1 - Did not interfere with activity; Grade 2 - Interfered with activity (criteria for injection site pain and headache also included repeated use of non-narcotic pain reliever >24 hours; criteria for arthralgia also excluded medical intervention); Grade 3 - Prevented daily activity (criteria for injection site pain and headache also included any use of narcotic pain reliever; criteria for arthralgia also required medical intervention). No Grade 4 events were reported.
[†] Includes participants with unknown toxicity grade or size.
[‡] Percentages are calculated based on the number of participants with temperature data.

As shown in the table above, the solicited AR data reported for Study V114-007 are comparable to the safety data presented for the larger Phase 3 studies included in this memo. Across study groups, injection site pain was the most frequently reported local AR and fatigue and myalgia were the most frequently reported systemic ARs.

Unsolicited AEs (Non-Serious): 14 days postvaccination
The rates of unsolicited AEs within 14 days postvaccination across groups were similar, with ~66% of all participants reporting ≥1 adverse event. As observed with the larger studies reviewed in this memo, the most frequently reported AEs were under the SOCs *General disorders and administration site conditions, Musculoskeletal and connective tissue disorders,* and *Nervous system disorders*.

> ***Reviewer Comment:*** *The safety data from Study V114-007 support the overall safety findings across the larger Phase 3 studies included in this review memo.*

6.6.12.3 Deaths
There were no deaths reported in this study.

6.6.12.4 Nonfatal Serious Adverse Events
There were two reports of SAEs in the study, both in the PCV13 group (myocardial infarction and peri-prosthetic hip fracture), both of which were not considered related to study vaccination.

6.6.12.7 Dropouts and/or Discontinuations
There were 253 participants randomized across study groups, and 100% of participants were vaccinated and completed the study.

6.6.13 Study Summary and Conclusions

Study V114-007 was a Phase 2 study designed to descriptively evaluate the potential impact of prior receipt of PPV23 on the safety and immunogenicity of a single dose of PCV15 compared to PCV13 in adults ≥65 years of age. When compared to PCV13, the OPA GMT responses for the shared serotypes at Day 30 postvaccination were similar, and the responses to the two unique serotypes were higher than the PCV13 group. In general, the OPA data from this Phase 2 study align with the immunogenicity data from the larger Phase 3 studies described in prior sections. The exploratory analyses evaluating the potential impact of prior PPV23 vaccination on OPA responses demonstrated differences in the proportion of participants achieving ≥4-fold rise in OPA titers based on time since receipt of PPV23. In general, a greater proportion of participants 65 to 74 years achieved a 4-fold-rise, when a longer duration of time had elapsed since PPV23 receipt (>3 years). The safety findings were comparable to the overall safety data generated with the larger Phase 3 studies, and the solicited adverse reaction data are included in the prescribing information for individuals ≥65 years of age with a history of PPV23 vaccination (≥1 year). This study also served as the basis for further clinical development of the formulation selected for late phase trials. The data generated from this study support the inclusion of solicited adverse reaction safety data in PPV23-experienced adults ≥65 years of age in Section 6 of the USPI.

6.7 Trial #7 (Study V114-018)

NCT03480802
"A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX™ 23 Eight Weeks Later in Adults Infected with HIV "PNEU–WAY"

Study Overview: This study was designed to descriptively (without hypothesis testing) evaluate the safety and immunogenicity of PCV15 compared to PCV13 in HIV-infected adults ≥18 years of age, and to describe serotype-specific pneumococcal immune responses to the 15 serotypes contained in PCV15 when PPV23 was given approximately 8 weeks after PCV15 or PCV13.

6.7.1 Objectives

Primary Objectives

- To evaluate the safety of PCV15 and PCV13
  - *Endpoints:* Same as Study V114-016
  - Duration of SAE monitoring: Day 1 to Week 8
- To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PCV15 and with PCV13 (described for each study group separately)
  - *Endpoints:* OPA GMTs and IgG GMCs for the 15 serotypes in PCV15 (Day 30)

Secondary Objectives

- To evaluate the safety of PPV23 administered 8 weeks following PCV15 or PCV13 (described for each study group separately)
  - *Endpoints:* Same as Study V114-016
    - Duration of SAE monitoring: Week 8 to Month 6
- To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days after PPV23 (Week 12) (described for each study group separately)
  - *Endpoints:* OPA GMTs and IgG GMCs for the 15 serotypes in PCV15 (Week 12)

Exploratory Objectives

- To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PCV15 compared with PCV13.
  - *Endpoints:* OPA GMTs and IgG GMCs for the 15 serotypes in PCV15 (Day 30)
- To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PPV23 (Week 12) in participants who initially received PCV15 compared to participants who initially received PCV13
  - *Endpoints:* OPA GMTs and IgG GMCs for the 15 serotypes in PCV15 (Week 12)
- To evaluate serotype-specific OPA and IgG response (GMFRs and proportions of participants with a ≥4-fold increase) at Day 30 compared to Day 1, and at Week 12 compared to Day 1

6.7.2 Design Overview

Study V114-018 is a randomized, double-blind (participant and study investigator), active-controlled, multi-site study in a total of 302 HIV-infected adults ≥18 years of age. Participants were randomized 1:1 (152 subjects for PCV15 and 150 subjects for PCV13) and enrollment was stratified by CD4+ T-cell count as follows, Stratum 1: ≥50 to <200 cells/µL; Stratum 2: ≥200 to <500 cells/µL; and Stratum 3: ≥500 cells/µL, with 50% of participants enrolled into Stratum 2.

Participants received PPV23 eight weeks after pneumococcal conjugate vaccination, as recommended by the ACIP for HIV+ individuals over the age of 2 years.

Blinding: PCV15 and PCV13 differ in appearance; therefore, the study vaccine preparer/administrator was unblinded to the treatment assignment. PPV23 was administered open-label. The vaccine preparer/administrator was not involved in collecting safety information.

6.7.3 Population

Inclusion criteria

- ≥18 years of age
- Females: same criteria as Study V114-019.
- Infected with HIV and CD4+ T-cell count ≥50 cells/µL and plasma HIV RNA <50000 copies/mL tested at Screening (Visit 1)
- Receiving combination ART for at least 6 weeks prior to study entry with no intended changes to combination ART therapy for 3 months after randomization

Exclusion criteria

Same as Study V114-020 with the following exceptions:

- Prior administration of any pneumococcal vaccine was not an exclusion criterion
- History of opportunistic infections within 12 months before the first vaccination at Day 1
- History of non-infectious acquired immune deficiency syndrome-related illness such as Kaposi's sarcoma, wasting syndrome, or HIV-associated nephropathy

Temporary exclusion criteria

History of active hepatitis with elevation in pretreatment aspartate transaminase or alanine transaminase >5x ULN within 6 months before the first vaccination at Day 1. History of active hepatitis with elevation in pretreatment aspartate transaminase or alanine transaminase >5x ULN within 6 months before the first vaccination at Day 1. The remaining temporary exclusion criteria were the same as Study V114-019.

6.7.4 Study Treatments or Agents Mandated by the Protocol

Table 41. Vaccinations Administered in Study V114-018

Study Group	Vaccines	Vaccination Regimen
PCV15	PCV15	Single dose at Visit 2 (Day 1)
	PPV23	Single dose at Visit 4 (Week 8)
PCV13	PCV13	Single dose at Visit 2 (Day 1)
	PPV23	Single dose at Visit 4 (Week 8)

PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine (Prevnar 13).
PPV23: 23-valent pneumococcal polysaccharide vaccine (Pneumovax23).

Vaccine Composition
PCV15: same as Study V114-020. Lot #WL00068290
PCV13: same as Study V114-020. Lot #0000793304 and #0000814723
PPV23: same as Study V114-016. Lot #0000794346

6.7.5 Directions for Use

PCV15, PCV13, and PPV23: single dose (0.5mL) administered IM

6.7.6 Sites and Centers

13 centers (US 34.4%, Peru 22.5%, Thailand 16.6%, South Africa 13.6%, France 12.9%)

6.7.7 Surveillance/Monitoring

Same safety monitoring as Study V114-016 with the following exceptions:

- Clinical laboratory assessments
  - Serum HIV serology
  - Blood sample for CD4+ T cell count and plasma HIV RNA testing
- Duration of SAE monitoring
  - After pneumococcal conjugate vaccination: Day 1 to Week 8
  - After PPV23: Week 8 to Month 6

Immunogenicity Monitoring

- Blood samples were drawn prior to PCV15 or PCV13 vaccination (Day 1), 30 days after pneumococcal conjugate vaccination (Day 30), and 30 days after PPV23 vaccination (Week 12).
- MOPA and pneumococcal ECL assays: same as Study V114-020. See Section 6.2.7.

6.7.8 Endpoints and Criteria for Study Success

See Section 6.7.1.

6.7.9 Statistical Considerations & Statistical Analysis Plan

All analyses were descriptive.

Sample size calculations: Planned enrollment of 150 participants per study group was anticipated to result in 135 evaluable participants per study group.

Statistical methods for immunogenicity and safety analyses were the same as Study V114-017.

6.7.10 Study Population and Disposition

6.7.10.1 Populations Enrolled/Analyzed

Analysis Populations: same as Study V114-017.

6.7.10.1.1 Demographics

Table 42. Demographic and Baseline Characteristics, Study V114-018

Demographic Characteristic	PCV15 N=152 n (%)	PCV13 N=150 n (%)	Total N=302 n (%)
Sex	-	-	-
Male	120 (78.9)	118 (78.7)	238 (78.8)
Female	32 (21.1)	32 (21.3)	64 (21.2)
Age (Years)	-	-	-
18-29	25 (16.4)	33 (22.0)	58 (19.2)
30-39	48 (31.6)	36 (24.0)	84 (27.8)
40-49	34 (22.4)	42 (28.0)	76 (25.2)
50-64	37 (24.3)	36 (24.0)	73 (24.2)
≥65	8 (5.3)	3 (2.0)	11 (3.6)
Mean	42.4	41.3	41.9
SD	12.5	12.3	12.4
Median	40.0	41.5	41.0
Range	23 to 74	21 to 69	21 to 74
Race	-	-	-
American Indian Or Alaska Native	0 (0.0)	1 (0.7)	1 (0.3)
Asian	24 (15.8)	30 (20.0)	54 (17.9)
Black Or African American	51 (33.6)	43 (28.7)	94 (31.1)
Multiple	36 (23.7)	26 (17.3)	62 (20.5)
Native Hawaiian Or Other Pacific Islander	0 (0.0)	2 (1.3)	2 (0.7)
White	41 (27.0)	48 (32.0)	89 (29.5)
Ethnicity	-	-	-
Hispanic Or Latino	49 (32.2)	45 (30.0)	94 (31.1)
Not Hispanic Or Latino	102 (67.1)	104 (69.3)	206 (68.2)
Not Reported	1 (0.7)	1 (0.7)	2 (0.7)
CD4+ T-cell Count	-	-	-
≥50 to <200	2 (1.3)	2 (1.3)	4 (1.3)
≥200 to <500	76 (50.0)	76 (50.7)	152 (50.3)
≥500	74 (48.7)	72 (48.0)	146 (48.3)

Source: Adapted from STN 125741.0, P018V114 report. Table 10-5 Participant Characteristics (All Vaccinated Participants).
PCV15: 15-valent pneumococcal conjugate vaccine. PCV13: 13-valent pneumococcal conjugate vaccine (Prevnar 13).
%: n/N. #n: #participants with available data for relevant endpoint. N: # of subjects in the All Vaccinated Population. SD = standard deviation.
AUDIT-C Alcohol Use Disorders Identification Test-Consumption. CAIH = Center for American Indian Health.

6.7.10.1.3 Participant Disposition

In the PCV15 group, 152 participants were randomized, 152 were vaccinated with PCV15, 150 were vaccinated with PPV23, 145 (95.4%) completed the study, and 7 discontinued from the study. In the PCV13 group, 150 participants were randomized, 150 were vaccinated with PCV13, and 148 were vaccinated with PPV23, 147 (98.0%) completed the study and 30 discontinued from the study.

6.7.11 Immunogenicity Analyses

6.7.11.1 Analyses of Primary Endpoint(s)

Primary Objective #1: OPA GMTs at 30 days postvaccination

The table below provides the 30-day postvaccination OPA GMTs for the 15 serotypes in PCV15.

Table 43. OPA GMTs at 30 Days Postvaccination, Per-Protocol Population, Study V114-018

Pneumococcal Serotype	PCV15 N=126-131 Observed GMT	PCV15 N=126-131 95% CI	PCV13 N=116-131 Observed GMT	PCV13 N=116-131 95% CI
1	238.8	[173.1, 329.3]	200.9	[142.7, 282.7]
3	116.8	[94.9, 143.7]	72.3	[58.6, 89.2]
4	824.0	[618.8, 1097.2]	1465.5	[1154.5, 1860.3]
5	336.7	[242.4, 467.7]	276.7	[197.9, 386.7]
6A	6421.0	[4871.6, 7602.8]	5645.1	[4278.9, 7447.4]
6B	4772.9	[3628.3, 6278.7]	3554.0	[2751.0, 4591.4]
7F	6085.8	[4871.6, 7602.8]	6144.3	[4982.8, 7576.6]
9V	2836.3	[2311.5, 3480.4]	2133.9	[1721.8, 2644.5]
14	3508.7	[2730.6, 4508.5]	3000.3	[23.50.0, 3830.5]
18C	3002.2	[2435.5, 3700.8]	1560.3	[1213.8, 2005.6]
19A	4240.7	[3415.4, 5265.3]	3715.9	[2949.2, 4681.8]
19F	2438.6	[1972.7, 3014.6]	2042.0	[1618.9, 2575.5]
23F	1757.4	[1276.1, 2420.2]	1787.0	[1309.9, 2437.9]
22F	3943.7	[3049.2, 5100.5]	109.3	[66.2, 180.3]
33F	11342.4	[9184.3, 14007.6]	1807.6	[1357.3, 2407.3]

Source: Adapted from STN 125741.0, Summary of OPA GMTs at Day 30 (Per-Protocol Population), GMT: Geometric Mean Titers, N: #participants in PPAS, CI: confidence interval.

Primary Objective # 2: IgG GMCs at 30 days postvaccination

PCV15 was immunogenic as assessed by IgG GMCs at 30 days postvaccination for all 15 serotypes contained in the vaccine.

6.7.11.2 Analyses of Secondary Endpoints

Secondary Objective #1: OPA GMTs and IgG GMCs following PPV23

PCV15 or PCV 13 followed by PPV23 was immunogenic for all 15 serotypes as assessed by OPA GMTs and IgG GMCs at 30 days postvaccination with PPV23. PPV23 elicited an immune response for serotypes 22F and 33F at 30 days postvaccination with PPV23 in the PCV13 group.

Table 44. OPA GMTs at 3 Timepoints Postvaccination, Per-Protocol Population, Study V114-018

Pneumococcal Serotype	Postvaccination Timepoint	PCV15 N=122-144 Observed GMT	PCV15 95% CI	PCV13 N=113-143 Observed GMT	PCV13 95% CI
1	Day 1	7.2	(6.0, 8.6)	7.4	(6.2, 8.9)
	Day 30	238.8	(173.1, 329.3)	200.9	(142.7, 282.7)
	Week 12	212.0	(160.5, 280.2)	154.0	(111.6, 212.4)
3	Day 1	15.5	(13.3, 18.1)	15.1	(13.1, 17.5)
	Day 30	116.8	(94.9, 143.7)	72.3	(58.6, 89.2)
	Week 12	102.8	(83.0, 127.2)	96.6	(79.5, 117.4)
4	Day 1	32.7	(27.0, 39.6)	41.8	(33.0, 53.0)
	Day 30	824.0	(618.8, 1097.2)	1465.5	(1154.5, 1860.3)
	Week 12	915.4	(722.9, 1159.1)	984.7	(772.1, 1255.7)
5	Day 1	18.1	(15.9, 20.5)	16.6	(14.8, 18.6)

Pneumococcal Serotype	Postvaccination Timepoint	PCV15 N=122-144 Observed GMT	PCV15 95% CI	PCV13 N=113-143 Observed GMT	PCV13 95% CI
	Day 30	336.7	(242.4, 467.7)	276.7	(197.9, 386.7)
	Week 12	418.1	(312.1, 560.3)	274.5	(199.9, 376.8)
6A	Day 1	277.8	(228.4, 337.8)	318.0	(258.5, 391.1)
	Day 30	6421.0	(4890.4, 8430.7)	5645.1	(4278.9, 7447.4)
	Week 12	4065.4	(3052.1, 5415.1)	4593.2	(3543.0, 5954.7)
6B	Day 1	144.9	(104.4, 201.0)	165.0	(119.3, 228.2)
	Day 30	4772.9	(3628.3, 6278.7)	3554.0	(2751.0, 4591.4)
	Week 12	3661.1	(2735.1, 4900.6)	2826.4	(2202.7, 3626.8)
7F	Day 1	351.9	(255.6, 484.5)	397.5	(286.3, 552.0)
	Day 30	6085.8	(4871.6, 7602.8)	6144.3	(4982.8, 7576.6)
	Week 12	5983.5	(4788.9, 7476.1)	5516.5	(4522.2, 6729.5)
9V	Day 1	516.9	(417.9, 639.4)	418.8	(330.0, 531.5)
	Day 30	2836.3	(2311.5, 3480.4)	2133.9	(1721.8, 2644.5)
	Week 12	2454.8	(2008.7, 3000.0)	1929.9	(1567.7, 2375.7)
14	Day 1	297.4	(221.5, 399.2)	327.8	(243.0, 442.2)
	Day 30	3508.7	(2730.6, 4508.5)	3000.3	(2350.0, 3830.5)
	Week 12	3634.0	(2935.6, 4498.5)	2539.3	(1960.6, 3288.9)
18C	Day 1	145.1	(118.0, 178.5)	162.9	(131.8, 201.2)
	Day 30	3002.2	(2435.5, 3700.8)	1560.3	(1213.8, 2005.6)
	Week 12	2511.5	(1958.7, 3220.3)	1753.8	(1428.6, 2153.1)
19A	Day 1	219.9	(165.5, 292.1)	283.2	(212.5, 377.3)
	Day 30	4240.7	(3415.4, 5265.3)	3715.9	(2949.2, 4681.8)
	Week 12	3358.1	(2679.6, 4208.4)	3300.3	(2638.7, 4127.7)
19F	Day 1	203.7	(164.2, 252.6)	239.4	(188.9, 303.4)
	Day 30	2438.6	(1972.7, 3014.6)	2042.0	(1618.9, 2575.5)
	Week 12	2230.7	(1803.6, 2759.0)	1994.1	(1630.7, 2438.4)
23F	Day 1	76.2	(58.7, 99.0)	86.3	(65.6, 113.6)
	Day 30	1757.4	(1276.1, 2420.2)	1787.0	(1309.9, 2437.9)
	Week 12	1641.2	(1217.2, 2212.9)	1266.5	(944.3, 1698.5)
22F	Day 1	59.1	(37.7, 92.7)	62.9	(40.0, 98.8)
	Day 30	3943.7	(3049.2, 5100.5)	109.3	(66.2, 180.3)
	Week 12	3399.9	(2697.6, 4285.0)	2952.7	(2207.7, 3949.1)
33F	Day 1	1783.2	(1338.3, 2376.0)	1623.4	(1241.1, 2123.5)
	Day 30	11342.4	(9184.3, 14007.6)	1807.6	(1357.3, 2407.3)
	Week 12	10576.3	(8383.1, 13343.4)	11926.3	(9085.9, 15654.6)

Source: Adapted from STN 125741.0, P018V114, Table 11-5. N: #participants in PPAS, CI: confidence interval.

Reviewer Comments: *When PPV23 was administered after either PCV15 or PCV13 OPA GMTs were numerically lower for most serotypes. However, the OPA GMT CIs overlapped for all 15 serotypes at Day 30 and Week 12 within each vaccine group. The benefit of administration of PPV23 can be observed for serotypes 22F and 33F in the PCV13 group. OPA titers for the additional serotypes in PPV23 were not evaluated.*

6.7.11.3 Subpopulation Analyses

PCV15 was immunogenic within each age subgroup (18 to 49 and ≥50 years of age). PCV15 was immunogenic in two of the three CD4+ T-cell count subgroups (≥200 to <500 cells/μL and ≥500 cells/μL). In both study groups, GMTs and GMCs at Day 30 were generally higher in participants with CD4+ T-cell counts ≥500 cells/μL than in participants with lower CD4+ T-cell counts. The number of participants in the CD4+ T-cell subgroup ≥50 to <200 was too low in both study groups to determine

immunogenicity in this group. Analyses of immunogenicity by gender, race, and ethnicity were generally consistent with those in the overall study population.

6.7.11.4 Dropouts and/or Discontinuations

Missing immunogenicity data were not imputed. No test or search for outliers were performed.

6.7.11.5 Exploratory and Post Hoc Analyses

Exploratory Objective #1: Comparisons of OPA and IgG between PCV15 and PCV13

OPA GMTs were generally comparable between the 2 vaccination groups for the 13 shared serotypes and higher in PCV15 for serotypes 22F and 33F.

Exploratory Objective #2: Comparisons of OPA GMTs and IgG GMCs following PPV23

OPA GMTs and IgG GMCs were generally comparable between the 2 vaccination groups for all 15 serotypes.

Exploratory Objective #3: Percentages of participants with a ≥4-fold increase from Day 1 to Day 30

PCV15 was immunogenic for all 15 serotypes contained in the vaccine and PCV13 was immunogenic for the 13 serotypes contained in the vaccine as assessed by GMFRs and proportions of participants with a ≥4-fold increase from Day 1 to Day 30. The majority of participants in both groups demonstrated a ≥4-fold increase in OPA titers.

Exploratory Objective #4: Percentages of participants with a ≥4-fold increase from Day 1 to 30 days postvaccination with PPV23

PCV15 was immunogenic for all 15 serotypes contained in the vaccine and PCV13 was immunogenic for the 13 serotypes contained in the vaccine as assessed by GMFRs and proportions of participants with a ≥4-fold increase from Day 1 to Week 12. GMFRs at week 12 were generally comparable with those observed at Day 30. The majority of participants in both groups demonstrated a ≥4-fold increase in OPA titers.

6.7.12 Safety Analyses

6.7.12.1 Methods

See Section 6.7.2.

6.7.12.2 Overview of Adverse Events

Safety Overview

The following table provides an overview of the rates of adverse events during the study period.

Table 45. Proportion of Participants Reporting an Adverse Event Following Pneumococcal Conjugate Vaccination, All Participants as Treated, Study V114-018

AE Type: Monitoring Period*	PCV15 N=152 n (%)	PCV13 N=150 n (%)
Immediate AEs: 30 minutes	5 (3.3)	12 (8.0)
Solicited injection site AEs: 5 days	94 (61.8)	80 (53.3)
Solicited systemic AEs: 14 days	49 (32.2)	39 (26.0)
Temperature ≥38.0°C: 5 days[1]	2 (1.3)	1 (0.7)
Unsolicited AEs: 14 days	35 (23.0)	33 (22.0)

AE Type: Monitoring Period*	**PCV15 N=152 n (%)**	**PCV13 N=150 n (%)**
SAEs: 2 months	3 (2.0)	0 (0.0)
Deaths: 2 months	0 (0.0)	0 (0.0)

Source: Study V114-018 Clinical Study Report including Table 12-1, Table 12-3, Table 12-11.
PCV15: 15-valent pneumococcal conjugate vaccine.
%: n/N. n: #participants who experienced the relevant type of AE; N: #participants in All Participants as Treated Population (APaT).
AE: Adverse event. SAE: Serious adverse event.
* Monitoring Period: time interval that the relevant type of AE was monitored for postvaccination.
[l] Percentages are calculated based on the number of participants with temperature data (N=152 in the PCV15 group and N=150 in the PCV13 group).

The majority of participants in both groups experienced at least 1 AE (PCV15: 73.0%; PCV13: 62.7%). The proportions of participants who experienced SAEs were low in both groups (PCV15: 2.0%; PCV13: 0.0%) with none determined to be vaccine related.

Solicited Adverse Reactions
The following table includes the proportion of participants in the PCV15 and PCV13 groups who reported any, Grade 1, Grade 2, or Grade 3 solicited reactions on the VRC for the 5 days postvaccination for local reactions and fever, and 14 days postvaccination for systemic reactions based on the APaT Set. The solicited AR data presented below reflect VRC information as assessed and revised by the investigators (see Section 6.2.7 for further details).

Table 46. Intensity Grading of Adverse Events

--	**PCV15 (N=1134) (% = n/N)**	**PCV13 Group (N=378) (% = n/N)**
Local (injection site)	--	--
Injection site pain	--	--
Total	57.2%	51.3%
Mild	48.0%	48.7%
Moderate	9.2%	2.7%
Injection site erythema	--	--
Total	4.6%	3.3%
NA (0 to ≤2.4cm)	2.6%	2.7%
Grade 1 (>2.4 to ≤5.0cm)	1.3%	0.7%
Unknown	0.7%	0.0%
Injection site swelling	--	--
Total	11.8%	4.0%
NA (0 to ≤2.4cm)	6.6%	3.3%
Grade 1 (>2.4 to ≤5.0cm)	3.9%	0.7%
Grade 2 (>5.0 to ≤7.4cm)	0.7%	0.0%
Grade 2 (>7.4 to ≤10.0cm)	0.7%	0.0%
Systemic	--	--
Arthralgia	--	--
Total	3.3%	4.0%
Mild	2.6%	2.0%
Moderate	0.7%	2.0%
Fatigue	--	--
Total	20.4%	13.3%
Mild	17.1%	12.0%
Moderate	3.3%	1.3%

--	PCV15 (N=1134) (% = n/N)	PCV13 Group (N=378) (% = n/N)
Headache	--	--
Total	13.2%	9.3%
Mild	9.9%	6.7%
Moderate	2.6%	2.7%
Severe	0.7%	0.0%
Myalgia	--	--
Total	12.5%	9.3%
Mild	8.6%	8.0%
Moderate	3.9%	1.3%
Fever	--	--
<100.4 °F	98.7%	99.3%
≥100.4 °F and <102.2 °F	1.3%	0.7%

Source: Adapted from STN 125741.0, P018V114 Table 12-7 Participants With Select Solicited Adverse Reactions by Maximum Intensity (Incidence >0% in One or More Vaccination Groups). #n: #participants with available data for relevant endpoint, N= #participants in SafAS.
*Grade 3 (pain, myalgia, headache, malaise): significant, prevents daily activity.

The most common unsolicited AEs between both groups were: *Infections and infestations* (1.1% and 0.8%), *Nervous system disorders* (0.5% and 0.3%), *Gastrointestinal disorders* (0.4% and 0.5%), and *Psychiatric disorders* (0.3% and 0.5%).

Subpopulation Analyses
Within each study group, participants whose race was "multiple" experienced generally higher proportions of AEs than participants who were Asian, Black or African American, or White. Within each study group, generally higher proportions of participants with solicited AEs were observed among participants who were Hispanic or Latino compared with participants who were not Hispanic or Latino. Safety results observed within each sex and CD4+ T-cell count subgroup were generally consistent with those of the overall population.

6.7.12.3 Deaths
There were no deaths reported for this study.

6.7.12.4 Nonfatal Serious Adverse Events
During the analysis period, 3 participants reported one or more nonfatal SAEs; all were in the PCV15 group. Proportions of reported SAEs were 2.0% in the PCV15 group and 0.0% in the PCV13 group. Proportions of participants with SAEs following vaccination with PPV23 were similar between study groups with 1.3% in the PCV15 group and 4.1% in the PCV13 group.

One participant reported a non-fatal SAE within the 30 days after PCV13 vaccination:

- PCV15: 51-year-old with a history of HIV infection, pain in extremity, gout, and peripheral neuropathy developed left-sided knee pain and swelling on Day 23 and was diagnosed with bilateral pyrophosphate chondrocalcinosis leading to hospitalization on Day 26 with resolution on Day 36.

One participant reported a non-fatal SAE within the 30 days after PPV23 vaccination:

- PCV13: 60-year-old with a history of HIV infection, herpes zoster, and atopic dermatitis developed fever, left facial swelling and rash to the face and neck on Day 86 (Day 29 postvaccination PPV23). He was admitted to the hospital on Day 89 and diagnosed with herpes zoster affecting the left eye. He had resolution of his symptoms on Day 91 and was discharged from the hospital.

None of the SAEs were considered by the investigator or this reviewer to be related to study vaccine.

6.7.12.6 Clinical Test Results
The mean change from baseline in CD4+ T-cell count at Day 30 and Week 12 was <15 cells/µL in both study groups. The proportion of participants with undetectable plasma HIV RNA was similar at screening, Day 30, and Week 12 within each study group.

6.7.12.7 Dropouts and/or Discontinuations
No participants discontinued study vaccine due to an AE.

6.7.13 Study Summary and Conclusions

In this descriptive study that enrolled pneumococcal vaccine-naïve, HIV-infected adults, PCV15 had a safety profile generally comparable to PCV13. PCV15 induced OPA GMTs and IgG GMCs antibodies for all 15 pneumococcal serotypes at 30 days postvaccination compared to baseline. After sequential administration with PPV23, OPA GMTs observed at 30 days after PPV23 vaccination were numerically similar across the two vaccination groups for all 15 serotypes contained in PCV15. These findings were summarized in Section 8.6 (Individuals at Increased Risk for Pneumococcal Disease) of the USPI.

7. Integrated Overview of Efficacy

The Applicant did not conduct an integration of immunogenicity data, as outlined in the Statistical Analyses Plan (July 9, 2019) that was submitted to the IND and agreed upon with CBER. The application is based on comparisons of OPA antibody responses to those of PCV13, the pneumococcal conjugate vaccine for which effectiveness for the prevention of invasive pneumococcal disease caused by vaccine serotypes was demonstrated in adults (Prevnar 13, USPI). Formal evaluations of OPA antibody responses via hypothesis testing of PCV15 compared to PCV13 in non-inferiority analyses were performed with individual studies as described in the study objectives for V114-019, V114-020, V114-021). All three studies with formal hypothesis testing (V114-019, V114-020, V114-021) met the protocol-defined statistical criteria for success for PCV15 when compared to PCV13.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

Safety data included in this application and reviewed to characterize the safety profile of the final formulation of PCV15 were from the following sources:

Main trials: V114-020, V114-019, V114-021, V114-016, V114-017, V114-018, V114-007

The Applicant had integrated safety data across Phase 3 studies V114-020, V114-019, and V114-016 because of similarities in study design and study population that included only pneumococcal vaccine-naïve adults ≥50 years of age.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

There were 7 studies (V114-020, V114-019, V114-021, V114-016, V114-017, V114-018, V114-007) included in this application to describe the safety profile of PCV15. The safety database across these 7

clinical trials were conducted in adults ≥18 years of age and included 5630 PCV15 recipients and 1808 PCV13 recipients who were enrolled in 18 countries.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Across these 7 studies, 23% were 18 to 49 years, 77% were ≥50 years, 45% were ≥65 years, and ~9% were ≥75 year, with a median age of 62 years (range: 18 to 98 years). Overall, ~55% were female and ~72% were White, while Black/African American, American Indian/Alaska Native, Asian were each between ~7% and 10% of the overall population. There were ~20% Hispanic/Latino participants across studies. The majority of PCV15 recipients were enrolled at sites in North America (~63%) and Europe (22%), followed by South America (5.1%), Australia (4.8%), Asia (4.7%), and Africa (0.4%). The PCV15 exposure by age cohort is included in the table below.

Table 47. PCV15 Exposure by Age Cohort

Age Group	Studies	Number of Participants
18 years and above	All Studies	5630
18-49 years	V114-017, V114-018	1241
50-64 years	V114-020, V114-019, V114-021, V114-016	1911
65-74 years	V114-020, V114-019, V114-021, V114-016, V114-007	1999
≥75 years	V114-020, V114-019, V114-021, V114-016, V114-007	479

8.2.3 Categorization of Adverse Events

Safety data collected across the main 3 studies (V114-020, V114-019, and V114-016) included the following:

- *Clinical Assessments*: physical exam before vaccination (Day 1)
- *AE Monitoring:*
  - *Immediate AEs:* 30 minutes postvaccination observation period
  - Solicited Local
    - Injection site swelling, redness, pain. Days 1-5 postvaccination
  - Solicited Systemic:
    - Muscle pain, joint pain, headache, fatigue. Days 1-14 postvaccination
  - Fever
    - Defined as oral/tympanic: ≥100.4°F, axillary/temporal: ≥99.4°F
    - Temperature reported from Day 1 through Day 14; recorded in eVRC on Days 1-5 postvaccination
  - Any other unsolicited injection site or systemic AEs. Days 1-14 postvaccination
  - Concomitant medications and non-study vaccinations. Days 1-14 postvaccination.
  - SAEs, AEs leading to withdrawal: Day 1 through Month 6 postvaccination.
  - Pregnancy testing conducted prior to vaccination

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

Safety data were not pooled across studies for the proportion of participants reporting solicited adverse reactions, however adverse event data, including SAEs in comparable study populations were evaluated together. Of note, the duration of the safety follow-up period for serious adverse events postvaccination with PCV15 was 1 month in V114-007; 2 months following PCV15 in V114-018; 6 months in Studies V114-019, V114-020, V114-017 and V114-021; and 12 months in Study V114-016.

8.4 Safety Results

8.4.1 Deaths

Across the 3 integrated studies in participants ≥50 years of age, there were 4 deaths in PCV15 recipients and 1 death in PCV13 recipients. There were 11 participants[8] who died during the safety follow-up period across all 7 studies, including 8 PCV15 recipients and 3 PCV13 recipients. All deaths occurred more than 40 days following study vaccinations. The case narratives for all deaths were reviewed individually; none were considered related to study vaccination by the review team.

8.4.2 Nonfatal Serious Adverse Events

Case narratives for SAEs reported by PCV15 participants are described in the review of individuals studies (Section 6). The rates of reported SAEs were low and the types of SAEs across groups were similar and included clinical events that are often reported in the populations evaluated. The case narratives for all SAEs were reviewed individually; none were considered related to study vaccination by the review team.

8.4.3 Study Dropouts/Discontinuations

8.4.4 Common Adverse Events and Solicited Adverse Events

Safety data was pooled for the following 3 studies: V114-020, V114-019, V114-016 that enrolled 3032 PCV15 participants and 1154 PCV13 recipients ≥50 years. Across these 3 studies, the rates of AEs were comparable to each study individually; ~69% of PCV15 recipients and 58% of PCV13 recipients reported ≥1 solicited adverse reaction. The most frequently reported solicited ARs included injection site pain (PCV15: 58.2% vs PCV13: 45.1%), fatigue (PCV15: 20.2% vs PCV13: 18%), and myalgia (PCV15: 19.5% vs PCV13: 14.8%). For all 3 studies, the proportion of participants reporting ≥1 AE was 72.3% for PCV15 vaccine recipients and 62.2% for PCV13 recipients, of which the most frequently reported SOCs were *General disorders and administration site conditions* (PCV15: 67% vs PCV13: 55.2%), *Musculoskeletal and connective tissue disorders* (PCV15: 24.4% vs PCV13: 18.8%), followed by *Nervous system disorders* (PCV15: 15.2% vs PCV13: 15.1%).

8.4.8 Adverse Events of Special Interest

Review of adverse events of clinical interest (non-serious AEs) did not identify any safety concerns by the CBER clinical reviewers.

8.6 Safety Conclusions

In a total of 7 randomized clinical trials conducted in 18 countries, 5630 participants received one dose of PCV15 and provided postvaccination safety data. Higher observed rates and severity of local and systemic adverse reactions were observed following PCV15 when compared to PCV13, however, the overall reactogenicity profile was similar to that of other licensed vaccines in the evaluated these age cohorts. No additional safety concerns were identified when a single dose of PCV15 was administered to adults ≥18 years of age, with or without prior pneumococcal vaccine exposure.

[8] One additional PCV15 recipient died after the safety follow-up period (death not considered related to study vaccination).

9. Additional Clinical Issues

9.1 Special Populations

Section 8 of the prescribing information included the information in Sections 9.1.1 through 9.1.5 of this memo, below.

9.1.1 Human Reproduction and Pregnancy Data

Risk Summary
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 24% and 15% to 20%, respectively.

There are no adequate and well-controlled studies of PCV15 in pregnant women, and human data available from clinical trials with PCV15 have not established the presence or absence of vaccine associated risk during pregnancy. There are no adequate and well-controlled studies of PCV15 in pregnant women, and human data available from clinical trials with PCV15 have not established the presence or absence of vaccine associated risk during pregnancy.

Developmental toxicity studies have been performed in female rats administered PCV15 on four occasions; twice prior to mating, once during gestation and once during lactation. Each dose was the adult human dose. These studies revealed no evidence of harm to the fetus due to PCV15 (see *Animal Data)*.

Animal Data
Developmental toxicity studies have been performed in female rats. In these studies, female rats received PCV15 (32 mcg/rat/dose) a human dose of PCV15 by intramuscular injection on day 28 and day 7 prior to mating, and on gestation day 6 and on lactation day 7. There was no evidence of embryofetal lethality or fetal malformations and variations and no adverse effect on pup weights was observed.
No vaccine related fetal malformations or variations were observed. No adverse effect on pup weight up to post-natal day 21 were noted.

9.1.2 Use During Lactation

Risk Summary
Human data are not available to assess the impact of PCV15 on milk production, its presence in breast milk, or its effects on the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PCV15 and any potential adverse effects on the breastfed child from PCV15 or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

> ***Reviewer Comment:*** *The information provided in the BLA regarding pregnancy and lactation was reviewed in consultation with the CBER toxicology reviewer for this BLA and found to be accurate and appropriate for inclusion in the prescribing information.*

9.1.3 Pediatric Use and PREA Considerations

The proposed indication is for active immunization for the prevention of invasive disease 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 safety and effectiveness of PCV15 in individuals younger than 18 years of age have not yet been established. As specified by the Pediatric Research Equity Act (PREA) the

assessment of PCV15 in pediatric age cohorts is required. The Applicant requested that the assessment of PCV15 in pediatric individuals be addressed as follows:

Partial Waiver
Pediatric age group to be waived: 0 to <6 weeks of age.
- Statutory reason for waiving pediatric assessment requirements:
  Section 505B(a)(B)(iii): The product does not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and is not likely to be used.

- Justification for waiver:
  Due to limitations of the neonatal immune response, initiating vaccination at 0 to<6 weeks of age with PCV15 will not provide a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age.

  With the exception of Hepatitis B vaccine, for which a birth dose is routinely recommended to prevent perinatal transmission of hepatitis B virus, infant immunizations in the US are generally not administered before 6 weeks of age

Partial Deferral
Pediatric age group to be deferred: 6 weeks through 17 years of age (<18 years).
- Statutory reason for deferring pediatric assessment requirements:
  Section 505B(a)(3)(A)(i): The biological product is ready for approval for use in individuals 18 years of age and older before all pediatric studies are complete

The Applicant is conducting 4 studies (V114-029, V114-024, V114-027, V114-030) in children 6 weeks through 17 years of age as part of their pediatric clinical development plans. The review team concurred with the Applicant's proposal that these 4 studies are sufficient to support a pediatric assessment in the US for this age group. Please see Section 11.6 of the clinical review memo for timelines for conducting these studies.

The Applicant's requests for partial waiver and partial deferral of the required pediatric assessment was presented to FDA's Pediatric Review Committee on May 4, 2021. The committee agrees with the requests, including partial waiver, partial deferral and the proposed timelines for each study completion and submission.

9.1.4 Immunocompromised Patients

Adults with HIV infection
In Study V114-018, the safety and immunogenicity of PCV15 were descriptively evaluated in pneumococcal vaccine-naïve HIV-infected adults ≥18 years of age, with CD4+ T-cell count ≥50 cells per µL and plasma HIV RNA value <50000 copies/mL. Participants were randomized to receive PCV15 (n=152) or PCV13 (n=150), followed by PPV23 two months later. Anti-pneumococcal opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) were higher after administration of PCV15, compared to pre-vaccination, for the 15 serotypes contained in PCV15. After sequential administration with PPV23, OPA GMTs observed at 30 days after PCV15 vaccination were numerically similar between the two vaccination groups for all 15 serotypes contained in PCV15. The safety profile of PCV15 was similar between the two vaccination groups. The effectiveness of PCV15 in HIV-infected individuals has not been evaluated.

9.1.5 Geriatric Use

Of the 4344 individuals ages 50 years and older who received PCV15, 2470 (56.9%) were 65 years of age and older, and 479 (11.0%) were 75 years of age and older.

10. Conclusions

In healthy immunocompetent adults ≥50 years without prior history of pneumococcal vaccination, immunogenicity (inferred effectiveness) was demonstrated in Study V114-019 and lot consistency was demonstrated in Study V114-020. Study V114-019 demonstrated non-inferiority for the 13 shared serotypes and statistically significantly greater immune responses for serotypes 22F, 33F, and 3 following a single dose of PCV15 compared to a single dose of PCV13. In pneumococcal vaccine-naïve, immunocompetent adults 18 through 49 years of age with or without risk factors for pneumococcal disease, the safety profile of PCV15 was similar to that of PCV13 and support inclusion in the USPI.

In Study V114-021, noninferior OPA responses were demonstrated for the 15 serotypes in PCV15 when PCV15 was administered concomitantly with a quadrivalent influenza vaccine (QIV) compared to when PCV15 was administered one month after QIV. In addition, non-inferior HAI responses were demonstrated for all 4 influenza strains when a QIV (Fluarix) was administered concomitantly with PCV15 compared to when QIV was administered one month prior to PCV15.

Exploratory analyses of the impact of prior PPV23 vaccination on OPA responses following pneumococcal conjugate vaccinations (PCV15 or PCV13) demonstrated differences in the proportion of participants achieving ≥4-fold rise in OPA titers based on time since receipt of PPV23, with a greater proportion of participants ages 65 to 74 years achieving ≥4-fold rise when there was a longer duration of time elapsed since PPV23 receipt (>3 years).

Across all studies, PCV15 was moderately more reactogenic following a single dose when compared to a single dose of PCV13, however overall safety profiles were comparable across groups. No important safety concerns were identified in the clinical review, and no safety signals were detected that would require further assessment in post-marketing safety studies.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 48. Risk-Benefit Assessment of Primary Dose Vaccination With PCV15, Pneumococcal Conjugate Vaccine for Use in Individuals 18 Years and Older

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *S. pneumoniae* can cause meningitis and bacteremia in adults, resulting in substantial morbidity and mortality. Pneumococcal meningitis commonly results in neurologic sequelae, including hearing loss and brain damage. • Adults with decreased immune function, functional or anatomic asplenia, chronic heart, pulmonary, liver or renal disease, cigarette smoking, alcoholism, diabetes mellitus, cerebrospinal fluid leak, and cochlear implant are at risk of serious pneumococcal disease.	• Invasive pneumococcal disease (IPD) is a serious and life-threatening condition that can result in significant morbidity and mortality in adults ≥18 years of age. • The risk of serious pneumococcal disease is greatest in immunocompromised adults and immunocompetent adults with certain risk factors.
Unmet Medical Need	• Prevnar 20, Prevnar 13, and Pneumovax 23 are three pneumococcal vaccines approved for use in persons ≥18 years of age in the US. PCV15 includes 13 serotypes in common with PCV13 and 15 serotypes in common with PPV23. • IPD caused by the 2 unique serotypes included in PCV15 but not PCV13 represents 14% of the non-PCV13 IPD burden in adults ≥65 years of age in 2017-2018, despite ACIP recommendation for PPV23 administration to adults ≥65 years of age. • Effective antibiotic therapy is available for the treatment of IPD in adults; however, antibiotic resistance is increasingly common, making treatment more difficult.	• In adults ≥18 years of age, there is an unmet medical need for effective prevention of invasive pneumococcal disease caused by serotypes 22F and 33F, which are included in PCV15 but not PCV13. • PCV13 serotype 3 performance has not been consistent with other PCV13 serotypes. PCV15 induced OPA GMT to serotype 3 that was statistically superior compared to that induced by PCV13. • As a result of conjugation to the carrier protein CRM_{197}, PCV15 is thought to elicit a T-cell dependent immune response, which is characterized by immunologic memory, affinity maturation, and an antibody response of longer duration than is achieved by the unconjugated polysaccharide vaccine, PPV23.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• The immunogenicity of PCV15, administered as a single dose, was evaluated in 7 randomized, double-blind clinical studies, altogether a total of 7438 adults (5630 PCV15 recipients and 1808 PCV13 recipients) 18 years and older, compared to PCV13. • For all age groups, PCV15 effectiveness against IPD was inferred from OPA responses compared to a single dose of PCV13: ✓ In pneumococcal vaccine-naïve adults ≥50 years of age - For 13 common serotypes: non-inferiority of OPA GMTs after a single dose of PCV15 to the corresponding OPA GMTs after a single dose of PCV13, and - For serotypes 22F, 33F, and 3: statistically superior OPA GMTs after a single dose of PCV15 compared to corresponding OPA GMTs after a single dose of PCV13 [22F and 33F are not contained in PCV13] ✓ In pneumococcal vaccine-naïve adults 18-49 years of age, OPA GMTs after PCV15 or PCV13 vaccination were generally comparable for the 13 common serotypes, and numerically higher for serotypes 22F and 33F after PCV15 compared to PCV13. Same conclusion for pneumococcal vaccine-experienced adults ≥65 years old. • Immunological interference was not observed when PCV15 was co-administered with a seasonal inactivated influenza vaccine [Fluarix] based on pneumococcal OPA GMT and HAI GMT antibody responses.	• The immunogenicity data support the effectiveness of PCV15 to prevent vaccine-serotype IPD.
Risk	• The rates of solicited injection site and systemic adverse reactions (AR) after PCV15 were as follows: local pain (67-76%), local erythema (11-15%), local swelling (15-22%), fatigue (22-34%), myalgia (27-29%), and headache (19-27%). Most solicited ARs were reported as mild/Grade 1 (<50%) or moderate/Grade 2 (<20%) in adults. Solicited adverse reactions reported as severe were uncommon and accounted for < 1%.	• The data from PCV15 clinical studies adequately characterize the safety of PCV15. The safety profile is acceptable of PCV15 is acceptable for its intended use.
Risk Management	• See "Clinical Benefit" and "Risk" sections above.	• The reactogenicity of PCV15 described in the prescribing information and routine pharmacovigilance adequately mitigate the risks. The reactogenicity of PCV15 described in the prescribing information and routine pharmacovigilance adequately mitigate the risks.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of PCV15 in individuals 18 years and older in preventing invasive pneumococcal disease is favorable compared to the risks associated with vaccination. Data submitted to this original BLA establish the safety and effectiveness of single-dose vaccinations in individuals 18 years of age and older. The safety of PCV15 is adequately described in the prescribing information, and the Applicant's routine pharmacovigilance is adequate for monitoring AEs postmarketing.

11.3 Discussion of Regulatory Options

PCV15 induces OPA against the serotypes contained within the vaccine. The application is based on immunobridging of OPA immune responses to PCV13, the pneumococcal conjugate vaccine for which effectiveness for the prevention of invasive pneumococcal disease by vaccine serotypes was demonstrated in adults. Immunologic non-inferiority to a US licensed pneumococcal conjugate vaccine, PCV13 based on OPA response rates was used to establish the effectiveness of this newer generation pneumococcal conjugate vaccine.

PCV15 contains two serotypes (22F, 33F) not contained in Prevnar 13, which offer additional clinical benefit relative to PCV13 based on clinical trial data. For serotype 3, for which PCV13 performance has not been consistent with other PCV13 vaccine serotypes, PCV15 may also provide additional protection against IPD, based on OPA antibody responses when compared to those elicited by PCV13.

11.4 Recommendations on Regulatory Actions

The clinical data provided in the application support the safety and effectiveness of PCV15 in individuals 18 years of age and older in preventing invasive pneumococcal disease.

11.5 Labeling Review and Recommendations

The proprietary name VAXNEUVANCE® was reviewed by the Advertising and Promotional Labeling Branch and found acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

Studies that the Applicant is required to conduct following licensure are listed below and include the following 4 PREA deferred studies:

1. Deferred Study V114-029: to evaluate the safety and immunogenicity of PCV15 in infants and toddlers as a 4-dose schedule (2, 4, 6 and 12-15 months of age)
   Final Protocol Submission: February 22, 2019
   Study Completion Date: December 31, 2021
   Final Report Submission: April 30, 2022

2. Deferred Study V114-024: to evaluate the safety and immunogenicity of PCV15 when given as catch-up vaccination in children 7 months to 17 years of age
   Final Protocol Submission: December 5, 2019
   Study Completion Date: September 30, 2021
   Final Report Submission: December 31, 2021

3. Deferred Study V114-027: to evaluate the safety and immunogenicity of PCV15 when administered to infants and toddlers who previously received PCV13 at 2, 4 or 6 months of age

Final Protocol Submission: August 16, 2018
Study Completion Date: April 30, 2021
Final Report Submission: July 31, 2021

4. Deferred Study V114-030: to evaluate the safety and immunogenicity of PCV15 in HIV-infected children 6 years through 17 years of age
   Final Protocol Submission: December 5, 2019
   Study Completion Date: August 31, 2022
   Final Report Submission: December 31, 2022