

### BLA Clinical Review Memorandum

Application Type	Efficacy Supplement to Biologics License Application
STN	125741/6
CBER Received Date	September 30, 2021
PDUFA Goal Date	July 1, 2022
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	Yes
Reviewer Name	Mark Connelly, MD Clinical Reviewer Clinical Review Staff, DVRPA, OVRR, CBER
Review Completion Date / Stamped Date	June 17, 2022
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Applicant	Merck & Co., Inc.
Established Name	Pneumococcal 15-valent Conjugate Vaccine
Trade Name	VAXNEUVANCE
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Each dose (0.5 mL) contains 4 mcg PS of serotype 6B 2 mcg PS for each serotype: 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, & 33F 125 mcg aluminum (AlPO <sub>4</sub> ) as adjuvant
Dosage Forms and Routes of Administration	Dosage form: Suspension Route of Administration: Intramuscular
Dosing Regimen	Infants: 4-dose Children/adolescents: Single dose
Indication and Intended Populations	Indication: active immunization for the prevention of invasive disease caused by <i>Streptococcus pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F in infants, children, and adolescents from 6 weeks through 17 years of age (prior to 18th birthday)
Orphan Designated (Yes/No)	No

## Table of Contents

<b>List of Abbreviations.....</b>	<b>5</b>
<b>1. Executive Summary .....</b>	<b>7</b>
1.1 Demographic Information: Subgroup Demographics and Analysis Summary .....	10
1.2 Patient Experience Data.....	10
<b>2. Clinical and Regulatory Background.....</b>	<b>10</b>
2.1 Disease or Health-Related Condition(s) Studied.....	10
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) .....	11
2.3 Safety and Effectiveness of Pharmacologically Related Products.....	11
2.4 Previous Human Experience with the Product (Including Foreign Experience).....	11
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission .....	11
<b>3. Submission Quality and Good Clinical Practices .....</b>	<b>12</b>
3.1 Submission Quality and Completeness.....	12
3.2 Compliance with Good Clinical Practices and Submission Integrity .....	12
3.3 Financial Disclosures.....	12
<b>4. Significant Effectiveness/Safety Issues Related to Other Review Disciplines .....</b>	<b>13</b>
4.1 Chemistry, Manufacturing, and Controls .....	13
4.2 Assay Validation .....	13
4.3 Nonclinical Pharmacology/Toxicology.....	13
4.4 Clinical Pharmacology .....	13
4.4.1 Mechanism of Action .....	13
4.5 Statistical.....	14
4.6 Pharmacovigilance .....	14
<b>5. Sources of Clinical Data and Other Information Considered in the Review .....</b>	<b>14</b>
5.1 Review Strategy .....	14
5.2 BLA Documents That Serve as the Basis for the Clinical Review.....	14
5.3 Overview of Clinical Trials.....	15
5.5 Literature Reviewed.....	16
<b>6. Discussion of Individual Studies/Clinical Trials .....</b>	<b>17</b>
<b>6.1 Trial #1: V114-029.....</b>	<b>17</b>
6.1.1 Objectives (as stated in study protocol V114-029, Amendment 2).....	17
6.1.2 Design Overview.....	23
6.1.3 Population.....	23
6.1.4 Study Treatments or Agents Mandated by the Protocol .....	24
6.1.5 Directions for Use .....	26
6.1.6 Sites and Centers .....	26
6.1.7 Surveillance/Monitoring.....	26
6.1.8 Endpoints and Criteria for Study Success .....	29
6.1.9 Statistical Considerations & Statistical Analysis Plan.....	29
6.1.10 Study Population and Disposition .....	33
6.1.11 Immunogenicity Analyses .....	37
6.1.12 Safety Analyses.....	46
6.1.13 Study Summary and Conclusions.....	52
<b>6.2 Trial #2: V114-031.....</b>	<b>53</b>
6.2.1 Objectives (as stated in study protocol V114-031, Amendment 1).....	53
6.2.2 Design Overview.....	54

6.2.3 Population.....	54
6.2.4 Study Treatments or Agents Mandated by the Protocol.....	54
6.2.5 Directions for Use .....	55
6.2.6 Sites and Centers .....	55
6.2.7 Surveillance/Monitoring.....	55
6.2.8 Endpoints and Criteria for Study Success .....	55
6.2.9 Statistical Considerations & Statistical Analysis Plan.....	55
6.2.10. Study Population and Disposition .....	56
6.2.11 Immunogenicity Analyses .....	58
6.2.12 Safety Analyses.....	62
6.2.13 Study Summary and Conclusions.....	67
<b>6.3 Trial #3: V114-027.....</b>	<b>68</b>
6.3.1 Objectives (as stated in study protocol V114-027, Amendment 0).....	68
6.3.2 Design Overview.....	69
6.3.3 Population.....	70
6.3.4 Study Treatments or Agents Mandated by the Protocol.....	70
6.3.5 Directions for Use .....	70
6.3.6 Sites and Centers .....	70
6.3.7 Surveillance/Monitoring.....	71
6.3.8 Endpoints and Criteria for Study Success .....	71
6.3.9 Statistical Considerations & Statistical Analysis Plan.....	71
6.3.10 Study Population and Disposition .....	72
6.3.11 Immunogenicity Analyses .....	74
6.3.12 Safety Analyses.....	79
6.3.13 Study Summary and Conclusions.....	85
<b>6.4 Trial #4: V114-024.....</b>	<b>85</b>
6.4.1 Objectives (as stated in study protocol V114-024, Amendment 0).....	86
6.4.2 Design Overview.....	87
6.4.3 Population.....	87
6.4.4 Study Treatments or Agents Mandated by the Protocol.....	87
6.4.5 Directions for Use .....	88
6.4.6 Sites and Centers .....	88
6.4.7 Surveillance/Monitoring.....	88
6.4.8 Endpoints and Criteria for Study Success .....	88
6.4.9 Statistical Considerations & Statistical Analysis Plan.....	88
6.4.10 Study Population and Disposition .....	89
6.4.11 Immunogenicity Analyses .....	91
6.4.12 Safety Analyses.....	94
6.4.13 Study Summary and Conclusions.....	101
<b>6.5 Trial #5: V114-030.....</b>	<b>101</b>
6.5.1 Objectives (as stated in protocol V114-030, Amendment 0).....	101
6.5.2 Design Overview.....	102
6.5.3 Population.....	103
6.5.4 Study Treatments or Agents Mandated by the Protocol.....	103
6.5.5 Directions for Use .....	104
6.5.6 Sites and Centers .....	104
6.5.7 Surveillance/Monitoring.....	104
6.5.8 Endpoints and Criteria for Study Success .....	104
6.5.9 Statistical Considerations & Statistical Analysis Plan.....	104
6.5.10 Study Population and Disposition .....	105
6.5.11 Immunogenicity Analyses.....	107
6.5.12 Safety Analyses.....	111
6.5.13 Study Summary and Conclusions.....	115
<b>6.6 Trial #6: V114-023.....</b>	<b>115</b>
6.6.1 Objectives (as stated in study protocol V114-023, Amendment 0).....	116

6.6.2 Design Overview.....	116
6.6.3 Population.....	116
6.6.4 Study Treatments or Agents Mandated by the Protocol.....	118
6.6.5 Directions for Use .....	118
6.6.6 Sites and Centers .....	118
6.6.7 Surveillance/Monitoring.....	118
6.6.8 Endpoints and Criteria for Study Success .....	118
6.6.9 Statistical Considerations & Statistical Analysis Plan.....	118
6.6.10 Study Population and Disposition .....	119
6.6.11 Immunogenicity Analyses .....	121
6.6.12 Safety Analyses.....	124
6.6.13 Study Summary and Conclusions.....	126
<b>6.7 Trial #7: V114-008.....</b>	<b>126</b>
6.7.1 Primary Immunogenicity Objective:.....	126
6.7.2 Design Overview.....	127
6.7.11 Immunogenicity Results.....	127
6.7.12 Safety Results .....	127
6.7.13 Study Summary and Conclusion .....	129
<b>7. Integrated Overview of Immunogenicity.....</b>	<b>129</b>
<b>8. Integrated Overview of Safety .....</b>	<b>131</b>
8.1 Safety Assessment Methods .....	131
8.2 Safety Database.....	131
8.2.1 Studies/Clinical Trials Used to Evaluate Safety .....	131
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations.....	131
8.2.3 Categorization of Adverse Events .....	132
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials.....	132
8.4 Integrated Safety Results .....	132
8.5 Safety Conclusions.....	134
<b>9. Additional Clinical Issues.....</b>	<b>134</b>
9.1 Special Populations.....	134
9.1.1 Pediatric Use and PREA Considerations.....	134
9.1.2 Immunocompromised Patients .....	134
<b>10. Conclusions.....</b>	<b>135</b>
<b>11. Risk-Benefit Considerations and Recommendations .....</b>	<b>137</b>
11.1 Risk-Benefit Considerations .....	137
11.2 Risk-Benefit Summary and Assessment .....	139
11.3 Recommendations on Regulatory Actions.....	139
11.4 Labeling Review and Recommendations.....	139

## List of Abbreviations

ACIP: Advisory Committee on Immunization Practices  
AIHA: autoimmune hemolytic anemia  
APaT: all participants as treated  
AE: adverse event  
AMs: amendments  
Anti-PnP: anti-pneumococcal polysaccharide  
AR: adverse reaction  
BIMO: Bioresearch monitoring  
BLA: Biologics License Application  
CBER: Center for Biologics Evaluation and Research  
CDC: Centers for Disease Control  
CI: confidence interval  
COVID-19: disease caused by infection with SARS-CoV-2  
DOD: differential optical depth  
ELISA: enzyme-linked immunosorbent assay  
eVRC: electronic vaccine report card  
FAS: Full Analysis Set  
EGA: estimated gestational age  
GCP: Good Clinical Practice  
GMC: geometric mean concentration  
GMT: geometric mean titer  
(b) (4)  
HiB: *Haemophilus influenzae* type B  
HIV: Human Immunodeficiency Virus  
IgG: immunoglobulin G  
IPD: invasive pneumococcal disease  
IM: intramuscular  
iSAP: integrated statistical analysis plan  
IV: intravenous  
LB: lower bound of the 95% confidence interval  
LLOQ: lower limit of quantification  
mIU: milli-International Units  
mL: milliliters  
MedDRA: Medical Dictionary for Regulatory Activities  
NI: non-inferiority  
OD: optic density  
OPA: opsonophagocytic activity  
PCV: pneumococcal conjugate vaccine, any valency  
PCV7: 7-valent pneumococcal conjugate vaccine, trade name Prevnar  
PCV10: 10-valent pneumococcal conjugate vaccine, ex-US trade name Synflorix  
PCV13: 13-valent pneumococcal conjugate vaccine, trade name Prevnar 13  
PCV15: 15-valent pneumococcal conjugate vaccine, trade name Vaxneuvance  
PCV20: 20-valent pneumococcal conjugate vaccine, trade name Prevnar 20  
PD3: post-dose 3  
PD4: post-dose 4

PIIS: premature infant immunogenicity substudy  
PMR: post-marketing requirement  
PnECL v2.0: pneumococcal electrochemiluminescence assay version 2.0  
PO: by mouth  
PP: Per-Protocol  
PPSV23: 23-valent pneumococcal polysaccharide vaccine, trade name Pneumovax 23  
SAE: serious adverse event  
sBLA: supplement to the Biologics License Application  
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2  
SCD: sickle cell disease  
SOC: System Organ Class as per the Medical Dictionary for Regulatory Activities  
US: United States of America  
USPI: United States prescribing information  
V114: 15-valent pneumococcal vaccine (PCV15), trade name Vaxneuvance  
WHO: World Health Organization

## 1. Executive Summary

A supplement to Biologics License Application (sBLA) 127541 has been submitted by Merck Sharp & Dohme Corp. (subsidiary of Merck & Co., Inc) for candidate pneumococcal 15-valent conjugate vaccine (CRM<sub>197</sub> 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, 2, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 22F, and 33F in infants, children, and adolescents ages 6 weeks through 17 years of age.

The Applicant submitted data from seven clinical studies as part of this sBLA, including six Phase 3 studies 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. Three studies (V114-029, V114-031, V114-027) evaluated the safety and effectiveness of a 4-dose series of PCV15 in pneumococcal vaccine-naïve infants. One study, V114-024, evaluated PCV15 as a 1 to 3 dose series for catch-up immunization for un- and under-vaccinated children 7 months to <18 years of age. Two additional studies (V114-030 and V114-023) evaluated PCV15 in children with HIV infection and sickle cell disease (SCD). One supportive Phase 2 study (V114-008) evaluated 2 different formulations of PCV15, including the proposed final formulation, as a 4-dose series in infants.

### *Immunogenicity Analyses:*

In all six studies, immunogenicity endpoints were used to infer PCV15 effectiveness for the prevention of invasive pneumococcal disease (IPD) in participants 6 weeks to <18 years of age. The PCV15 licensure approach relied on immunologic comparisons to 13-valent pneumococcal conjugate vaccine (Prevnar 13 [PCV13], Wyeth Pharmaceuticals, Inc.) by evaluation of immunoglobulin G (IgG) concentrations following doses 3 and 4 of the 4-dose series in infants and the percentages of participants with IgG concentrations  $\geq 0.35$   $\mu\text{g/mL}$  following dose 3 to each of the 13 serotypes shared by PCV15 and PCV13 using pre-specified non-inferiority criteria. The test level of 0.35  $\mu\text{g/mL}$  was chosen based on the World Health Organization (WHO) recommendation as an immunogenicity bridge to the efficacy against IPD as demonstrated for PCV7 ([WHO, 2013](#)). For the 2 serotypes unique to PCV15, predetermined success criteria compared the IgG responses in PCV15 recipients to the lowest shared serotype response in PCV13 recipients not including the response to serotype 3. Serotype 3 was excluded as the incidence of IPD was not significantly decreased following licensure of PCV13, suggesting potential underperformance of this serotype in PCV13 ([Pilishvili, 2019](#)).

Study V114-029 was the main study evaluating the effectiveness of a 4-dose series of PCV15 in infants ages 6 weeks through 3 months of age at enrollment. For the 13 shared serotypes in PCV15 and PCV13, noninferiority was determined if the lower bound (LB) of the 2-sided 95% CI of the IgG geometric mean concentration (GMC) ratio was  $> 0.5$  for each serotype post-doses 3 and 4, and if the LB of the 2-sided 95% CI of the difference between the proportion of participants in the PCV15 group and the PCV13 group with an IgG response  $\geq 0.35$   $\mu\text{g/mL}$  was  $> 10\%$  for each serotype post-dose 3. For the serotypes unique to PCV15, noninferiority was determined using the same statistical criteria but using the serotypes in the PCV13 group with lowest GMC response and response rate, not including serotype 3, as the comparators. Other secondary immunogenicity objectives evaluated the superiority of the responses to serotypes

22F, 33F, and serotype 3 among PCV15 recipients. For 22F and 33F, the superiority criteria were a LB of the 95% CI >10% for the difference in the seroresponse rates evaluated at  $\geq 0.35$   $\mu\text{g/mL}$  between the PCV15 group and the PCV13 group post-dose 3 for each serotype and a LB of the 95% CI >2.0 for the GMC ratio of the responses of the PCV15 group to the responses of the PCV13 group for each serotype post-doses 3 and 4. For serotype 3, superiority criteria were a LB of the 95% CI >0 for the seroresponse rate evaluated at  $\geq 0.35$   $\mu\text{g/mL}$  and a LB of the 95% CI >1.2 for the GMC ratio of the responses of the PCV15 group compared to the responses of the PCV13 group for each serotype post-doses 3 and 4.

Study V114-029 demonstrated non-inferior IgG responses for the 13 shared serotypes and 2 unique serotypes in PCV15 when compared to responses induced by PCV13. IgG responses to serotypes 22F, 33F and 3 were statistically superior in PCV15 recipients compared to PCV13, which lacks serotypes 22F and 33F. There was no evidence of immunologic interference with the concomitantly administered routine infant vaccines. The pattern of serotype-specific OPA responses, evaluated in a subset of the immunogenicity population, was similar to the pattern of IgG responses.

Study V114-031 descriptively evaluated the IgG responses of PCV15 specifically in pre-term infants born at <37 weeks gestational age. IgG responses to the 13 shared serotypes were generally comparable between PCV15 and PCV13 recipients. PCV15 recipients had greater responses to the two serotypes unique to PCV15. The pattern of serotype-specific OPA responses, evaluated in a subset of the immunogenicity population, were similar to the IgG responses.

Study V114-027 descriptively evaluated the immunogenicity of 4-dose PCV regimens in infants who completed 1 to 3 doses of PCV15 as compared to a 4-dose regimen composed entirely of PCV13 against the 13 shared serotypes. Responses to the 13 shared serotypes were generally comparable across study groups.

Study V114-024 descriptively evaluated the immunogenicity of 1 to 3 doses of PCV15, based on age at enrollment, as compared to PCV13 given to un- or under-vaccinated children 7 months through 17 years of age or children who had received a primary series of PCV7 or PCV10. The immune responses elicited at 30 days following the final dose of the PCV series were generally comparable across study groups for the 13 shared serotypes and higher in the PCV15 group for the 2 serotypes unique to PCV15.

Study V114-030 descriptively evaluated the serotype-specific IgG and OPA responses of single dose of either PCV15 or PCV13 followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) approximately 2 months later in children 6 years through 17 years of age living with HIV infection. The IgG responses elicited against the 13 shared serotypes were generally comparable across study groups following PCV and higher in the PCV15 group against the 2 unique serotypes. Following PPSV23, IgG responses against all 15 serotypes were comparable across study groups. The pattern of OPA responses was similar to the pattern of IgG responses.

Study V114-023 descriptively evaluated the IgG and OPA responses 1 month after a single dose of either PCV15 or PCV13 in children 5 years through 17 years of age with sickle cell disease.



The pattern of IgG responses was generally comparable across study groups for the 13 shared serotypes and superior for the 2 serotypes unique to PCV15 and was similar to the pattern of OPA responses.

#### *Safety Analyses*

Post-vaccination safety data were reviewed from 3298 healthy infants (from studies V114-029, V114-027, V114-031, and the phase 2 study V114-08) who received 4 doses of PCV15. The most frequently reported solicited adverse reactions (ARs) among infant recipients of 4 doses of PCV15 included irritability, somnolence, and injection site pain. Reports of fever were somewhat more common in infant PCV15 recipients, particularly after doses 3 and 4.

Post-vaccination safety data were also reviewed from 303 healthy children 7 months through 17 years of age. Among participants 7 to 11 months of age (3 dose recipients), the most commonly reported solicited ARs were irritability (32.8%), injection site erythema (28.1%), and somnolence (21.9%). Among participants 12 through 23 months of age (2-dose recipients), the most commonly reported solicited ARs were irritability (35.5%), injection site pain (33.9%), and somnolence (24.2%). Among participants 2 years through 17 years of age (1-dose recipients), the most commonly reported solicited ARs were injection site pain (54.8%), myalgia (23.7%), and injection site swelling (20.9%).

Across all studies, the rates of reported serious adverse events (SAEs) among PCV15 recipients were similar to the rates reported in the comparator groups. The types of reported SAEs were consistent with conditions that are often reported in the evaluated populations. Four infant PCV15 recipients experienced SAEs that were considered related to PCV15 by the investigators. Two of these SAEs were fevers and were considered serious because they resulted in hospitalization for evaluation of the fever; both SAEs resolved without sequelae. One SAE was a febrile seizure in a 9-week-old that required hospitalization and resolved without sequelae. The fourth SAE was purpura that required evaluation in the emergency department and resolved without sequelae. There were no vaccination-related participant deaths in any of the clinical studies and no new safety concerns identified.

#### *Concomitant Vaccination*

Immune non-interference of PCV15 with Advisory Committee on Immunization Practices (ACIP)-recommended routine infant vaccines was evaluated in Study V114-029 for vaccines to prevent diphtheria, tetanus, pertussis, Hemophilus influenzae type B (Hib) and polio (Pentacel), hepatitis A (VAQTA), measles mumps and rubella (M-M-R II), varicella (Varivax), and Hib (Hiberix) and in Study V114-027 for vaccines to prevent hepatitis B (Recombivax HB) and rotavirus (Rotateq) disease. These studies found no evidence of immune interference of PCV15 with the responses to these vaccines.

#### *Pediatric Assessment and Pediatric Research Equity Act*

Studies V114-029, V114-027, V114-024, and V114-030 included as a part of this supplemental BLA application were submitted to fulfill the deferred post-marketing requirements (PMRs) agreed upon with the initial BLA application for use of Vaxneuvance in adults. The Pediatric Review Committee at FDA agreed that these PMRs are fulfilled.

*Clinical Reviewer Recommendation:*

The totality of clinical safety and effectiveness data presented in this application support approval of the 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 children 6 weeks through 17 years of age.

### **1.1 Demographic Information: Subgroup Demographics and Analysis Summary**

For each study, demographic characteristics, with the exception of prematurity at birth, were reviewed individually. There were no substantial differences identified in the safety and immunogenicity profiles of the evaluated demographic subgroups.

#### *Preterm Infants*

The immunogenicity and safety profiles of PCV15 in pre-term infants were generally comparable with those of PCV15 in full-term infants. Safety data supported the comparability of PCV15 with PCV13 within this subgroup. In descriptive analyses, immunogenicity data showed comparable patterns of IgG and OPA responses for the 13 shared serotypes among pre-term infants across study groups and higher IgG and OPA responses for the 2 unique serotypes among PCV15 recipients.

### **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 Condition(s) Studied**

Pneumococcal disease is an important cause of global morbidity and mortality, especially in children under the age of 5 years, among whom an estimated half a million deaths occur annually. *S. pneumoniae* is the leading cause of fatal pneumonia in all age groups ([CDC, 2021](#)). Other common clinical manifestations include sinusitis, otitis media, bacteremia, and meningitis.

*S. pneumoniae* is a diverse species with 100 identified serotypes based on capsular polysaccharide antisera ([CDC, 2021](#)). Despite the potential for any pneumococcal serotype to cause invasive pneumococcal disease (IPD), most invasive disease is caused by a select group of serotypes. Type-specific antibody production enabling opsonophagocytosis of *S. pneumoniae* is protective against IPD. The first conjugated pneumococcal vaccine, PCV7, was licensed in 2000 and contained polysaccharide antigens representing the seven serotypes most commonly associated with disease at the time (4, 6B, 9V, 14, 18C, 19F, and 23F). Following the inclusion of PCV 7 in the routine infant vaccine schedule, there was a significant decline in IPD, especially due to infections with the included serotypes. Subsequently, some serotypes not included in PCV7 were increasingly recognized as important causes of IPD in children. In 2010, PCV13 was licensed in the United States with a subsequent decrease in invasive disease due to the 5 of the 6 additional included serotypes. However, the decrease in the incidence of IPD due to serotype 3 has not been pronounced since the introduction of PCV13, despite the inclusion of this serotype in PCV13 ([Pilishvili, 2019](#)). Also, IPD due to serotypes 22F and 33F has become more common. Due to this changing epidemiology, the Applicant has developed PCV15, which includes 22F and 33F and has been designed to improve the immune response to serotype 3.

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

According to the American Academy of Pediatrics Report of the Committee on Infectious Diseases, 32nd Ed ([Red Book, 2021](#)), the recommended initial treatment of bacterial meningitis that is known or suspected to be caused by *S. pneumoniae* is intravenous (IV) vancomycin and a third-generation cephalosporin (cefotaxime for infants  $\leq 1$  month of age or ceftriaxone if  $> 1$  month of age). Once *S. pneumoniae* infection is confirmed, therapy may be narrowed to either an IV third generation cephalosporin or IV penicillin based on the demonstrated susceptibility of the isolate. For children who are critically ill with non-meningeal invasive disease that is known or suspected to be caused by *S. pneumoniae*, a similar therapeutic approach is recommended.

## **2.3 Safety and Effectiveness of Pharmacologically Related Products**

Two pneumococcal vaccines are licensed and available for use in children in the United States. Prevnar 13 (PCV13) is indicated for the prevention of invasive disease in children 6 weeks through 17 years of age. Pneumovax 23 (PPSV23), a vaccine comprised of unconjugated purified polysaccharides from 23 pneumococcal serotypes, is approved for use in persons  $\geq 2$  years of age who are at increased risk for pneumococcal disease and is administered as a single dose.

In adults  $\geq 18$  years of age, there are four pneumococcal vaccines that are licensed for use. Prevnar 20 (PCV20), Vaxneuvance (PCV15), and PCV13 are indicated for the prevention of invasive disease in adults. PCV20 and PCV13 are also indicated for the prevention of pneumonia in a subset of included serotypes. PPSV23 is approved for use in adults  $\geq 50$  years of age. The safety and immunogenicity of each vaccine in adults and children, as applicable, are described in their corresponding prescribing information.

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

PCV15 was licensed for use in adults  $\geq 18$  years of age in the United States in June of 2021. The safety and immunogenicity of PCV15 in adults are described in the prescribing information and the BLA clinical review memorandum.

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

### *Regulatory Pathway to Licensure:*

The licensure approach relied on an evaluation of effectiveness based on measurement of immunoglobulin G (IgG) levels specific for each of the 15 *S. pneumoniae* serotypes in PCV15 in blood samples following vaccination. The proportion of participants who had serum IgG concentrations  $\geq 0.35$   $\mu\text{g/mL}$  following a third dose administered at 6 months of age was selected as a benchmark for IgG response, as determined by a standardized ELISA assay, based on the 2013 recommendations from the World Health Organization (WHO) as an immunogenicity bridge to the efficacy against IPD demonstrated for PCV7 ([WHO, 2013](#)). In addition, geometric mean concentrations (GMCs) were evaluated after dose 3 administered at 6 months of age, and dose 4 administered at 12-15 months of age. *In vivo* protection from IPD is conferred mainly by IgG directed against *S. pneumoniae* capsular polysaccharides and resultant opsonophagocytic activity (OPA) against the *S. pneumoniae* bacterium. As there is variability in the performance of the OPA assay across pediatric age groups and there is no standardized OPA assay or established

level of OPA that is predictive of protection against IPD, IgG evaluations were chosen as the primary comparators to demonstrate the non-inferiority of PCV15 to PCV13.

#### *Major Regulatory Activity*

The following timeline includes a list of major regulatory activity associated with the submission of this sBLA:

- August 13, 2009: Initial Pediatric IND filing
- May 10, 2019: Break Through Therapy Designation request
  - Breakthrough therapy designation granted
- July 28, 2021: Type B – Pre-sBLA Meeting
  - The Applicant sought CBER concurrence on the clinical data supporting the review of the sBLA submission.
- November 29, 2021: Priority Review classification
  - CBER classified the sBLA submission for Priority Review

### **3. Submission Quality and Good Clinical Practices**

#### **3.1 Submission Quality and Completeness**

The submission of this sBLA 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 (V114-029, V114-031, V114-027, V114-024, V114-030, V114-023) to support this efficacy supplement for PCV15 and were conducted in accordance with Good Clinical Practice and International Committee on Harmonization guidelines. The informed consent form for each study contained all the essential elements as stated in 21CFR 50.25. The studies that enrolled from foreign sites included V114-029, V114-031, V114-027, V114-024, V114-030, and V114-023.

Bioresearch monitoring (BIMO) inspections were issued for 3 clinical study sites that participated in the conduct of Study V114-029. The inspections did not reveal substantive issues that impact the data submitted in this application.

#### **3.3 Financial Disclosures**

**Table 1. Covered Clinical Studies: V114-029, -031, -027, -024, -030, -023, and -008**

Was a list of clinical investigators provided? Yes
Total number of investigators and sub-investigators identified: <u>1192</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>

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)):

Significant payments of other sorts: 1

Is an attachment provided with details of the disclosable financial interests/arrangements? Yes

Is a description of the steps taken to minimize potential bias provided? Yes

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

The sponsor certified that 1191 investigators had absence of financial interests and/or arrangements. However, they reported that 1 investigator had a significant payment of other sorts (n=1). The sponsor provided the following financial information pertaining to this investigator:

- Principal Investigator Liset Olarte Carhuaz (Study V114-029/Site 0171) received significant payment that was reported as 'Investigator-initiated study research grant' in the amount of (b) (4) Received to date (b) (4) on April 9, 2019.

#### **4. Significant Effectiveness/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 with the initial BLA submission and were found to be adequate to support licensure. The stability data support an 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 sBLA 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, clinical serologic assays, and assays evaluating immune non-interference with concomitant vaccines were adequate to support effectiveness evaluations as determined by CBER Product and Assay reviewers.

##### **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 IPD is conferred mainly by serotype-specific IgG antibodies and opsonophagocytic killing of *S. pneumoniae*. PCV15 induces IgG antibody production and 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 VaxneuvancePCV15 for use in children.

#### **4.6 Pharmacovigilance**

The CBER Epidemiology/Pharmacovigilance reviewer did not identify any safety concerns or potential risk for PCV15 use in children that would require a post-marketing study or a Risk Evaluation and Mitigation Strategy.

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

#### **5.1 Review Strategy**

This BLA included clinical data from 6 main studies (V114-029, -031, -027, -024, -030, -023) to support immunogenicity (inferred clinical effectiveness) and safety for use in:

- Infants 6 weeks to 3 months of age who are initiating a 4-dose series. Two studies (V114-029 and V114-027) evaluated the noninferiority of ACIP-recommended infant vaccines when administered concomitantly with PCV15, as compared to PCV13, in this population.
- Children 7 months through 17 years of age as a catch-up vaccination series (1 to 3 doses) for those who have either never received a pneumococcal conjugate vaccine (PCV) or who have received an incomplete or complete series of a lower-valency PCV
- Children 5 years through 17 years of age living with HIV infection and the safety and immunogenicity of subsequently administered PPSV23
- Children 6 years through 17 years of age with sickle cell disease (SCD)

The submission also included 1 supportive Phase 2 study of a 4-dose series of 2 different formulations (including the final formulation) of PCV15 as compared with PCV13.

The clinical, labeling, and financial disclosure information section of the application were reviewed with detailed analyses of the main trials' study reports, pertinent line listings, case report forms, and datasets. ACIP vaccine recommendations for the prevention of pneumococcal disease and current pneumococcal US surveillance data were also reviewed.

#### **5.2 BLA Documents That Serve as the Basis for the Clinical Review**

The following STN#125741/6 Amendments (Am) and modules were reviewed:

- Am 0: 1, 2, 3, 4, and 5
- Am 1: 1 and 5
- Ams 4, 6, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26, 27, 29: 1.11.3

### 5.3 Overview of Clinical Trials

**Table 2. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of PCV15**

<b>Study Number</b>	<b>Region</b>	<b>Description</b>	<b>Population</b>	<b>Study Groups: # Enrolled</b>
Trial #1 V114-029 Pivotal Immunogenicity Safety Concomitant Vaccines	Australia Canada Finland Germany Israel Malaysia Peru Taiwan US	A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 4-dose Regimen of PCV15 in Healthy Infants	Healthy pneumococcal vaccine-naïve children 6 weeks to 3 months of age at enrollment	PCV15: 860 PCV13: 860
Trial #2 V114-031 Safety Immunogenicity*	Australia Canada Finland Germany Israel Malaysia Peru Taiwan US	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety and Tolerability of V114 in Healthy Infants	Healthy pneumococcal vaccine-naïve children 6 weeks to 3 months of age at enrollment	PCV15: 1967 PCV13: 436
Trial #3 V114-027 Safety Concomitant Vaccines	Puerto Rico Thailand Turkey US	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Interchangeability of PCV15 and PCV13 in Healthy Infants	Healthy pneumococcal vaccine-naïve children 6 weeks to 3 months of age at enrollment	Group 1 (4/0) <sup>#</sup> : 179 Group 2 (3/1): 181 Group 3 (2/2): 178 Group 4 (1/3): 179 Group 5 (0/4): 179
Trial #4 V114-024 Safety Immunogenicity	-Finland -Malaysia -Poland -Russian Federation- Thailand	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of Catch-up Vaccination Regimens of PCV15 in Healthy Infants, Children, and Adolescents	Healthy children who were either pneumococcal vaccine-naïve (ages 7 months through 17 years) or who had previously received a partial or full series of lower-valency pneumococcal vaccination (ages 2 years through 17 years)	7-11 months PCV15: 64 PCV13: 64 12-23 months PCV15: 62 PCV13: 64 2-17 years PCV15: 177 PCV13: 175

Study Number	Region	Description	Population	Study Groups: # Enrolled
Trial #5 V114-030 Safety Immunogenicity	South Africa Thailand Ukraine	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety and Immunogenicity of PCV15 in Children Infected with Human Immunodeficiency Virus (HIV)	Otherwise, healthy children 6 years through 17 years of age infected with HIV who were either pneumococcal vaccine naïve or previously vaccinated	PCV15: 203 PCV13: 204
Trial #6 V114-023 Safety Immunogenicity	Brazil Columbia Dominican-Republic Greece Italy Panama US	A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of PCV15 in Children with sickle cell disease (SCD)	Otherwise, healthy children 5 years through 17 years of age with SCD who were either pneumococcal vaccine naïve or previously vaccinated	PCV15: 69 PCV13: 34
Trial #7 V114-008 Safety Immunogenicity	Finland Spain Israel Denmark Canada US	A Phase 2 study to finalize formulation selection of PCV15 for subsequent Phase 3 clinical development	Healthy pneumococcal vaccine-naïve children 6 weeks to 3 months of age at enrollment	PCV15 Lot 1: 351 PCV15 Lot 2 <sup>†</sup> : 350 PCV13: 350

Abbreviations: HIV=human immunodeficiency virus; SCD=sickle cell disease\* Immunogenicity endpoints in pre-term infants only  
# (PCV13 doses administered / PCV15 doses received) by Group  
† Final PCV15 formulation selected for future clinical development

## 5.5 Literature Reviewed

CDC (2021), Global Pneumococcal Disease and Vaccination.

<https://www.cdc.gov/pneumococcal/global.html>. Accessed October 19, 2021.

Collett, D. (2002), Modelling Binary Data, 2nd edition.

Clopper, C.J. and Pearson, E.S. (1934), The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika*, 26, 404-413. <http://dx.doi.org/10.1093/biomet/26.4.404>.

Gierke, R. (2021), Current Epidemiology of Pneumococcal Disease, United States-2019 updates. Advisory Committee on Immunization Practices, June 25, 2021.

<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/02-Pneumococcal-Gierke-508.pdf>. Accessed June 17, 2022.

Miettinen, O. and Nurminen, M. (1985), Comparative analysis of two rates. *Statist. Med.*, 4: 213-226. <https://doi.org/10.1002/sim.4780040211>.

Pilishvili, T. (2019), 13-Valent Pneumococcal Conjugate Vaccine (Pcv13) Effects on Disease Caused by Serotype 3. National Center for Immunization and Respiratory Diseases. [13-valent pneumococcal conjugate vaccine \(PCV13\) effects on disease caused by serotype 3 \(cdc.gov\)](https://www.cdc.gov/ncidod/diseases/pneumococcal/13-valent-pneumococcal-conjugate-vaccine-pcv13-effects-on-disease-caused-by-serotype-3).

Red Book (2021), Report of the Committee on Infectious Diseases, 32nd Ed.



WHO Technical Report Series No. 977, 2013

## 6. Discussion of Individual Studies/Clinical Trials

### 6.1 Trial #1: V114-029

**NCT03893448:** A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 4-dose Regimen of V114 in Healthy Infants (PNEU-PED)

**Study Overview:** This was the main study designed to evaluate the safety, tolerability, and immunogenicity (inferred effectiveness) of a 4-dose series of PCV15 as compared to PCV13, and potential for immune interference when concomitantly administered with routine infant vaccines in healthy infants approximately two months of age at enrollment. The study enrolled 1,720 participants and was conducted at 75 sites in Puerto Rico, Thailand, Turkey, and the United States.

6.1.1 Objectives (as stated in study protocol V114-029, Amendment 2)

#### Primary Objectives

1. To evaluate the safety and tolerability of PCV15 with respect to the proportion of participants with adverse events:
  - Endpoints:
    - i. Solicited injection-site adverse events (AEs) from Day 1 through Day 14 following any vaccination with PCV15
    - ii. Solicited systemic AEs from Day 1 through Day 14 following any vaccination with PCV15
    - iii. Vaccine-related serious adverse events (SAEs) through completion of study participation
2. To compare the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype-specific IgG threshold value of  $\geq 0.35$   $\mu\text{g/mL}$ ) at 30 days PD3 for participants administered PCV15 versus participants administered PCV13.
  - Endpoints: Proportion of participants with anti-PnPs serotype-specific IgG achieving the threshold value of  $0.35$   $\mu\text{g/mL}$  for the 15 serotypes contained in PCV15 at 30 days Post-dose (PD) 3
    - i. Hypothesis 1 (H1): PCV15 was non-inferior to Prevnar 13™ for the 13 shared serotypes between V114 and Prevnar 13™.
      - The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI for the difference in the response rates [PCV15 minus Prevnar 13] to be greater than  $-0.1$
    - ii. Hypothesis 2 (H2): PCV15 was non-inferior to PCV13 for the 2 unique PCV15 serotypes based on the response rate of the 2 unique PCV15 serotypes compared with the lowest response rate of any of the shared serotypes in PCV13, excluding serotype 3

- The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI for the difference in the response rates [PCV15 minus PCV13] to be greater than  $-0.1$ .
3. To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days PD3 for participants administered PCV15 versus participants administered PCV13.
- Endpoints: Anti-PnPs serotype-specific IgG GMC for the 15 serotypes contained in PCV15
    - i. Hypothesis 3 (H3): PCV15 was non-inferior to PCV13 for the 13 shared serotypes between PCV15 and PCV13 based on anti-PnPs serotype-specific IgG GMCs at 30 days PD3
      - The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (PCV15/ PCV13) to be greater than 0.5
    - ii. Hypothesis 4 (H4): PCV15 was non-inferior to PCV13 for the 2 unique PCV15 serotypes based on the anti-PnPs serotype-specific IgG GMCs of the 2 unique PCV15 serotypes compared with the lowest IgG GMC of any of the shared serotypes in PCV13, excluding serotype 3
      - The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (PCV15/ PCV13) to be greater than 0.5
4. To compare anti-PnPs serotype-specific IgG GMCs at 30 days PD4 for participants administered PCV15 versus participants administered PCV13
- Endpoints: Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in PCV15 at 30 days PD4
    - i. Hypothesis (H5): PCV15 was non-inferior to PCV13 for the 13 shared serotypes between PCV15 and PCV13 based on anti-PnPs serotype-specific IgG GMCs
      - The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (PCV15/ PCV13) to be greater than 0.5.
    - ii. Hypothesis (H6): PCV15 was non-inferior to PCV13 for the 2 unique PCV15 serotypes based on anti-PnPs serotype-specific IgG GMCs of the 2 unique PCV15 serotypes compared with the lowest IgG GMC of any of the shared serotypes in PCV13, excluding serotype 3.
      - The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (PCV15/ PCV13) to be greater than 0.5.

Reviewer Comments:

1. Applicant's approach to demonstrating PCV15 effectiveness using immune endpoints: The World Health Organization (WHO) Expert Committee on Biological Standardization recommends that an in-house assay used in immunogenicity studies designed to evaluate the protection against IPD for new and/or higher valency

pneumococcal conjugate vaccines, be bridged to the WHO reference assay to maintain the link between immune response to vaccination and the clinical demonstration of effectiveness against IPD conferred by the 7 conjugated polysaccharides (4, 6B, 9V, 14, 18C, 19F, and 23F) in Prevnar for which clinical efficacy in preventing IPD had been previously demonstrated ([WHO, 2013](#)). Under the IND, the Applicant had completed studies that formally bridged their pneumococcal electrochemiluminescence assay (PnECLv2.0) to the WHO enzyme-linked immunosorbent assay (ELISA) to determine the PnECL serotype-specific threshold values that correspond to 0.35 µg/mL in the WHO ELISA for the 7 Prevnar serotypes, the additional 6 serotypes in Prevnar 13™ (1, 3, 5, 6A, 7F, 19A), and the two unique serotypes in PCV15 (22F, 33F). The studies demonstrated good concordance between the PnECL and WHO ELISA around the 0.35 µg/mL threshold value for all 15 serotypes included in PCV15.

2. Applicant's approach to demonstrating PCV15 effectiveness for two unique serotypes: Serotype 3 responses in PCV13 recipients were not considered adequate comparators due to CDC surveillance data following PCV13 vaccination in infants suggesting PCV13 vaccine serotype 3 may not have impacted the incidence of serotype 3 IPD relative to the other PCV13 vaccine serotypes ([Pilishvili, 2019](#)) and the immunological responses to serotype 3 in PCV 13 recipients were not consistent with the responses observed to other PCV13 vaccine serotypes. For these reasons, the Applicant agreed to evaluate the noninferiority of the immune responses to the two unique serotypes in PCV15 (22F and 33F) as compared to the lowest IgG response of the 13 shared serotypes, excluding serotype 3.

### Secondary Objectives

1. To compare the antigen-specific response rate to each antigen included in Pentacel at 30 days PD3 for participants administered PCV15 concomitantly with Pentacel versus participants administered PCV13 concomitantly with Pentacel.
  - Hypothesis (H7): Pentacel administered concomitantly with PCV15 was non-inferior to Pentacel administered concomitantly with PCV13 at 30 days PD3 for each antigen included in Pentacel. The respective immune endpoints and statistical testing criteria for success for each antigenic component in Pentacel are listed below.
    - i. Diphtheria toxoid and tetanus toxoid:
      - Proportion of participants with  $\geq 0.1$  IU/mL for diphtheria toxoid and tetanus toxoid
        - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -10% for diphtheria toxoid and was greater than -5% for tetanus toxoid.
    - ii. Pertussis antigens:
      - Proportion of participants with  $\geq 5$  EU/mL for pertussis toxin (PT), pertussis filamentous hemagglutinin (FHA), and pertussis pertactin (PRN); and  $\geq 20$  EU/mL for pertussis fimbriae types 2/3 (FIM 2/3)

- The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -10%
- GMCs for each pertussis antigen (PT, FHA, FIM 2/3, PRN)
  - The statistical criterion for noninferiority required that the lower bound of 2-sided 95% CI of the GMC ratio of PCV15 responses/PCV13 responses was greater than 0.67
- iii. Poliovirus antigens
  - Proportion of participants with neutralizing antibodies  $\geq 1:8$  dilution for poliovirus serotypes 1, 2, and 3
    - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -5%
- iv. Haemophilus influenzae type b (Hib) antigens:
  - Proportion of participants with  $\geq 0.15$   $\mu\text{g/mL}$  Haemophilus influenzae type b polyribosylribitol phosphate (PRP)
    - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -10%

Reviewer Comment: The seroresponse thresholds in (b) (4) used to evaluate the responses to pertussis antigens are not considered by CBER as the primary outcome for assessing the non-interference of concomitant vaccines with protection against pertussis infection. CBER's assessment for immune interference with concomitant vaccines relied on GMCs for evaluation of the pertussis antigens.

2. To compare the response rate to anti-hepatitis A antigen at 30 days PD4 for participants administered PCV15 concomitantly with VAQTA versus participants administered PCV13 concomitantly with VAQTA. The respective immune endpoints and statistical testing criteria for success are listed below
  - Hypothesis (H8): VAQTA administered concomitantly with PCV15 was non-inferior to VAQTA administered concomitantly with PCV13 at 30 days PD4.
    - i. Hepatitis A antigen
      - Proportion of antibody responses  $\% \geq 10$  mIU/mL
        - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -10%
3. To compare the response rate to each antigen included in M-M-R II at 30 days PD4 for participants administered PCV15 concomitantly with M-M-R II versus participants administered PCV13 concomitantly with M-M-R II. The respective immune endpoints and statistical testing criteria for success for each antigenic component in M-M-R II are listed below:
  - Hypothesis (H9): M-M-R II administered concomitantly with PCV15 was non-inferior to M-M-R II administered concomitantly with PCV13 at 30 days PD4 for each antigen included in M-M-R II.

- i. Measles antigen
    - Proportion of antibody responses that are  $\geq 255$  mIU/mL
      - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -5%
  - ii. Mumps antigen
    - Proportion of antibody responses that are  $\geq 10$  mumps antibody units/mL
      - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -5%
  - iii. Rubella antigen
    - Proportion of antibody responses that are  $\geq 10$  IU/mL
      - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -5%
4. To compare the response rate to anti-varicella antigen at 30 days PD4 for participants administered PCV15 concomitantly with Varivax versus participants administered PCV13 concomitantly with Varivax
  - Hypothesis (H10): Varivax administered concomitantly with PCV15 was non-inferior to Varivax administered concomitantly with PCV13 at 30 days PD4.
    - i. Varicella-zoster virus (VZV) antigen
      - Proportion of antibody responses that are  $\geq 5$  (b) (4) units/mL
        - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -10%
5. To compare the response rate to anti-PRP antigen at 30 days PD4 for participants administered PCV15 concomitantly with Hiberix versus participants administered PCV13 concomitantly with Hiberix
  - Hypothesis (H11): Hiberix administered concomitantly with PCV15 was non-inferior to Hiberix administered concomitantly with PCV13 at 30 days PD4.
    - i. Hib-PRP antigen
      - Proportion of antibody responses that are  $\geq 0.15$   $\mu\text{g/mL}$ 
        - The statistical success criteria for noninferiority required that the lower bound of 2-sided 95% CI was greater than -10%
6. To compare the anti-PnPs serotype-specific IgG responses for the 2 unique PCV15 serotypes (22F and 33F) at 30 days PD3 for participants administered PCV15 versus participants administered PCV13.
  - Hypothesis (H12): PCV15 was superior to PCV13 for the 2 unique PCV15 serotypes based on the response rates  $\geq 0.35$   $\mu\text{g/mL}$  at 30 days PD3.
    - i. The statistical success criteria for superiority required that the lower bound of 2-sided 95% CI was greater than 10% for PCV15-PCV13

- Hypothesis (H13): PCV15 was superior to PCV13 for the 2 unique PCV15 serotypes based on anti-PnPs serotype-specific IgG GMCs.
    - ii. The statistical success criteria for superiority required that the lower bound of 2-sided 95% CI was greater than 2.0 for PCV15/PCV13
7. To compare the anti-PnPs serotype-specific IgG responses for the 2 unique PCV15 serotypes (22F, 33F) at 30 days PD4 for participants administered PCV15 versus participants administered Prevnar 13
- Hypothesis (H14): PCV15 was superior to PCV13 for the 2 unique PCV15 serotypes based on anti-PnPs serotype specific IgG GMCs at 30 days PD4
    - i. The statistical success criteria for superiority required that the lower bound of 2-sided 95% CI was greater than 2.0 for PCV15/PCV13
8. To compare the anti-PnPs serotype 3 IgG responses at 30 days PD3 for participants administered PCV15 versus participants administered PCV13
- Hypothesis (H15): PCV15 was superior to PCV13 for serotype 3 based on the response rates at 30 days PD3
    - i. The statistical success criteria for superiority required that the lower bound of 2-sided 95% CI was greater than 0% for PCV15–PCV13
  - Hypothesis (H16): PCV15 was superior to PCV13 for serotype 3 based on anti-PnPs IgG GMCs at 30 days PD3
    - i. The statistical success criteria for superiority required that the lower bound of 2-sided 95% CI was greater than 1.2 for the GMC ratio of PCV15/PCV13
9. To compare the anti-PnPs serotype 3 IgG GMCs at 30 days PD4 for participants administered PCV15 versus participants administered Prevnar 13
- Hypothesis (H17): PCV15 was superior to PCV13 for serotype 3 based on anti-PnPs IgG GMCs
    - i. The statistical success criteria for superiority required that the lower bound of 2-sided 95% CI was greater than 1.2 for the GMC ratio of PCV15/PCV13
10. To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) and response rates at 30 days PD3 by each vaccination group in the OPA subset
- Descriptive analysis without formal hypothesis testing

Reviewer Comments: Following CBER’s review of the original protocol (submitted IND14115, Amendment 240), the Applicant agreed to revise the primary analyses, to only include non-inferiority statistical testing for the two unique serotypes (22F and 33F) compared to the lowest non-serotype 3 PCV13 serotype. Subsequently, the Applicant revised the protocol (V114-029, Am. 1, dated Feb 2020) to include superiority testing (Hypothesis 12 through 14) for serotypes 22F and 33F as secondary immunogenicity endpoints. Because demonstration of statistical superiority of IgG antibody responses was not sufficient alone to

support clinical superiority in prevention of IPD, the clinical reviewer recommends that labeling language be limited to ‘statistically significantly greater immune responses’ to characterize the findings of these study hypotheses.

With the submission of the revised protocol (V114-029, Am. 2, dated March 2021), the Applicant had included two additional secondary analyses with superiority testing for serotype 3 (Hypotheses 15 through 17). As above, the clinical reviewer recommends that description of results for these hypotheses in labeling be limited to the immune response, as the clinical relevance of the proposed superiority testing approach for serotype 3 is not known.

### **Tertiary/Exploratory Objectives**

1. To evaluate the anti-PnPs serotype-specific IgG GMCs immediately prior to dose 4 by each vaccination group.
  - Descriptive analysis without formal hypothesis testing
2. To evaluate the anti-PnPs serotype-specific OPA GMTs and response rates immediately prior to dose 4 and 30 days PD4 by each vaccination group.
  - Descriptive analysis without formal hypothesis testing
3. To evaluate the response rate to anti-PRP antigens with an alternative threshold value by each vaccination group:
  - for participants administered Pentacel concomitantly with PCV15 and participants administered Pentacel concomitantly with PCV13 at 30 days PD3
  - for participants administered Hiberix concomitantly with PCV15 and participants administered Hiberix concomitantly with PCV13 at 30 days PD4
    - i. Proportion of antibody responses to Hib-PRP  $\geq 1.0 \mu\text{g/mL}$ 
      1. Descriptive analysis without formal hypothesis testing

#### **6.1.2 Design Overview**

Study V114-029 was a multicenter, randomized, active-controlled, and double-blind study in children between 6 weeks and 3 months of age at enrollment. A total of 1620 children were enrolled and randomized in a 1:1 ratio to receive 4 doses of either PCV15 or PCV13 at ~2months, ~4months, ~6months and 12 – 15months of age.

#### **6.1.3 Population**

A participant was eligible for inclusion in the study if the participant:

1. Was healthy (based on a review of medical history and physical examination) based on the clinical judgement of the investigator.
2. Was male or female from 42 days through 90 days of age at the time of obtaining the informed consent.
3. Has a legally acceptable representative who understands the study procedures, alternate treatments available, and risks involved with the study and voluntarily agrees to participate by giving written informed consent. The legally acceptable representative may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Enrollees were excluded if they had a history of:

- Invasive pneumococcal disease (defined by a history of a positive blood culture, cervical spinal fluid culture, or culture from another sterile site)
- Hypersensitivity to any component of the pneumococcal vaccine or any component of the license pediatric vaccines to be administered concomitantly in the study or any diphtheria toxoid containing vaccine
- Contraindication to the concomitant study vaccines
- Recent febrile illness (defined by rectal temperature  $\geq 38.1^{\circ}\text{C}$  or axillary temperature  $\geq 37.8^{\circ}\text{C}$ ) within 72 hours prior to receipt of any study vaccine
- Known or suspected immunodeficiency (either congenital or acquired)
- Maternal history of HIV infection or hepatitis B infection
- Functional or anatomic asplenia
- Failure to thrive
- Any contraindication to intramuscular vaccination
- History of autoimmune disease
- Known neurological or cognitive disorder
- Prior receipt of a pneumococcal vaccine
- >1 dose of monovalent hepatitis B vaccine or hepatitis B based combination vaccine
- Any dose of a pertussis containing vaccine, *Haemophilus influenzae* type b conjugate vaccine, poliovirus vaccine, or rotavirus vaccine
- Systemic corticosteroid therapy  $\geq 2$  mg/kg/day or systemic corticosteroids within 14 days prior to receipt of any study dose or was expected to require systemic corticosteroids within 30 days after any study vaccination
- Receipt of other licensed non-live vaccines within 14 days before or 30 days after any study vaccine (with exception of inactivated influenza vaccine with intervals of 7 days before or 15 days after any study vaccine)
- Receipt of any live vaccine within 30 days before or after a study vaccine
- Receipt of a blood transfusion or blood products.

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

PCV15: 15-valent pneumococcal conjugate vaccine

- Dose: 0.5mL administered IM
- Schedule of administration: visits at 2, 4, 6, and 12 to 15 months
- Composition: Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F
- Presentation: Sterile suspension in a pre-filled syringe
- Lot #0000957291

PCV13: 13-valent pneumococcal conjugate vaccine (diphtheria CRM197 protein)

- Dose: 0.5mL administered IM
- Schedule of administration: visits at 2, 4, 6, and 12 to 15 months
- Composition: Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Presentation: Sterile suspension in a prefilled syringe
- Lot #: 0000921112, 0000940410 (EU)
- Lot #: 0000896670, 0000947747, 0001043617 (US)



#### M-M-R II

- Dose: 0.5mL administered SC
- Schedule of administration: Single dose at 12 to 15 month visit
- Composition:
  - Measles Virus Vaccine Live, an attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture
  - Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture
  - Rubella Virus Vaccine Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts
- Presentation: Sterile suspension
- Lot #: 0001065631

#### Recombivax HB

- Dose: 0.5mL administered IM
- Schedule of administration: visits at 2, 4, and 6 months
- Composition: Hepatitis B antigen harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adv* subtype of HBsAg
- Presentation: Sterile suspension
- Lot #: 0000957906

#### Rotateq

- Dose: 1 mL administered PO
- Schedule of administration: visits at 2, 4, and 6 months
- Composition: 5 live reassortant rotaviruses: 4 reassortant rotaviruses expressing one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (type P7) from the bovine rotavirus parent strain and the fifth reassortant virus expressing the attachment protein, P1A (genotype P[8])
- Presentation: Sterile solution
- Lot # 0000955070, 0001069362

#### Hiberix

- Dose: 0.5mL administered IM
- Schedule of administration: Single dose at 12 through 15-month visit
- Composition: *Haemophilus influenzae* type b capsular polysaccharide (PRP) conjugated to tetanus toxoid
- Presentation: Sterile solution
- Lot # 0001047437, 0001088213

#### VAQTA

- Dose: 0.5mL administered IM
- Schedule of administration: Single dose at 12-to-15-month visit

- Composition: inactivated whole hepatitis A virus grown in cell culture in human MRC-5 diploid fibroblasts
- Presentation: Sterile suspension
- Lot # 0000927751, 0001008950

Pentavac 0.5mL:

- Dose: 0.5mL administered IM
- Schedule of administration: visits at 2, 4, and 6 months
- Composition: diphtheria, tetanus, 2 component acellular pertussis, inactivated poliovirus, and Hib polysaccharide-conjugate antigens
- Presentation: Sterile suspension
- Lot# 0000974006, 0000995761, 0001067383

Reviewer Comment: Pentavac was administered as a study vaccine in studies V114-029 and V114-027 to participants enrolled from sites in Thailand and Turkey. It contains 2 acellular pertussis antigens, rather than the 5 contained in Pentacel, and is not approved for use in the United States. For this reason, immunogenicity and solicited safety endpoints in these studies were evaluated excluding Pentavac recipients (see Sections [6.1.10](#), [6.1.11](#), [6.1.12](#), [6.3.10](#), [6.3.11](#), and [6.3.12](#)).

Pentacel

- Dose: 0.5mL administered IM
- Schedule of administration: visits at 2, 4, and 6 months
- Composition: diphtheria toxoid, tetanus toxoid, 5 component acellular pertussis antigens (detoxified pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbriae types 2 and 3 (FIM)), inactivated polioviruses [Type 1 (Mahoney), Type 2 (MEF-1), Type 3 (Saukett)], and Hib antigen covalently bound to tetanus toxoid (PRP-T).
- Presentation: Sterile suspension
- Lot # 0000930355, 0000955089, 0001069427

6.1.5 Directions for Use

See [Section 6.1.4](#)

6.1.6 Sites and Centers

Study V114-029 was conducted at 75 sites in Puerto Rico, Thailand, Turkey, and the United States. United States sites enrolled 1033 participants (60% of all participants).

6.1.7 Surveillance/Monitoring

Safety Monitoring

- Clinical Assessments: physical exam before vaccination (Day 1)
- AE Monitoring:
  - Immediate ARs: 30 minutes postvaccination period
  - Solicited Local/Injection Site: Days 1 through 14 postvaccination
    - Swelling, redness, pain or tenderness, and hard lump
  - Solicited Systemic: Days 1 through 14 postvaccination

- Irritability, drowsiness, appetite lost, and hives or welts
- Temperature recorded daily in electronic vaccine report card (eVRC) from Day 1 through 7 postvaccination, temperature should also be measured on Days 8 through 14 postvaccination if fever (defined as rectal temperature  $\geq 38.1^{\circ}\text{C}$  [ $\geq 100.5^{\circ}\text{F}$ ] or axillary temperature  $\geq 37.8^{\circ}\text{C}$  [ $\geq 100.0^{\circ}\text{F}$ ]) was suspected
- Any other unsolicited injection-site or systemic AEs Day 1 through Day 14 postvaccination
- Use of any analgesic or antipyretic on the day of vaccination
- Concomitant medications and non-study vaccinations Day 1 to Day 14 postvaccination
- SAEs and deaths through 6 months after study dose 4

The participant's legal representative recorded all relevant safety data in an eVRC.

#### *Investigator Assessment of Vaccination Report Card*

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 and one month following postvaccination to ensure consistency with protocol definitions. Data reported on the eVRC were used to inform the investigator's final assessment of solicited adverse reaction (AR) events. Therefore, safety data analyses presented for solicited AR events reflect the information as assessed by the investigators. An external Data Monitoring Committee (DMC) conducted periodic reviews *ad hoc* of safety and tolerability data and served as the primary reviewer of study safety data. The safety data could be unblinded for the Applicant's Executive Oversight Committee (EOC) in the event of a recommendation from the DMC for either study halting or modification.

*Study withdrawal/discontinuation:* all activities scheduled for the final study visit (Visit 6) 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.

#### 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  $\mu\text{g}/\text{mL}$  (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)
- (b) (4) measured neutralizing (functional) antibodies to poliovirus serotypes 1, 2 and 3 in serial dilutions of serum using Polio (b) (4). Results are determined by the (b) (4) where the (b) (4) ranging from a titer of (b) (4) (b) (4)
- Hepatitis A Virus Enzyme Immunoassay: measured total anti-HAV antibodies in human serum. A (b) (4) controls spanning a range of assay concentrations were included on each assay (b) (4). Antibody concentration was measured in milli-International Units per milliliter (mIU/mL). (b) (4)
- Bulk Measles IgG (b) (4) measured total IgG antibody to measles virus. The reference standard was a (b) (4) that had been calibrated against the (b) (4) anti-measles reference standard, (b) (4). The concentration of anti-measles antibody in a sample was reported in mIU/mL of serum. (b) (4)
- Mumps (b) (4) measured IgG antibody to mumps virus. Quantitation of the human IgG antibody to mumps virus, or antibody concentration, was determined by comparison of the resulting test (b) (4) to a standard curve. The reference standard was an (b) (4). Results for the assay are reported as the concentration of antibody in Mumps antibody units/mL. (b) (4)
- Bulk Rubella IgG (b) (4) measured total IgG antibody to rubella virus. Quantitation of the human IgG antibody to rubella virus or titer is determined by comparison of the resulting analysis (b) (4) to a standard curve. The reference standard was an individual (b) (4) that has been calibrated against the (b) (4) anti-rubella reference standard. The concentration of anti-rubella antibody in a sample was reported in International Units per milliliter (IU/mL) of serum. (b) (4)
- Varicella Zoster Virus (VZV) (b) (4) (b) (4) measured IgG antibody to VZV. The DOD was determined by (b) (4) from its corresponding VZV (b) (4). Assay results were reported as concentration of antibody in (b) (4) units/mL. (b) (4)
- Haemophilus Influenza Type b (Hib) IgG (b) (4) measured specific IgG antibodies against (b) (4) in human serum uses the (b) (4). Human Anti-Haemophilus influenzae Type b (b) (4) purchased from (b) (4). (b) (4). Levels of anti-Hib IgG were quantified by interpolation from a

standard curve that had been calibrated to the (b) (4) reference serum. (b) (4)  
(b) (4)

- Diphtheria, Tetanus, and acellular Pertussis assay: The diphtheria, tetanus, and pertussis 6-valent IgG (DTP-6 IgG) assay measured total IgG antibodies specific to the following antigens: Pertussis Toxin (PT), Filamentous Hemagglutinin (FHA), Pertactin (PRN), Fimbriae types 2/3 (FIM 2/3), Diphtheria toxoid, and Tetanus toxoid. (b) (4)  
(b) (4) Quantitation of the human IgG antibodies to DTP-6 antigens, or titer, was determined by comparison of the resulting test fluorescence measurement to the reference standard sera. (b) (4)  
(b) (4)

Reviewer Comment: These assays were reviewed by the CBER clinical assay reviewers and were determined to be validated and adequate to support evaluation of effectiveness

#### 6.1.8 Endpoints and Criteria for Study Success

Refer to [Section 6.1.1](#).

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

##### **Primary Hypotheses #1 and #2 (H1 and H2)**

For each of the 13 shared serotypes (H1) and two unique serotypes (H2), the percentage of participants in the PCV15 cohort vs. the PCV13 cohort with an IgG seroresponse greater than or equal to 0.35 µg/mL at 30 days after vaccination with the third dose of either PCV15 or PCV13 were assessed via the following noninferiority hypotheses:

1. For H1 and H2, H0:  $p_1 - p_2 \leq -0.1$  vs. H1:  $p_1 - p_2 > -0.1$ ,
2. For H1:  $p_1$  was the seroresponse rate  $\geq 0.35$  µg/mL in the PCV15 group and  $p_2$  was the seroresponse rate  $\geq 0.35$  µg/mL in the PCV13 group for each of the shared antigens
3. For H2:  $p_1$  was the seroresponse rate  $\geq 0.35$  µg/mL in the PCV15 group for each of the two unique serotypes (22F and 33F) and  $p_2$  was the seroresponse rate  $\geq 0.35$  µg/mL in the PCV13 group for the antigen with the lowest response rate not including serotype 3
4. The Miettinen and Nurminen method was used for this analysis ([Miettinen and Nurminen, 1985](#))
5. PCV15 was considered non-inferior to PCV13 if the lower bound of the 2-sided 95% CI was greater than  $-0.1$  ( $-10$  percentage points)

##### **Primary Hypotheses #3 through #6 (H3, H4, H5, and H6)**

For Hypotheses #3 through 6 the non-inferiority of the serotype-specific IgG GMC responses for the PCV15 group as compared to those in the PCV13 group were assessed with the following non-inferiority hypotheses:

1. H0:  $GMC_1 / GMC_2 \leq 0.5$  vs. H1:  $GMC_1 / GMC_2 > 0.5$
2. For the 13 shared serotypes, GMC1 was the anti-PNPs serotype-specific IgG GMC for the PCV15 group 30 days PD3 (H3) and 30 days PD4 (H4) and GMC2 was the anti-PNPs serotype-specific IgG GMC for the PCV13 group 30 days PD3 (H3) and 30 days PD4 (H4)

3. For the 2 unique serotypes, GMC1 was the anti-PNPs serotype-specific IgG GMC for the PCV15 group 30 days PD3 (H5) and 30 days PD4 (H6) and GMC2 was the anti-PNPs serotype-specific IgG GMC for the PCV13 group for the antigen with the lowest response rate, not including serotype 3, 30 days PD3 (H5) and 30 days PD4 (H6)
4. A ratio of 0.5 corresponds to a 2.0-fold decrease of anti-PnPs serotype-specific IgG GMCs in the PCV15 group as compared with the PCV13 group
5. PCV15 was considered non-inferior to PCV13 if the lower bound of the 2-sided 95% CI for the GMC ratios (PCV15/PCV13) was greater than 0.5

For both the shared and unique serotypes, estimation of the IgG GMC ratios and computation of the corresponding 95% confidence intervals (CIs) were calculated using t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody titers as the response and a single term for vaccination group.

### **Secondary Hypotheses #7 through #11 (H7, H8, H9, H10, and H11)**

Hypotheses #7 through #11 evaluated the noninferiority of routine infant vaccinations in the PCV15 group as compared to the PCV13 group. These hypotheses used the following noninferiority criteria to evaluate the objectives at the time points detailed in [Section 6.1.1](#):

1. H0:  $p_1 - p_2 \leq \delta$  vs. H1:  $p_1 - p_2 > \delta$
2.  $p_1$  was the response rate for each concomitant vaccine antigen in the PCV15 group,  $p_2$  was the response rate for each concomitant vaccine antigen in the PCV13 group, and  $\delta$  are the following prespecified noninferiority margins for each concomitant vaccine:
  - -5%: Tetanus toxoid; Poliovirus 1, 2, and 3; Measles; Mumps; Rubella
  - -10%: Diphtheria toxoid; Pertussis antigens, Hib-PRP, Hepatitis A, VZV
3. The Miettinen and Nurminen method was used for these analyses ([Miettinen and Nurminen, 1985](#))

### **Secondary Hypothesis #12 (H12)**

This hypothesis assessed the superiority of the rates of IgG GMCs  $\geq 0.35$   $\mu\text{g/mL}$  in response to serotypes 22F, 33F (H12) in PCV15 recipients as compared to PCV13 recipients 30 days after dose 3. This hypothesis used the following superiority criteria:

1. H0:  $p_1 - p_2 \leq 0.1$  vs. H1:  $p_1 - p_2 > 0.1$
2.  $p_1$  was the seroresponse rate  $\geq 0.35$   $\mu\text{g/mL}$  in the PCV15 group and  $p_2$  was the seroresponse rate  $\geq 0.35$   $\mu\text{g/mL}$  in the PCV13 group for each of the antigens
3. The Miettinen and Nurminen method was used for this analysis ([Miettinen and Nurminen, 1985](#)).

### **Secondary Hypotheses #13 and #14 (H13 and H14)**

These hypotheses evaluated the superiority of the serotype-specific IgG GMC responses to the two unique antigens (22F and 33F) for the PCV15 group as compared to those in the PCV13 group 30 days after dose 3 (H13) and dose 4 (H14) and used the following superiority criteria:

1. H0:  $\text{GMC1}/\text{GMC2} \leq 2.0$  vs. H1:  $\text{GMC1}/\text{GMC2} > 2.0$
2. GMC1 was the anti-PNPs serotype-specific IgG GMC for the PCV15 group and GMC2 was the anti-PNPs serotype-specific IgG GMC for the PCV13 group

3. Estimation of the IgG GMC ratios and computation of the corresponding 95% confidence intervals (CIs) were calculated using t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody titers as the response and a single term for vaccination group.

### **Secondary Hypotheses #15 (H15)**

This hypothesis assessed the superiority of the rates of IgG GMCs  $\geq 0.35$   $\mu\text{g/mL}$  in response to serotype 3 in PCV15 recipients as compared to PCV13 recipients 30 days after dose 3. This hypothesis used the following superiority criteria:

1.  $H_0: p_1 - p_2 \leq 0$  vs.  $H_1: p_1 - p_2 > 0$
2.  $p_1$  was the seroresponse rate  $\geq 0.35$   $\mu\text{g/mL}$  in the PCV15 group and  $p_2$  was the seroresponse rate  $\geq 0.35$   $\mu\text{g/mL}$  in the PCV13 group
3. The Miettinen and Nurminen method was used for this analysis ([Miettinen and Nurminen, 1985](#)).

### **Secondary Hypotheses #16 and #17 (H16, and H17)**

These hypotheses evaluated the superiority of the serotype-specific IgG GMC responses to serotype 3 for the PCV15 group as compared to those in the PCV13 group 30 days after dose 3 (H16) and dose 4 (H17) and used the following superiority criteria:

- $H_0: \text{GMC}_1/\text{GMC}_2 \leq 1.2$  vs.  $H_1: \text{GMC}_1/\text{GMC}_2 > 1.2$
- A ratio of 1.2 corresponds to a 1.2-fold increase of anti-PnPs serotype 3 IgG GMCs in the PCV15 group as compared with the PCV13 group.
- $\text{GMC}_1$  was the anti-PNPs serotype-specific IgG GMC for the PCV15 group and  $\text{GMC}_2$  was the anti-PNPs serotype-specific IgG GMC for the PCV13 group
- PCV15 was considered superior if the lower bound of the 2-sided 95% CI for the GMC ratios (PCV15/PCV13) was greater than 1.2
- Estimation of the IgG GMC ratios and computation of the corresponding 95% confidence intervals (CIs) were calculated using t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody titers as the response and a single term for vaccination group.

### *Other Secondary and Tertiary/Exploratory Endpoints (descriptive analyses only)*

For the 15 pneumococcal serotypes in PCV15 comparative analyses across study groups were performed for:

- IgG GMCs Predose 4
- Anti-PnPs serotype-specific OPA GMTs and response rates (percent of participants with OPA titers  $\geq$  lower limit of quantification (LLOQ) of the serotype specific OPA assay) at 30 days PD3, Predose 4, and at 30 days PD4
- Anti-PRP response rate using alternate threshold of  $\geq 1.0$   $\mu\text{g/mL}$  at 30 days PD3 of V114 or PCV13 when administered concomitantly with Pentacel™ and 30 days PD4 of V114 or PCV13 when administered concomitantly with Hiberix

The evaluations of these objectives were performed within each vaccination group separately. Descriptive statistics with point estimates and within-group 95% CIs were provided. For the continuous variables, the point estimates were calculated by exponentiating the estimates of the

mean of the natural log values and within-group CIs were derived by exponentiating the bounds of CIs of the mean of the natural log values based on the 1-sample t-distribution. For the dichotomous endpoints, the within-group CIs were calculated based on the exact method proposed by Clopper and Pearson ([Clopper and Pearson, 1934](#)).

*Safety Endpoints: % of participants with*

- Solicited injection site ARs during Days 1 through 14 postvaccination
- Solicited systemic ARs during Days 1 through 14 postvaccination
- Maximum temperature measurement
- Any AE, any vaccine-related AE during Days 1 through 14 postvaccination
- Any SAE, any vaccine-related SAE, and death from Day 1 post-study vaccination 1 through Month 6 following the final study vaccination

*Analyses of Safety Endpoints:* p-values (solicited local reactions and systemic ARs) and 95% CIs (any AE, any SAE, vaccine-related SAE, AEs leading to withdrawal, and deaths) were provided for between-treatment differences in the percentage of participants with events; these analyses were performed using the Miettinen and Nurminen method ([Miettinen and Nurminen, 1985](#)).

*Interim Analysis:* A periodic review of safety and tolerability data across the PCV15 Phase 3 pediatric program was conducted by an independent, unblinded, external DMC. The DMC was provided intervention-level ongoing safety reviews by an external unblinded statistician to the DMC who was not involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the safety reviews

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

**Protocol Amendments**

- Protocol Amendment 1 (February 28, 2020) to original protocol (January 30, 2019): Changed study protocol and statistical analysis plan to evaluate the superiority PCV15 to PCV13 for the 2 serotypes unique to PCV15 (22F and 33F) as secondary objectives (previously primary) and evaluate non-inferiority of PCV15 to PCV13 as primary objectives (previously secondary)
- Protocol Amendment 2 (March 16, 2021): This amendment included the evaluation of the superiority for serotype 3 immune responses as well as flexibilities in visit windows in response to the COVID-19 pandemic.

**Significant Changes in the Conduct of the Study & Planned Analyses:**

- February 28, 2020: Statistical analyses were changed to incorporate the changes in evaluation of the responses to the 2 serotypes unique to PCV15. Pertussis GMCs were added to secondary objective #1.
- March 16, 2021: Addition of 3 secondary hypotheses relating to the demonstration of superiority for serotype 3 immune responses. Visit windows for dose 3 vaccination, PD3 blood draw, and PD4 draw were also expanded to increase the immunogenicity database due to COVID-19 pandemic.



- Other COVID-19 Pandemic-Associated Changes:
  1. Modifications to the frequency of on-site and remote monitoring were allowed due to national and local travel restrictions and/or study site restrictions to onsite monitoring
  2. Study sites were queried as to the relationship of reported deviations, missing participant study data, participant discontinuations and the COVID-19 pandemic
  3. COVID-19 infection was reported following the protocol's AE and SAE reporting instructions
  4. Alternate clinical laboratory facilities were allowed for collection of samples for study participants unable to visit the study site
  5. Oral confirmation of participant informed consent was allowed when in person discussion and signature was not possible
  6. Home health services could be used to perform protocol specified activities for participants unable to visit the study site

Reviewer Comment: The changes made to study conduct do not appear to significantly impact the interpretability of the data generated from study V114-029.

#### 6.1.10 Study Population and Disposition

A total of 1720 participants were enrolled in the study. Study period: June 19, 2019 (first participant, first visit) to May 24, 2021 (last participant, last visit).

##### 6.1.10.1 Populations Enrolled/Analyzed

- Per Protocol (PP): The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s). Participants were included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the PP population. The final determination on protocol deviations, and thereby the composition of the PP population, was made prior to the final unblinding of the database.
- Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:
  - Failure to receive primary infant series vaccination (V114 or PCV13 Doses 1, 2, and 3) as per randomization schedule
  - Receipt of prohibited medication or prohibited vaccine prior to the first study vaccination
  - Failure to receive dose 4 of V114 or PCV13 according to vaccination schedule required at the timepoint for the analysis
  - Failure to receive Pentacel, VAQTA, M-M-R II, Varivax, or Hiberix according to vaccination schedule required at the timepoint for the analysis
  - Failure to receive the scheduled doses of V114 or PCV13 (at least 28 days between Doses 1 and 2 and between Doses 2 and 3 [for PD3 and Predose 4 analysis], 12 months to 1 day prior to 16 months of age for dose 4 [for PD4 analyses])
  - Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection

- Collection of blood sample at the timepoint for the analysis outside of the pre-specified window (as described in Section 1.3)
- Full Analysis Set (FAS): The FAS population consists of all randomized participants who received all study vaccinations required at the timepoint for the analysis and have serology result. Participants were included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the FAS population
- All Participants as Treated (APaT): All randomized participants who received at least one dose of study vaccination

*Demographics*

Among all vaccinated participants, there were more males (51.9%) than females. The median chronological age at enrollment was 8.0 weeks (range: 6 to 12 weeks). Infants born at less than 37 weeks gestational age accounted for 8.8% (n=150) of study participants (8.8%). The majority of participants (55%) were white followed by Asian (26.2%), Multiple (10.4%), and Black or African American (6.1%). 23.9% identified as Hispanic/Latino. The demographic characteristics of participants were similar between study groups and are shown in [Table 3](#).

**Table 3. Study V114-029: Demographic Characteristics**

<b>Characteristic</b>	<b>PCV15 N=858</b>	<b>PCV13 N=856</b>	<b>Total N=1,714</b>
Sex, n (%)	--	--	--
Male	461 (53.7)	429 (50.1)	890 (51.9)
Female	397 (46.3)	427 (49.9)	824 (48.1)
Age at enrollment (weeks)	--	--	--
Mean (SD)	8.4 (1.2)	8.4 (1.3)	8.4 (1.2)
Minimum, maximum	6, 12	6, 12	6, 12
Gestational age at birth, n (%)			
<37 weeks	74 (8.6)	76 (8.9)	150 (8.8)
≥37 weeks	784 (91.4)	780 (91.1)	1,564 (91.2)

<b>Characteristic</b>	<b>PCV15 N=858</b>	<b>PCV13 N=856</b>	<b>Total N=1,714</b>
Racial origin, n (%)	--	--	--
American Indian/Alaska Native	6 (0.7)	13 (1.5)	19 (1.1)
Asian	223 (26.0)	226 (26.4)	449 (26.2)
Black/African American	52 (6.1)	53 (6.2)	105 (6.1)
Multiple	98 (11.4)	80 (9.3)	178 (10.4)
American Indian/Alaska Native, Asian	0 (0.0)	2 (0.2)	2 (0.1)
American Indian/Alaska Native, Black/African American	1 (0.1)	1 (0.1)	2 (0.1)
American Indian/Alaska Native, Black/African American, white	3 (0.3)	1 (0.1)	4 (0.2)
American Indian/Alaska Native, white	7 (0.8)	5 (0.6)	12 (0.7)
Black/African American, Asian	1 (0.1)	1 (0.1)	2 (0.1)
Black/African American, Native	1 (0.1)	0 (0.0)	1 (0.1)
Hawaiian/other Pacific Islander, white			
Blac/ African American, white	71 (8.3)	59 (6.9)	130 (7.6)
Black/African American, white, Asian	1 (0.1)	1 (0.1)	2 (0.1)
Native Hawaiian/other Pacific Islander, Asian	1 (0.1)	1 (0.1)	2 (0.1)
Native Hawaiian/other Pacific Islander, white	0 (0.0)	2 (0.2)	2 (0.1)
White, Asian	12 (1.4)	7 (0.8)	19 (1.1)
Native Hawaiian/other Pacific Islander	6 (0.7)	4 (0.5)	10 (0.6)
White	472 (55.0)	480 (56.1)	952 (55.5)
Missing	1 (0.1)	0 (0.0)	1 (0.1)
Ethnicity, n (%)	--	--	--
Hispanic or Latino	206 (24.0)	203 (23.7)	409 (23.9)
Non-Hispanic and Non-Latino	639 (74.5)	643 (75.1)	1,282 (74.8)
Not Reported	11 (1.3)	5 (0.6)	16 (0.9)
Unknown	2 (0.2)	5 (0.6)	7 (0.4)

Source: Adapted from STN 125741.6, V114-029 Clinical Study Report: Table 10-5

Abbreviations: N=number of vaccinated participants for each cohort (participants with at least 1 vaccination of either PCV15 or PCV13); n=number of participants with indicated characteristic; SD=standard deviation

For Sex, Gestational Age at birth, Racial Origin and Ethnicity: n indicates number of subjects fulfilling the item in each category, (%) indicates % of all vaccinated participants represented in each category

### *Participant Disposition*

Of the 1720 study participants, 477 (27.7%) had at least one important protocol deviation. 239 (13.9%) participants had clinically important protocol deviations. Most of these clinically important protocol deviations were due to administration of the study vaccine outside of the protocol defined window (112 participants, collection of the immunogenicity blood sample outside of the protocol defined window (93 participants), and receipt of non-study vaccines (62 participants) during a protocol-prohibited period. The dispositions of the study participants are shown in [Table 4](#) below.

**Table 4. Study V114-029: Summary of Participant Disposition**

<b>Disposition</b>	<b>PCV15 N=860</b>	<b>PCV13 N=860</b>	<b>Total N=1,720</b>
Enrolled, n (%)	860	860	1,720
Vaccinated, n (%)	858 (99.8)	856 (99.5)	1,714 (99.7)
Completed, n (%)	758 (88.1)	734 (85.3)	1,492 (86.7)
APaT* - Safety, n (%)	858 (100.0%)	855 (99.4%)	1,713 (99.6%)
FAS** (IgG), n (%)	--	--	--
30 Days PD3	748 (87.0)	721 (83.8)	1,469 (85.4)
30 Days PD4	730 (84.9)	702 (81.6)	1,432 (83.3)
≥1 important protocol deviation, n (%)	238 (27.7)	239 (27.8)	477 (27.7)
Pentacel recipients***	600 (69.8)	604 (70.2)	1204 (70.0)
PP**** (IgG), n (%)	--	--	--
30 Days PD3	455 (54.7)	430 (50.0)	885 (51.4)
Prior to Dose 4	494 (57.4)	481 (55.9)	975 (56.7)
30 Days PD4	470 (54.7)	447 (52.0)	917 (53.3)
PP**** (OPA), n (%)	--	--	--
30 Days PD3	124 (14.4)	114 (13.2)	218 (12.7)
Prior to Dose 4	47 (5.5)	45 (5.2)	92 (5.3)
30 Days PD4	45 (5.2)	46 (5.3)	91 (5.3)

Source: Adapted from STN 125741.6, V114-029 Clinical Study Report: Table 10-1, Table 10-3, Table 10-4, Table 14 1-4, Table 14.2-7, Table 14.2-8, Table 14.2-11, Table 14.2-12, Information request responses received March 17, 2022: Table 10, Table 11, and Information request responses received April 13, 2022: Table 1

Abbreviations: APaT=All Participants as Treated; FAS=full analysis set; IgG=immunoglobulin G; N=number of participants enrolled; n=indicates number of participants fulfilling the item for each cohort; PD=post-dose; PP=per-protocol

\* All randomized participants who received at least one dose of study vaccination. Participants who received an incorrect study vaccination were excluded from the APaT

\*\* All randomized participants who received all study vaccinations required at the timepoint for the analysis and have serology result

\*\*\*Participants enrolled to receive Pentacel concomitantly with either PCV15 or PCV13 (excludes Pentavac recipients)

\*\*\*\* Population consists of all randomized participants, excluding Pentavac recipients, without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s)

Reviewer Comment: Under the IND, the Applicant had indicated that Study V114-029 participants would receive Pentacel, a US-licensed vaccine, concomitantly PCV15/PCV13 at 2, 4, 6 months of age.

However, during the sBLA review, the Applicant clarified (STN 125741.6/Am13) that Pentavac was used in place of Pentacel for participants enrolled at non-US sites (i.e., Turkey and Thailand) for DTaP-IPV-Hib vaccinations at 2,4,6 months of age. The Applicant reported that 30% of participants received Pentavac concomitantly with either PCV15 or PCV13.

As Pentavac is not approved for use in the US, immunogenicity and key safety endpoints were evaluated excluding Pentavac recipients ([Section 6.1.11](#)). The proportion of participants excluded from analyses were balanced across groups, as well as the frequencies and types of clinically important protocol deviations ([Section 6.1.10](#)). The exclusion of Pentavac participants did not significantly impact the interpretability of study results. The key immunogenicity results did not differ from those presented in the CSR, except as reviewed under the relevant immunogenicity analyses in [Section 6.1.11](#). The rates of safety events following the exclusion of Pentavac recipients were similar to those presented in the CSR

### 6.1.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints but did include serologic immune endpoints to assess the response to study vaccines as discussed in [Section 6.1.1](#).

#### Primary Analyses-Hypotheses 1 & 2: Seroresponse Rates $\geq 0.35$ $\mu\text{g/mL}$ , PD3

Primary immunogenicity analyses for H1 and H2 evaluated proportion of participants with anti-pneumococcal serotype-specific IgG  $\geq 0.35$   $\mu\text{g/mL}$  at 30 days PD3 in the PCV15 group compared to the PCV13 group. For the 13 shared serotypes, V114 was non-inferior to PCV13 if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar13™) was greater than -10 percentage points. For the 2 unique serotypes, noninferiority was evaluated using the same statistical criteria, as compared to the seroresponse rate of in PCV13 recipients to the lowest response rate not including serotype 3.

The results of these non-inferiority analyses are shown in [Table 5](#). PCV15 met the noninferiority criteria for the 13 shared serotypes and 2 unique serotypes as compared to PCV13 recipients. PCV15 also met criteria for statistical superiority for the two unique serotypes.

**Table 5. Study V114-029: Proportion of Participants With Anti-PnP IgG  $\geq 0.35$   $\mu\text{g/mL}$ , 30 Days PD3, PP**

Serotype	PCV15	PCV13	% Difference (95% CI)
	N=452-455 % $\geq 0.35$ $\mu\text{g/mL}$	N=426-430 % $\geq 0.35$ $\mu\text{g/mL}$	
1	93.8	98.6	-4.8 (-7.5, -2.4)
3	93.1	74.0	19.1 (14.4, 24.0)
4	94.7	98.1	-3.4 (-6.1, -1.0)
5	93.4	96.0	-2.6 (-5.7, 0.3)
6A	92.7	99.3	-6.6 (-9.4, -4.2)
6B	86.7	89.9	-3.2 (-7.5, 1.1)
7F	98.7	100.0	-1.3 (-2.9, -0.4)
9V	96.7	97.2	-0.5 (-2.9, 1.9)
14	97.8	98.	-0.3 (-2.4, 1.7)
18C	96.2	98.1	-1.9 (-4.3, 0.3)
19A	97.4	99.8	-2.4 (-4.3, -1.0)
19F	98.5	100.0	-1.5 (-3.2, -0.6)
23F	89.8	91.4	-1.5 (-5.4, 2.4)
22F*	98.0	89.9	8.1 (5.1, 11.5)
33F*	84.8	89.9	-5.1 (-9.5, -0.7)

Source: Adapted from response to Information Request received March 17, 2022: Table 13 and Table 14

Abbreviations: CI=confidence interval; IgG=immunoglobulin G; N=range of number of participants in PP population for IgG at 30 days after dose 3; PD=post-dose; PnP=pneumococcal polysaccharide; PP=per protocol population

Data presented excludes Pentavac recipients

Difference: Difference in % of participants with a serotype specific IgG concentration  $\geq 0.35$   $\mu\text{g/mL}$  between those randomized to receive PCV15 and those randomized to receive PCV13

\* Response rates for serotypes 22F and 33F in PCV15 were compared with the lowest IgG response rate of the shared serotypes in PCV13, excluding serotype 3, at 30 days after dose 3 (i.e., serotype 6B).

#### Primary Analyses-Hypotheses 3, 4, 5, & 6: IgG GMCs, PD3 and PD4

These primary immunogenicity analyses evaluated the GMC ratios of the serotype specific IgG responses in participants in the PCV15 group as compared to participants in the PCV13 group. For the 13 shared serotypes contained in V114 and PCV13, demonstration of noninferiority was based on the lower bound of the 2-sided 95% confidence interval being  $>0.5$ .

The results of the analyses of these endpoints are shown in [Table 6](#) below. Noninferiority criteria were met for all shared serotypes PD3, with the exception of serotype 6A for which lower bound of the 95% confidence interval was 0.48. Noninferiority criteria were met for all shared serotypes PD4.

**Table 6. Study V114-029: Anti-PnP IgG GMCs, Post Dose 3 and Post Dose 4, PP**

Serotype	PCV15	PCV13	GMC Ratio Ratio (95% CI) Ratio (95% CI)
	PD3 GMC PD4 GMC N=452-455 N=466-470	PD3 GMC PD4 GMC N=426-430 N=443-447	
1	1.02	1.54	0.66 (0.61, 0.73)
	1.21	1.82	
3	0.96	0.56	1.70 (1.54, 1.86)
	0.91	0.63	
4	1.07	1.11	0.97 (0.89, 1.06)
	1.07	1.42	
5	1.29	1.69	0.76 (0.68, 0.85)
	2.21	3.47	
6A	1.33	2.48	0.53 (0.48, 0.60)
	3.56	5.93	
6B	1.42	1.58	0.90 (0.76, 1.06)
	4.70	6.07	
7F	2.17	2.83	0.77 (0.70, 0.84)
	3.22	4.65	
9V	1.47	1.48	1.00 (0.90, 1.10)
	2.18	2.86	
14	4.17	5.57	0.75 (0.66, 0.85)
	5.09	6.21	
18C	1.29	1.55	0.83 (0.76, 0.91)
	2.37	2.59	
19A	1.39	1.88	0.74 (0.67, 0.82)
	3.86	4.93	
19F	1.82	2.33	0.78 (0.72, 0.85)
	3.32	4.02	
23F	1.09	1.23	0.89 (0.79, 1.01)
	1.85	2.88	
22F*	4.01	1.11	3.63 (3.26, 4.04)
	6.76	1.42	
33F*	1.38	1.11	1.25 (1.09, 1.44)
	3.80	1.42	

Source: Adapted from response to Information Request received March 17, 2022: Table15, Table 16, Table 17, Table 18

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; IgG=immunoglobulin G; N=range of number of participants in PP population for IgG after dose 3 and after dose 4; PD=post-dose; PnP=pneumococcal polysaccharide; PP=per protocol population. Data presented excludes Pentavac recipients. Ratio: ratio of the GMC of the serotype specific serotype IgG in PCV15 participants to the GMC of PCV13 participants \* GMCs for serotypes 22F and 33F in V114 were compared with the lowest IgG GMC of any of the shared serotypes in PCV13, excluding serotype 3 (serotype 4), at 30 days After Doses 3 and 4.

**Reviewer Comment:** Although the noninferiority criterion for the IgG GMC ratio PD3 for serotype 6A was not met, it is this reviewer’s judgment that the overall immunogenicity data support the noninferiority of the response to serotype 6A in the PCV15 group as compared to the PCV13 group. The lower bound of the IgG GMC ratio PD3 for serotype 6A narrowly missed the non-inferiority criterion for the lower bound of the 95% CI (0.48 vs. the predefined limit of 0.5) and PD4 noninferiority was successfully demonstrated. Also, the

PD3 seroresponse rate  $\geq 0.35$   $\mu\text{g/mL}$  for serotype 6A successfully demonstrated the noninferiority of the responses to 6A across groups (see Table 5).

### Secondary Analyses- Hypothesis 7: Concomitant Vaccinations PD3 -Pentacel

Secondary objectives of study V114-029 evaluated the noninferiority of concomitantly administered routine infant vaccines when administered after dose 3 or dose 4 of PCV15 as compared to PCV13. The immune responses to pertussis, diphtheria, tetanus, poliovirus, and *H. influenzae* type B (Hib) antigens all met the noninferiority criteria based on the response rates observed at 30 days PD 3, as shown in [Table 7](#).

**Table 7. Study V114-029: Concomitant Pentacel Antigen Response Rates and GMCs, Post-PCV Dose 3, PP**

Vaccine	CL	PCV15	PCV 13	Difference (95% CI) Ratio* (95% CI)
		N=401-456 % $\geq$ CL GMC*	N=380-431 % $\geq$ CL GMC*	
Pertussis	--	--	--	--
FHA	% $\geq 5$	98.7	99.1	-0.4 (-2.0, 1.2)
	EU/mL	41.95	45.16	0.93 (0.82, 1.05)
PT	% $\geq 5$	98.5	97.7	0.8 (-1.1, 2.9)
	EU/mL	33.40	33.12	1.01 (0.89, 1.14)
PRN	% $\geq 5$	95.0	93.0	1.9 (-1.2, 5.2)
	EU/mL	32.27	33.59	0.96 (0.83, 1.12)
FIM2/3	% $\geq 20$	92.8	91.0	1.8 (-1.8, 5.5)
	EU/mL	100.70	91.85	1.10 (0.94, 1.27)
Diphtheria	$\geq 0.1$ IU/mL	95.4	96.3	-0.9 (-3.6, 1.8)
Tetanus	$\geq 0.1$ IU/mL	100.0	99.8	0.2 (-0.6, 1.3)
Poliovirus 1	% with NAb $\geq 1:8$ dilution	99.8	99.7	0.0 (-1.1, 1.2)
Poliovirus 2	% with NAb $\geq 1:8$ dilution	100.0	100.0	0.0 (-0.9, 1.0)
Poliovirus 3	% with NAb $\geq 1:8$ dilution	100.0	100.0	0.0 (-0.9, 1.0)
Hib (Pentacel)	$\geq 0.15$ $\mu\text{g/mL}$	89.3	90.8	-1.5 (-5.8, 2.8)

Source: Adapted from Responses to IR sent March 4, 2022: Table 19 and Table 20

GMC: Geometric Mean Concentration

PP: Per protocol population

N=Range of number of participants in PP population for all Pentacel antigens at 30 days after Dose 3

CL: Comparison level for determination of response rate to each vaccine

%  $\geq$ CL: Percent of participants in the PP cohort who had a response rate equal to or greater than the comparison level

95% CI: 95 percent confidence interval

Difference: Difference in % of participants with a response greater than or equal to the comparison level between PCV15 recipients and PCV13 recipients

Ratio: ratio of the vaccine specific GMCs in PCV15 participants to the vaccine specific GMC of PCV13 participants

\* GMC and Ratio if available

**Reviewer Comment:** Study V114-029 evaluated the non-inferiority of the responses to the pertussis antigens in following 3 doses of Pentacel rather than the complete 4 dose series. The Applicant did not design the study to demonstrate the effectiveness of currently licensed

pertussis-containing vaccines when administered with PCV, but rather to demonstrate comparable antibody responses to other routinely administered pediatric vaccines when given with either PCV15 or PCV13 as a comparator. Although, the pertussis antigen GMC ratios and seroresponse rates met non-inferiority criteria, conclusions regarding the noninferiority of responses to a complete 4-dose regimen of Pentacel in PCV15 recipients cannot be reached on the basis of the submitted immunogenicity data.

### Secondary Analyses- Hypotheses 8, 9, 10, and 11: Concomitant Vaccinations Post-PCV dose 4- VAQTA, M-M-R II, Varivax, Hiberix

The immune responses to hepatitis A, measles, mumps, rubella, varicella, and Hib antigens also met the noninferiority criteria based on the response rates observed at 30 days post-PCV dose 4, as shown in [Table 8](#).

**Table 8. Study V114-029: Immune Responses to Concomitant Vaccinations, 30 Days Post-PCV Dose 4, PP**

Vaccine	Endpoints*	PCV15	PCV13	% Difference (95% CI)	NI Margin <sup>Q</sup>
		N=394-457 % Participants	N=381-440 % Participants		
Hepatitis A	≥10 mIU/mL	97.3%	97.4%	-0.2 (-2.6, 2.2)	-10%
VZV	≥5 (b) (4) units/mL	97.2%	97.3%	-0.1 (-2.3, 2.2)	-10%
Measles	≥255 mIU/mL	97.9%	98.4%	-0.6 (-2.3, 1.3)	-5%
Mumps	≥10 mumps Ab units/mL	94.4%	97.1%	-2.6 (-5.4, 0.0)	-5%
Rubella	≥10 IU/mL	97.2%	98.9%	-1.7 (-3.7, 0.2)	-5%
Hib (Hiberix)	≥0.15 µg/mL	98.5%	100.0%	-1.5 (-3.2, -0.5)	-10%

Source: Adapted from response to Information Request received March 28, 2022: Table1, Table 2, Table 3, Table 4

Abbreviations: CI=confidence interval; GMC=geometric mean concentration; N=number of participants (range) in PP population who received VAQTA, M-M-R II, Varivax, and Hiberix at 30 days after dose 4 of either PCV15 or PCV13; NI=non-inferiority; PCV=pneumococcal conjugate vaccine (either PCV15 or PCV13); PP=per-protocol population. Data excludes Pentavac recipients

Endpoints\*: Includes the proportion (%) of participants who achieved the pre-defined serologic assay threshold for each respective antigen and the GMC for pertussis antigens only

% Participants: proportion of participants in the PP cohort who had a response rate equal to or greater than the threshold level. GMC: Geometric Mean Concentration for pertussis antigens only

NI Margin<sup>Q</sup>: For each vaccine antigen and study endpoint, the non-inferiority margin (NI) is listed which is the lower limit (LL) of the 95% CI the difference of either the % difference in participants achieving the pre-defined serologic assay threshold or the LL of the 95% CI of the GMC

**Reviewer Comment:** Anti-PRP (Hib) responses among PCV15 recipients met non-inferiority criteria following 3 doses of Pentacel administered concomitantly with 3 doses of PCV and a single dose of Hiberix administered with dose 4 of PCV as determined by seroresponse rates using a threshold of ≥0.15 µg/mL. The mumps antigen response narrowly missed the pre-specified non-inferiority criterion. However, this result was likely due to the reduction in statistical power due to the exclusion of Pentavac recipients from the analysis rather than immune interference with the mumps antigen response (analysis with Pentavac recipients included met the noninferiority criterion).

### Secondary Analyses-Hypotheses 12, 13, & 14: Superiority Testing-Serotypes 22F & 33F

As described in [Section 6.1.1](#), Secondary Objectives 6 and 7 evaluated the statistical superiority of the two unique serotypes (22F, 33F) in PCV15 compared to PCV13, which did not include these two serotypes. The statistical success criteria following dose 3 required that the lower bound of 2-sided 95% CI was greater than 10% for the difference (PCV15–PCV13) in the



proportion of participants with serotype-specific IgG response rates  $\geq 0.35$   $\mu\text{g/mL}$ . The % difference (95% CI) across groups (excluding Pentavac recipients) were as follows:

- Post dose 3
  - ST22F: 94.7% (92.1, 96.5)
  - ST33F: 83.0% (79.1, 86.2)

In addition, following both dose 3 and dose 4, the statistical success criteria for superiority required that the lower bound of the 2-sided 95% CI was greater than 2.0 for the ratio (PCV15/PCV13) of serotype specific IgG GMCs. The IgG GMC ratio (95% CI) across groups for each serotype and each dose (excluding Pentavac recipients) were as follows:

- Post dose 3:
  - ST22F: 83.58 (73.75, 94.73)
  - ST33F: 28.15 (24.24, 32.70)
- Post dose 4
  - ST22F: 92.03 (83.47, 101.47)
  - ST33F: 45.25 (40.37, 50.73)

The statistical success criteria were met post-dose 3 and post-dose 4 for the respective superiority test for both serotypes (22F and 33F).

### **Secondary Analyses – Hypotheses 15, 16, &17: Superiority Testing-Serotype 3**

Secondary Objective 8 evaluated the statistical superiority of serotype 3 in PCV15 to serotype 3 in PCV13. The statistical success criteria following dose 3 required that the lower bound of 2-sided 95% CI was greater than 0% for the difference (PCV15–PCV13) in the proportion of participants with serotype-specific IgG response rates  $\geq 0.35$   $\mu\text{g/mL}$ .

The % difference (95% CI) across groups (excluding Pentavac recipients) was as follows:

- Post dose 3: 19.1% (14.4, 24.0)

In addition, following both dose 3 and dose 4, the statistical success criteria for superiority required that the lower bound of the 2-sided 95% CI was greater than 1.2 for the ratio (PCV15/PCV13) of serotype specific IgG GMCs. The IgG GMC ratio across groups for each dose were as follows:

- Post dose 4
  - ST22F: 1.70 (1.54, 1.86)
  - ST33F: 1.43 (1.30, 1.57)

Superiority criteria were met for the superiority of PD3 seroresponse rates ([Table 5](#)) and PD3 and 4 GMC ratios ([Table 6](#)) of PCV15 recipients.

### **Secondary Analyses (Descriptive): Anti-PnP OPA**

Serotype-specific anti-PnP opsonophagocytic activity against the 13 shared serotypes, assessed descriptively by OPA geometric mean titers (GMTs) and OPA response rate (percent of participants with OPA titers  $\geq$  LLOQ of the serotype-specific OPA assay) and were comparable between PCV15 and PCV13 recipients 30 days PD 3, prior to dose 4, and 30 days PD4. PD3 OPA responses were determined in the first 20% of participants in each group (OPA subset) who had sufficient volume to allow evaluation. Pre-dose and PD4 OPA responses were determined in approximately 50% of the OPA subset. OPA GMTs ([Table 9](#)) and responses rates greater than

endpoints ([Table 10](#)) were generally comparable across groups for the 13 shared serotypes at all time points and were higher in the PCV15 group for the two unique serotypes PD3 and PD4.

**Table 9. Study V114-029: OPA GMTs 30 Days PD3 and 30 Days PD4, PP**

Serotype	PCV15	PCV13
	N=122-124, PD3 GMT (95% CI) N=44-45, PD4 GMT (95% CI)	N=109-114, PD3 GMT (95% CI) N=41-46, PD4 GMT (95% CI)
1	50.4 (39.8, 63.9)	56.3 (42.4, 74.7)
	116.3 (82.4,164.1)	148.3 (98.0,224.6)
3	239.6 (210.9, 272.1)	174.2 (154.0, 197.2)
	331.3 (261.1,420.3)	367.5 (304.3,443.8)
4	1216.3 (1026.5, 1441.1)	1423.2 (1217.4, 1663.7)
	2220.0 (1658.4,2971.7)	2830.1 (2052.5,3902.3)
5	315.4 (256.6, 387.6)	369.2 (298.6, 456.6)
	1070.4 (772.1,1483.9)	1323.5 (931.2,1881.2)
6A	2083.1 (1758.1, 2468.2)	2776.8 (2309.4, 3338.8)
	5766.3 (4173.4,7967.1)	7114.1 (5104.6,9914.7)
6B	1635.5 (1323.4, 2021.1)	1653.9 (1318.5, 2074.6)
	5055.6 (3610.6,7078.8)	5740.1 (3974.9,8289.1)
7F	4358.7 (3666.4, 5181.8)	5941.2 (4926.5, 7164.8)
	9273.9 (6582.5,13065.7)	10246.7 (6727.3,15607.3)
9V	1163.5 (962.7, 1406.1)	1350.9 (1110.6, 1643.2)
	2502.6 (1798.8,3481.8)	3576.7 (2537.3,5041.7)
14	1985.2 (1574.5, 2503.1)	1223.3 (977.4, 1531.0)
	4101.5 (2941.7,5718.5)	2241.9 (1596.9,3147.6)
18C	1119 (952.9, 1313.9)	1136.3 (957.7, 1348.2)
	2333.3 (1743.2,3123.2)	2697.4 (2073.3,3509.3)
19A	777.4 (634.8, 952.0)	1224.3 (1018.4, 1471.7)
	3054.7 (2344.0,3980.9)	5073.2 (3786.9,6796.4)
19F	714.7 (605.6, 843.3)	815.4 (691.2, 961.9)
	2071.5 (1493.5,2873.3)	1881.3 (1439.8,2458.1)
23F	2058.4 (1738.5, 2437.1)	3221.5 (2577.7, 4026.2)
	5333.4 (3657.4,7777.2)	12189.4 (8156.9,18215.4)
22F	1767.3 (1492.3, 2092.9)	9.5 (7.9, 11.4)
	3208.1(2530.1,4067.6)	13.4 (8.1, 22.2)
33F	7624 (5833.4, 9964.3)	122.2 (78.7, 189.6)
	18505.8 (13028.1,26286.7)	889.5 (513.2, 1542.0)

Source: Adapted from response to Information Request received March 22, 2022: Table 8 and Information Request received April 13, 2022, Table 2

Abbreviations: CI=confidence interval; GMT=Geometric mean titer N=range of number of participants in the OPA Subset of PP population at 30 days PD 3, before dose 4, and PD 4; OPA=opsonophagocytosis activity; PD=post-dose; PP=per-protocol population; 95% CI: 95% confidence interval.

Data excludes Pentavac recipients

PD3: 30 days PD3

Pre-D4: Pre-dose 4

PD4: 30 days PD4

Ratio: ratio of the serotype specific OPA GMT in PCV15 participants to the OPA GMT of PCV13 participants

**Table 10. Study V114-029: OPA Response Rates\* 30 Days PD 3 and 30 Days PD 4, PP**

Serotype	PCV15	PCV13
	N=106-123, PD3% (95% CI) N=42-45, PD4% (95% CI)	N=8-113, PD3% (95% CI) N=41-46, PD4% (95% CI)
1	86.2 (78.8, 91.7) 100.0 (92.1,100.0)	84.2 (76.2, 90.4) 97.8 (88.5,99.9)
3	100 (97.0, 100.0) 100.0 (92.1,100.0)	100 (96.7, 100.0) 100.0 (92.3,100.0)
4	99.2 (95.5, 100.0) 100.0 (92.1,100.0)	100 (96.7, 100.0) 100.0 (92.1,100.0)
5	96.8 (91.9, 99.1) 100.0 (92.1,100.0)	97.4 (92.5, 99.5) 100.0 (92.3,100.0)
6A	97.6 (93.1, 99.5) 100.0 (92.1,100.0)	99.1 (95.1, 100.0) 100.0 (92.1,100.0)
6B	97.6 (93.0, 99.5) 100.0 (92.1,100.0)	99.1 (95.1, 100.0) 100.0 (92.3,100.0)
7F	100 (97.0, 100.0) 100.0 (92.1,100.0)	100 (96.7, 100.0) 97.8 (88.5,99.9)
9V	97.5 (93.0, 99.5) 97.8 (88.2, 99.9)	97.4 (92.5, 99.5) 100.0 (92.3,100.0)
14	98.3 (94.2, 99.8) 100.0 (92.1,100.0)	98.2 (93.7, 99.8) 100.0 (92.3,100.0)
18C	99.2 (95.6, 100.0) 100.0 (92.1,100.0)	99.1 (95.2, 100.0) 100.0 (92.3,100.0)
19A	97.6 (93.1, 99.5) 100.0 (92.1,100.0)	99.1 (95.2, 100.0) 100.0 (92.3,100.0)
19F	95.2 (89.8, 98.2) 100.0 (92.1,100.0)	98.2 (93.8, 99.8) 97.8 (88.5,99.9)
23F	100 (97.0, 100.0) 100.0 (92.1,100.0)	100 (96.7, 100.0) 100.0 (92.3,100.0)
22F	99.2 (95.6, 100.0) 100.0 (92.1,100.0)	7.4 (3.3, 14.1) 12.2 (4.1,26.2)
33F	98.4 (94.3, 99.8) 100.0 (92.1,100.0)	56.9 (47.0, 66.3) 90.9 (78.3,97.5)

Source: Adapted from response to Information Request received March 22, 2022: Table 7 and Information Request received April 13, 2022: Table 3

Abbreviations: CI=confidence interval; GMT=geometric mean titer; N=range of number of participants in the OPA Subset of PP population at 30 days after dose 3, before dose 4, and after dose 4; OPA=opsonophagocytosis activity; PD=post-dose; PP=per-protocol population

Data excludes Pentavac recipients

Endpoints\*: Includes the proportion (%) of participants with OPA titers  $\geq$  lower limit of quantitation of the serotype specific assay

PD3: 30 days PD3; Pre-D4: Pre-dose 4; PD4: 30 days PD4

Difference: Difference in % of participants with an OPA GMT  $\geq$  comparison level between those randomized to receive PCV15 and those randomized to receive PCV13

**Reviewer Comment:** OPA results followed similar trends as those observed with primary analyses evaluating IgG GMCs in that responses to the 13 shared serotypes were generally comparable between study groups and the responses to the 2 unique serotypes were higher in the PCV15 group and support the functional antibody responses to all vaccine serotypes after the 3<sup>rd</sup> and 4<sup>th</sup> doses of PCV15.

**Tertiary Analyses (Descriptive): Concomitant Vaccinations- Pentacel Post-PCV Dose 3 and Hiberix Post-PCV Dose 4 Using Alternate Endpoints**

The response rate to the Hib component of Pentacel at 30 days PD3 when administered concomitantly with either PCV15 or PCV13 was evaluated using an endpoint of  $\geq 1.0$   $\mu\text{g/mL}$ .

The anti-PRP response rates  $\geq 1.0$   $\mu\text{g/mL}$  to Pentacel post-PCV dose 3 were generally comparable between treatment groups (PCV15: 61.1% [56.1, 65.9]; PCV13: 69.5% [64.6, 74.1]).

The anti-PRP response rates  $\geq 1.0$   $\mu\text{g/mL}$  to Hiberix post-PCV dose 4 were also generally comparable between treatment groups (PCV15: 94.3% [91.6, 96.4]; PCV13: 98.2% [96.4, 99.3]).

Reviewer Comment: This clinical reviewer agrees with the Applicant's assessment that the anti-PRP responses to Pentacel 30 days following dose 3 of PCV and to Hiberix 30 days following PCV dose 4 were generally comparable across study groups consistent with a lack of immune interference.

#### **Exploratory Analyses (Descriptive): IgG GMCs to PCV15 Prior to Dose 4**

Serotype-specific IgG GMCs prior to dose 4 were determined for the 15 serotypes in PCV15. The IgG GMCs for the 13 shared serotypes were generally comparable between PCV15 and PCV13 recipients. IgG GMCs for the 2 serotypes unique to PCV15 were higher in PCV15 recipients.

#### **Exploratory Analyses (Descriptive): OPA Responses to PCV15 Pre- and 30 days PD4**

PCV15 elicited OPA responses comparable to PCV13 for the 13 shared serotypes and higher OPA responses for the two unique serotypes PD3, pre-, and PD4 as assessed by OPA GMTs and OPA response rates. PD4 OPA response rates were higher than Pre-D4 OPA response rates in both study groups for the 13 shared serotypes. PD4 OPA response rates were higher than Pre-D4 OPA response rates for the 2 unique serotypes in the PCV15 group. Pre-dose 4 OPA response rates to 22F and 33F were lower in the PCV13 group than in the PCV15 group (especially for serotype 22F) and were generally unchanged PD4.

#### **Subpopulation Analyses: Sex, Race, Ethnicity**

Subpopulation analyses were conducted for all primary immunogenicity endpoints for all subpopulations that contained  $\geq 5\%$  of the total number participants for the study group. Observed serotype-specific IgG GMCs and response rates for all 15 serotypes were consistent with those observed in the overall population for the following subgroups: male vs. female participants, race (black, White, Asian, and multiple races), ethnicity (Hispanic or Latino, not Hispanic or Latino).

#### **Subpopulation Analyses: Pre-term Infants vs Term Infants**

In a descriptive comparison, submitted to the sBLA as a 'Response to FDA Request for Information',<sup>1</sup> the immunogenicity of a 4-dose PCV15 series in pre-term infants was evaluated compared to that in term infants for Study V114-029. The findings of the primary analyses in term (EGA  $\geq 37$  weeks) infants were similar to those reported in all infants (EGA  $< 37$  weeks and EGA  $\geq 37$  weeks), as presented for the primary analyses.

The proportions of pre-term infants who received PCV15 with serotype-specific IgG responses  $\geq 0.35$   $\mu\text{g/mL}$  post-dose 3 were generally similar to those reported in all infants for the primary

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<sup>1</sup> Applicant submitted these descriptive analyses to the sBLA (STN 125741/6 Am10, dated March 14, 2022) in response to CBER Information Request, sent March 9, 2022,

analyses. The following table provides the descriptive analyses of the serotype-specific IgG response rates at 30 days post-dose 3 across vaccine groups for pre-term infants only.

**Table 11. Study V114-029: Proportion of Pre-Term Infants With IgG  $\geq 0.35$   $\mu\text{g/mL}$ , 30 Days PD3, PP**

Serotype	PCV15	PCV13	% Difference (95% CI)
	N=40 % $\geq 0.35$ $\mu\text{g/mL}$	N=43 % $\geq 0.35$ $\mu\text{g/mL}$	
1	97.5	100.0	-2.5 (-13.0,5.9)
3	97.5	86.0	11.5 (-0.8, 25.3)
4	97.5	97.7	-0.2 (-10.9, 9.9)
5	95.0	97.7	-2.7 (-14.6,7.8)
6A	92.5	100.0	-7.5 (-20.0, 1.1)
6B	92.5	86.0	6.5 (-8.0,21.1)
7F	97.5	100.0	-2.5 (-13.0,5.9)
9V	97.5	95.3	2.2 (-8.9,13.4)
14	100.0	97.7	2.3(-6.6,12.1)
18C	92.5	100.0	-7.5 (-20.0,1.1)
19A	95.0	100.0	-5.0 (-16.6,3.5)
19F	100.0	100.0	0.0 (-8.9,8.3)
23F	92.5	90.7	1.8 (-12.0,15.4)
22F*	92.5	86.0	6.5 (-8.0, 21.1)
33F*	90.0	86.0	4.0 (-11.3, 19.0)

Source: Adapted from Information Request response received April 13, 2020: Table 22 and Table 24

Abbreviations: CI=confidence interval; IgG=immunoglobulin G; N=range of number of participants in PP population for IgG at 30 days after dose 3; PD=post-dose; PnP=pneumococcal polysaccharide; PP=per-protocol population

Data excludes Pentavac recipients

Difference: Difference in % of participants with a serotype specific IgG concentration  $\geq 0.35$   $\mu\text{g/mL}$  between those randomized to receive PCV15 and those randomized to receive PCV13

\* Response rates for serotypes 22F and 33F in PCV15 were compared with the lowest IgG response rate (23F) of any of the shared serotypes in PCV13, excluding serotype 3, at 30 days after dose 3.

The IgG GMCs at post-dose 3 and post-dose 4 for PCV15 recipients were also comparable between pre-term and all infants reported for the primary analyses. The following table provides the descriptive analyses of the serotype-specific IgG GMCs at 30 days post-dose 3 and post-dose 4 for pre-term infant only.

**Table 12. Study V114-029: IgG GMCs in Pre-Term Infants, 30 Days Post Dose3 and Post Dose 4, PP**

Serotype	PCV15	PCV13	GMC Ratio Ratio (95% CI)
	N=40 PD3 GMC PD4 GMC	N=43 PD3 GMC PD4 GMC	
1	1.42	1.43	1.00 (0.77,1.30)
	1.45	1.98	0.73 (0.57, 0.93)
3	1.13	0.63	1.79 (1.32, 2.43)
	1.11	0.70	1.59 (1.27, 1.98)
4	1.26	1.14	1.10 (0.85, 1.43)
	1.34	1.38	0.97 (0.75, 1.27)
5	1.66	1.39	1.19 (0.85, 1.66)
	2.47	3.51	0.70 (0.54, 0.92)
6A	1.63	2.53	0.64 (0.45, 0.93)
	3.73	6.40	0.58 (0.43, 0.79)
6B	1.53	1.37	1.12 (0.64, 1.95)
	4.52	5.88	0.77 (0.56, 1.04)
7F	2.65	2.48	1.07 (0.79, 1.43)
	2.93	4.32	0.68 (0.49, 0.93)

Serotype	PCV15	PCV13	GMC Ratio Ratio (95% CI)
	N=40 PD3 GMC PD4 GMC	N=43 PD3 GMC PD4 GMC	
9V	2.08	1.38	1.51 (1.12, 2.03)
	2.67	2.68	1.00 (0.79, 1.26)
14	5.63	5.25	1.07 (0.75, 1.53)
	4.66	6.41	0.73 (0.51, 1.03)
18C	1.72	1.38	1.24 (0.92, 1.69)
	2.72	2.35	1.16 (0.88, 1.52)
19A	1.53	1.66	0.93 (0.68, 1.26)
	4.07	4.93	0.83 (0.65, 1.06)
19F	2.39	2.31	1.03 (0.80, 1.33)
	3.58	4.83	0.74 (0.58, 0.96)
23F	1.31	1.09	1.20 (0.83, 1.75)
	2.20	2.66	0.83 (0.61, 1.12)
22F*	3.94	1.29	3.30 (2.11, 5.15)
	7.66	1.38	5.57 (4.26, 7.29)
33F*	1.81	1.29	1.77 (1.14, 2.73)
	4.23	1.38	3.07 (2.33, 4.05)

Source: Adapted from Information Request response received April 13, 2022: Table 26 and Table 28

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; IgG=immunoglobulin G; N=range of number of participants in PP population for IgG after dose 3 and after dose 4; PnP=pneumococcal polysaccharide; PP=per-protocol population  
 Data excludes Pentavac recipients

Ratio: ratio of the GMC of the serotype specific serotype IgG in PCV15 participants to the GMC of PCV13 participants

\* GMCs for serotypes 22F and 33F in V114 were compared with the lowest IgG GMC (serotype 4) of any of the shared serotypes in PCV13, excluding serotype 3, at 30 days After Doses 3 and 4.

**Reviewer Comment:** Serotype-specific IgG responses were generally comparable between participants who were either full-term or pre-term gestational age at birth. Discussion of OPA responses in preterm infants is discussed in the Integrated Overview of Immunogenicity ([Section 7](#)). Immunogenicity data from pre-term infants support inclusion of this demographic in the label.

## 6.1.12 Safety Analyses

### Methods

See [Section 6.1.2](#).

### Overview of Adverse Events

[Table 13](#) provides an overview of AEs by type occurring for the PCV15 and PCV13 groups. Rates of SAEs and Solicited and Unsolicited AEs were generally comparable between study groups. There was one death in each group that was not considered related to the study product.

**Table 13. Study V114-029: Safety Overview, Proportion of Participants Reporting at Least One Adverse Event Following Any Vaccination Dose, APaT**

<b>AE Type*</b>	<b>V114 N=858</b>	<b>PCV13 N=855</b>
Any adverse event, n (%)	805 (93.8)	790 (92.4)
Injection site	598 (69.7)	595 (69.6)
Systemic	785 (91.5)	766 (89.6)
Serious adverse events, n (%)	38 (6.4)	40 (6.7)
AE leading to vaccine discontinuation, n (%)	0 (0)	0 (0)
Deaths, n (%)	1 (0.2)	0 (0)
<b>Vaccine-related<sup>a</sup> ARs**</b>	<b>N=598</b>	<b>N = 600</b>
Any vaccine-related adverse event n (%)	547 (91.5)	533 (88.8)
Injection-site	473 (79.1)	465 (77.5)
Systemic	471 (78.8)	460 (76.7)

Source: Adapted from Information Request response received March 17, 2022: Table 21

Abbreviations: AE=adverse event; APaT=All Participants as Treated; n=subjects who experienced the event

a. as determined by the Investigator

\* AEs include Pentacel and Pentavac recipients unless otherwise noted

\*\*Vaccine-related ARs exclude participants who received Pentavac

### **Solicited Adverse Reactions (ARs)**

As described in [Section 6.1.7](#), ARs were collected with eVRC with investigator adjudication of final assessment and reporting of any AR. Most participants (~93%) in both study groups experienced one or more solicited AR (either injection site or systemic).

[Table 14](#) provides the details for solicited adverse events in the 14 days following each study dose. The rates of adverse events occurring within 14 days after each study dose were generally comparable between the study groups.

Pain was the most common injection site reaction in the PCV15 group, especially following dose 1 (~40%). Reported occurrences of swelling, erythema, and induration were generally comparable across all doses. Irritability was the most common and somnolence were the most common systemic reactions.

AR severities were comparable between both groups and most ARs were mild (PCV15: 40% - 47%, PCV13: 40%-47%) or moderate (PCV15: 47% - 53%, PCV13: 47% - 53%) in severity and the majority (90.6%) of ARs in the PCV15 group resolved within 3 days or less.

**Table 14. Study V114-029: Comparison of Participants With Solicited Adverse Reactions From Day 1 Through Day 14 by Dose, APaT**

Solicited Adverse Reaction	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3	Dose 4	Dose 4
	PCV15 N=598	PCV13 N=600	PCV15 N=584	PCV13 N=570	PCV15 N=559	PCV13 N=540	PCV15 N=532	PCV13 N=507
Injection site reaction, n (%)	329 (55.0)	299 (49.8)	271 (46.4)	262 (46.0)	272 (48.7)	254 (47.0)	233 (43.8)	229 (45.2)
Erythema	82 (13.7)	88 (14.7)	96 (16.4)	128 (22.5)	114 (20.4)	129 (23.9)	114 (21.4)	122 (24.1)
Induration	84 (14.0)	76 (12.7)	77 (13.2)	92 (16.1)	86 (15.4)	88 (16.3)	73 (13.7)	74 (14.6)
Pain	241 (40.3)	237 (39.5)	187 (32.0)	164 (28.8)	172 (30.8)	145 (26.9)	138 (25.9)	127 (25.0)
Swelling	77 (12.9)	76 (12.7)	77 (13.2)	65 (11.4)	75 (13.4)	56 (10.4)	60 (11.3)	55 (10.8)
Systemic reaction, n (%)	452 (75.6)	474 (79.0)	392 (67.1)	388 (68.1)	371 (66.4)	340 (63.0)	337 (63.3)	326 (64.3)
Decreased appetite	109 (18.2)	114 (19.0)	111 (19.0)	91 (16.0)	79 (14.1)	96 (17.8)	93 (17.5)	83 (16.4)
Irritability	379 (63.4)	404 (67.3)	335 (57.4)	331 (58.1)	330 (59.0)	299 (55.4)	305 (57.3)	287 (56.6)
Somnolence	284 (47.5)	316 (52.7)	208 (35.6)	224 (39.3)	174 (31.1)	163 (30.2)	129 (24.2)	150 (29.6)
Urticaria	7 (1.2)	5 (0.8)	9 (1.5)	8 (1.4)	6 (1.1)	10 (1.9)	18 (3.4)	13 (2.6)

Source: Adapted from response to Information Request March 28, 2022: Table 5, Table 6, Table 7, Table 8  
 Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n (%)=number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort  
 Data excludes Pentavac recipients

**Reviewer Comment:** The median duration of reported ARs was 1 day (range 1 to 34 days). There was 1 participant with irritability that developed on day 13 following dose 1 of PCV15. This irritability was reported to have lasted 318 days; however, the investigator considered this event to not be related to the study vaccine and the event is not included among ARs in the reported range.

*Maximum Body Temperatures within 7 days post-vaccination*

The rate of reported fever belonging to the lower temperature increment (i.e., body temperature  $\geq 38.0^{\circ}\text{C}$ ) was higher in the PCV15 group after dose 1. Rates of reported fever belonging to the highest temperature increment (i.e., body temperature  $\geq 40.0^{\circ}$ ) were slightly higher in PCV15 recipients after doses 2, 3, and 4 as shown in [Table 15](#).



**Table 15. Maximum Body Temperature of Participants From Day 1 (Day of Vaccination) Through Day 7 Following Each Dose in Study V114-029, APaT**

	Dose 1 PCV15 N=594	Dose 1 PCV13 N=593	Dose 2 PCV15 N=558	Dose 2 PCV13 N=552	Dose 3 PCV15 N=536	Dose 3 PCV13 N=511	Dose 4 PCV15 N=512	Dose 4 PCV13 N=485
Temperature	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<38.0°C	485 (81.6)	496 (83.6)	444 (79.6)	432 (78.3)	429 (80.0)	409 (80.0)	444 (86.7)	417 (86.0)
≥38.0°C-39.0°C	103 (17.3)	93 (15.7)	103 (18.5)	100 (18.1)	92 (17.2)	88 (17.2)	62 (12.1)	64 (13.2)
≥39.0°C- 40.0°C,	6 (1.0)	4 (0.7)	9 (1.6)	19 (3.4)	13 (2.4)	13 (2.5)	4 (0.8)	4 (0.8)
≥40.0°C	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	2 (0.4)	0 (0.0)

Source: Adapted from response to IR received June 2, 2022: Tables 1 - 4

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort with at least 1 temperature measurement from Day 1 through Day 7 following the indicated vaccination; n (%) =number of participants experiencing a maximum temperature within the indicated range during the 7-day period post vaccine in each cohort and % of the APaT belonging to that cohort which experienced a maximum temperature within that range

Data presented for participants with available temperature data that excludes Pentavac recipients and reported as measured

Of the maximum temperature measurements, ~71% to ~78% were rectal measurements and ~22% to ~29% were axillary measurements

**Reviewer Comment:** The slightly higher rates of reported fevers  $\geq 40^{\circ}\text{C}$  in the PCV15 group for doses 2, 3, and 4 may represent a modest increase in reactogenicity of PCV15 as compared to PCV13. Overall, the reported occurrences of solicited ARs were generally comparable across groups and the rates of ARs in the PCV15 group were within the range observed following other vaccines licensed for use in infants and young children.

*Unsolicited AEs within 14 days post-vaccination (includes Pentavac recipients)*

Unsolicited AEs were documented by the participant’s legally acceptable representative in the eVRC and reviewed by the investigator at vaccine study visits and at 15 days following each vaccine dose. Rates of unsolicited AEs were generally comparable between study groups (PCV15: 62.2%, PCV13: 60.1%). The most frequently reported events, by MedDRA System Organ Class, were: General disorders and administration site conditions (PCV15: 33.6%, PCV13: 35.7%; Infections and infestations (PCV15: 26.3%, PCV13: 22.0%); and Gastrointestinal disorders (PCV15: 15.2%, PCV13: 12.5%).

**Reviewer Comment:** The reported rates and types of unsolicited adverse events were comparable across study groups and represent medical conditions that are common in children.

**Deaths**

There were two participant deaths during the study (one in the PCV15 group and one in the PCV13 group). The PCV15 participant died as a result complications of congenital heart disease. The PCV13 participant died of septic shock (not due to IPD) 185 days after dose 2 after suffering a head injury 21 days PD2. The investigators did not consider the reported deaths to be related to the study vaccinations.

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

### Nonfatal Serious Adverse Events (SAEs, includes Pentavac recipients)

SAEs were reported by 10.3% of PCV15 group (88 participants) and 9.5% of the PCV13 group (81 participants) during the study. Most SAEs belonged to the System Organ Class (SOC) *Infections and Infestations*. The three most frequently reported SAEs (by preferred term) occurring in the PCV15 group during the study were bronchiolitis (1.3% of group participants), Respiratory Syncytial Virus (RSV) bronchiolitis (0.8% of group participants), and gastroenteritis (0.8% of group participants) as shown in [Table 16](#). The majority of SAEs were considered serious due to hospitalization for monitoring and/or treatment.

**Table 16. Study V114-029: Participants Reporting SAEs\* by Preferred Term Following Any Dose During the Study, APaT**

<b>System Organ Class</b>	<b>PCV15</b>	<b>PCV13</b>
<b>Preferred Term</b>	<b>N=858</b>	<b>N=855</b>
	<b>n (%)</b>	<b>n (%)</b>
Bronchiolitis	11 (1.3)	6 (0.7)
Respiratory syncytial virus bronchiolitis	7 (0.8)	12 (1.4)
Gastroenteritis	7 (0.8)	11 (1.3)
Gastroenteritis viral	6 (0.7)	2 (0.2)
Pneumonia	5 (0.6)	5 (0.6)
Bronchitis	5 (0.6)	2 (0.2)
Pneumonia respiratory syncytial viral	4 (0.5)	1 (0.1)
Viral infection	4 (0.5)	2 (0.2)
Urinary tract infection	3 (0.3)	3 (0.4)
Febrile convulsion	3 (0.3)	2 (0.2)
Exanthema subitum	3 (0.3)	3 (0.4)
Upper respiratory tract infection	2 (0.2)	2 (0.2)
Viral rash	2 (0.2)	2 (0.2)
Viral upper respiratory tract infection	2 (0.2)	1 (0.1)
Bronchial hyperreactivity	2 (0.2)	0 (0.0)
Pyrexia	2 (0.2)	3 (0.4)
Anaphylactic reaction	2 (0.2)	0 (0.0)
Bacteremia	2 (0.2)	1 (0.1)
Diarrhea	2 (0.2)	1 (0.1)
COVID-19	2 (0.2)	1 (0.1)
Croup infectious	2 (0.2)	1 (0.1)
Influenza	2 (0.2)	1 (0.1)
Pharyngitis	2 (0.2)	0 (0.0)
Pneumonia viral	1 (0.1)	2 (0.2)
Respiratory syncytial virus infection	1 (0.1)	3 (0.4)
Brain contusion	1 (0.1)	0 (0.0)
Head injury	0 (0.0)	2 (0.2)

Source: Adapted from STN 125741.6, V114-029 Clinical Study Report: Table 12-8

\*: SAEs reported by greater than 1 participant during the study

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort receiving the indicated dose; n=number of participants experiencing indicated adverse even including Pentavac recipients; SAE=serious adverse event

The three most frequently reported SAEs after dose 1 of PCV15 were: bronchiolitis (including RSV bronchiolitis, n=7), bronchitis (n=3), and viral gastroenteritis (n=2). After dose 2, the most common SAEs were: bronchiolitis (including RSV bronchiolitis, n=10) and Influenza (n=2). Gastroenteritis (n=4), viral infection (n=4), and pneumonia (n=3) were the 3 most frequently reported SAEs after dose 3. Gastroenteritis (including viral gastroenteritis, n=5), RSV pneumonia (n=3), and febrile convulsion (n=3) were the three most commonly reported SAEs

following dose 4 of PCV15. The investigator did not consider any of the SAEs to be related to the study vaccinations. A similar distribution of SAEs was seen within 7 days of vaccination.

Reviewer Comment: This reviewer agrees with the investigators' conclusions that the reported SAEs were not related to the study intervention. Most SAEs were illnesses common in children.

#### **SAE of Interest: Kawasaki Disease**

There was one case of Kawasaki Disease (KD), considered unrelated to the study product, reported in the PCV15 group in a ~19-month-old Asian male without significant medical history 5.4 months after dose 4. Other vaccines received closest to the onset of KD included Japanese encephalitis vaccine and influenza vaccine. The participant presented with fever (39°C), rhinorrhea, rash, drowsiness, "strawberry" tongue, red/dry cracked lips, conjunctival injection with limbal sparing in both the eyes, and a palpable cervical lymph node (0.5 cm), and limb edema. The participant had elevated white blood cell ( $19.48 \times 10^9/L$ ) and platelet ( $475 \times 10^9/L$ ) counts with normal transaminase levels. Cardiac echocardiography findings were consistent with KD. The participant tested negative for SARS-CoV-2.

The participant was diagnosed with incomplete KD and treated with intravenous immunoglobulin (IVIG), aspirin, cetirizine, and paracetamol and was discharged after a total hospitalization of 4 days with aspirin and cetirizine. The condition was resolving at the time of the Applicant's clinical study report. The study investigator did not consider the SAE to be related to the study product.

Reviewer Comment: This clinical reviewer agrees with the investigator's assessment that the case of KD was not related to the study vaccine given the timeframe of onset of illness.

#### **SAEs of Interest: Febrile seizures**

A total of 5 febrile seizure events (with 1 event reported as respiratory failure) were reported by 4 participants in the PCV15 group (1 participant reported 2 separate febrile seizure episodes). These events occurred a median of 58 days (range 5 to 154 days) following the most recent dose of PCV15. All were considered by the primary investigators as unrelated to the study intervention as all occurred concurrently with likely viral illnesses.

Reviewer Comment: This clinical reviewer agrees with the investigators assessments that the reported cases of febrile seizures, including the case reported as respiratory failure, were not related to the study vaccine given the time of onset and the presence of concurrent illnesses. Although febrile seizures were reported more frequently in the PCV15 group (PCV15: N= 4 [0.46%] and PCV13: N= 2 [0.23%]), the evidence does not support inclusion in the prescribing information.

#### **Subpopulation Analyses:**

Safety results were reported for all subpopulations that contained  $\geq 5\%$  of the total number participants for the study group. Safety results were generally comparable across subpopulations and with those of the overall population for each of the following subpopulations: male vs.

female participants, race (black, white, Asian, and multiple races), ethnicity (Hispanic or Latino, not Hispanic or Latino).

### Dropouts and/or Discontinuations

A total of 228 discontinuations occurred during the study, 102 in the PCV15 group and 126 in the PCV13 group. 88.1 and 85.3% of each group completed the study. Most discontinuations were due to withdrawal by parent/guardian and loss to follow-up as shown in [Table 17](#).

**Table 17. Study V114-029: Participant Dropouts and/or Discontinuations During the Study**

<b>Reason*</b>	<b>PCV15 N=860</b>	<b>PCV13 N=860</b>	<b>Total N=1720</b>
All discontinued, n (%)	102 (11.9)	126 (14.7)	228 (13.3)
Withdrawal**, n (%)	59 (6.9)	85 (9.9)	144 (8.4)
Lost to follow-up, n (%)	34 (4.0)	27 (3.1)	61 (3.5)
Physician decision, n (%)	8 (0.9)	14 (1.6)	22 (1.3)
Death, n (%)	1 (0.1)	0 (0.0)	1 (0.1)

Source: Adapted from STN 125741.6, V114-029 Clinical Study Report: Table 12-8  
 Abbreviations: N=all randomized participants; n=number of discontinued participants

There were no discontinuations due to adverse events in either study group.

**Reviewer Comments:** Regarding dropouts and discontinuations, during the study, a measles outbreak in Turkey made it necessary for all participants at Turkish sites to receive M-M-R II vaccination at nine months of age. This was prior to the protocol specified time point of 12 to 15 months of age. These participants were excluded from the PP population for the M-M-R II analysis.

[Table 18](#) shows the discontinuations and dropouts that occurred in the study excluding those participants who received concomitant Pentavac. Discontinuations were generally comparable across study groups and did not impact the interpretability of those endpoints that excluded Pentavac recipients.

**Table 18. Study V114-029: Participant Dropouts and/or Discontinuations During the Study Excluding Pentavac recipients**

<b>Reason*</b>	<b>PCV15 N=600</b>	<b>PCV13 N=604</b>	<b>Total N=1204</b>
All discontinued, n (%)	91 (15.2)	111 (18.4)	202 (16.8)
Withdrawal**, n (%)	49 (8.2)	71 (11.8)	120 (10.0)
Lost to follow-up, n (%)	34 (5.7)	26 (4.3)	60 (5.0)
Physician decision, n (%)	7 (1.2)	14 (2.3)	21 (1.7)
Death, n (%)	1 (0.2)	0 (0.0)	1 (0.1)

Source: Adapted from response to Information Request March 4, 2022: Table 10  
 Abbreviations: N=all randomized participants excluding those who received Pentavac; n=number of discontinued participants

\* Reason for discontinuation

\*\*Withdrawal by parent or guardian

### 6.1.13 Study Summary and Conclusions

Study V114-029 was designed to demonstrate the safety and immunogenicity (inferred effectiveness) of a 4 dose primary series of PCV15 as compared to PCV13 in healthy infants. The primary objectives evaluated the immunologic noninferiority of the 13 serotypes shared

between PCV15 and PCV13 and the noninferiority of the two serotypes unique to PCV15 as compared to the lowest shared serotype response, not including serotype 3, after the third and fourth vaccine dose. The secondary immunogenicity objectives evaluated the noninferiority of concomitantly administered routine infant vaccines.

The study overall met the predefined statistical criteria for successful demonstration of noninferiority of all primary and secondary immunogenicity endpoints. Secondary immunogenicity endpoints also showed a statistically significantly greater responses to serotypes 22F, 33F, and serotype 3 in the PCV15 group as discussed in the reviewer comment in [Section 6.1.1](#) of this memo. The data from this study support the safety and effectiveness of PCV15 for use as a 4-dose series in infants and comparative serotype-specific IgG seroresponse rates and GMC data were included in the USPI to support PCV15 effectiveness.

## **6.2 Trial #2: V114-031**

**NCT03692871:** A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety and Tolerability of V114 in Healthy Infants (PNEU-LINK)

**Study Overview:** The purpose of this descriptive study was to evaluate the safety and tolerability of a 4-dose series of PCV15 as compared to PCV13 in ~2400 healthy infants approximately two months of age at enrollment. This study was conducted in response to a CBER request to provide a safety database of at least 3000 PCV15 recipients. The study also evaluated the immunogenicity of PCV15 in premature infants born before 37 weeks EGA to provide supportive data for use in this demographic. The study was conducted at 67 sites in Australia, Canada, Finland, Germany, Israel, Malaysia, Peru, Taiwan, and the United States.

### 6.2.1 Objectives (as stated in study protocol V114-031, Amendment 1)

#### **Primary Objective**

1. To evaluate the safety and tolerability of PCV15 with respect to the proportion of participants with adverse events
  - Endpoints: Refer to [Section 6.1.1](#)

#### **Secondary Objectives (Premature Infant Immunogenicity Substudy [PIIS] only)**

1. To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days PD3, prior to dose 4 and at 30 days PD4 for each vaccination group.
  - Endpoints: Anti-PnP serotype-specific IgG responses for the 15 serotypes contained in PCV15
    - i. Descriptive analyses without formal hypothesis testing
2. To evaluate the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of  $\geq 0.35$   $\mu\text{g/mL}$ ) at 30 days PD3 for each vaccination group.

- Endpoints: Anti-PnP serotype-specific IgG response rates for the 15 serotypes contained in PCV15 at 30 days PD3
  - i. Descriptive analyses without formal hypothesis testing

#### Exploratory Objectives (PIIS only)

1. To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) GMTs at 30 days following dose 3, prior to dose 4 and at 30 days following dose 4 for each vaccination group.
  - Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in PCV15 at 30 days PD3, Predose 4 and at 30 days PD4
    - i. Descriptive analyses without formal hypothesis testing

#### 6.2.2 Design Overview

Study V114-031 was a randomized, active controlled double-blind study with PCV13 as the comparator for the investigational product, PCV15. A total of 2409 infants were randomized in a 5:1 ratio for the overall study population to receive either a 4-dose series of PCV15 or PCV13. Enrollment was stratified so that approximately 1% to 2% of the total study population was made of infants born prior to 37 weeks EGA (PIIS). Participants in the PIIS were randomized in 1:1 ratio to either PCV15 or PCV13.

Reviewer Comment: Studies V114-029, V114-031, and V114-027 evaluating 4-dose infant series (2,4,6,12-15 months) in the PCV15 pediatric clinical development program did not include restrictions on enrollment based on predefined minimum gestational age. Therefore, all studies included pre-term infants (<37 weeks), however the study design for Study V114-031 included a PIIS that randomized pre-term infants 1:1 (PCV15:PCV13), though the overall randomization ratio for Study V114-031 was 5:1. Based on demographic information, the Applicant estimated that preterm infants would comprise approximately 1 to 2% of the total number of participants enrolled across all infant studies, with ~50-100 preterm infants included in the pooled preterm database. As reviewed in [Section 6.2.10](#) below, Study V114-031 had 99 pre-term infants randomized, including 51 PCV15 recipients and 48 PCV13 recipients. All three studies (V114-029, V114-029, V114-027) had 286 pre-term infants randomized, including 142 PCV15 recipients and 144 PCV13 recipients who were included in the safety populations.

#### 6.2.3 Population

Refer to [Section 6.1.3](#) for inclusion and exclusion criteria

#### 6.2.4 Study Treatments or Agents Mandated by the Protocol

PCV15: 15-valent pneumococcal conjugate vaccine

- Refer to [Section 6.1.4](#) for Dose, Schedule of Administration, Composition, and Presentation
- Lot # WL00068289, WL00068571, WL00068572, WL00068941

PCV13: 13-valent pneumococcal conjugate vaccine (diphtheria CRM197 protein)

- Refer to [Section 6.1.4](#) for Dose, Schedule of Administration, Composition, and Presentation
- Lot #s: 0000867885, 0000884276, 0000921112, 0000940410 (EU)

- Lot #: 0000873135, 0001043617 (US)

All participants received routine infant immunizations according to the recommended schedule for the respective region.

#### 6.2.5 Directions for Use

Refer to [Section 6.2.4](#).

#### 6.2.6 Sites and Centers

Study V114-031 was conducted at 67 sites in Australia, Canada, Finland, Germany, Israel, Malaysia, Peru, Taiwan, and the US. US sites enrolled 533 participants (22% of all participants).

#### 6.2.7 Surveillance/Monitoring

Refer to [Section 6.1.7](#).

#### 6.2.8 Endpoints and Criteria for Study Success

Refer to [Section 6.2.1](#).

#### 6.2.9 Statistical Considerations & Statistical Analysis Plan

Secondary and Exploratory Endpoints (descriptive analyses in PIIS PP population only)  
Evaluation of the secondary and exploratory endpoints regarding anti-PnPs serotype-specific IgG GMCs and OPA GMTs at 30 days PD3, prior to dose 4 and at 30 days PD4 for the 15 serotypes contained in PCV15 were performed within each vaccination group separately. Point estimates were calculated by exponentiating the estimates of the mean of the natural log values and the CIs were derived by exponentiating the CIs of the mean of the natural log values based on the 1-sample t-distribution.

For the anti-PnPs serotype-specific IgG response rates at 30 days PD3 based on the 15 serotypes contained in PCV15, the within-group CIs were calculated based on the exact method proposed by Clopper and Pearson ([Collett, 2002](#)).

#### *Safety Endpoints and Analyses: % of participants with:*

- Solicited injection site ARs during Days 1 through 14 postvaccination
- Solicited systemic ARs during Days 1 through 14 postvaccination
- Maximum temperature measurement
- Any AE, any vaccine-related AE during Days 1 through 14 postvaccination
- Any SAE, any vaccine-related SAE, and death from Day 1 post-study vaccination 1 through Month 6 following the final study vaccination

#### Protocol Amendments

- Protocol Amendment 1 (February 11, 2019) to the original protocol (September 6, 2018): An exploratory objective was added for the PIIS PP to evaluate anti-PnPs serotype specific OPA GMTs PD3 and PD4.

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

- February 11, 2019: OPA GMTs were added as an exploratory immunogenicity endpoint for the PP in the PIIS

Refer to [Section 6.1.9](#) for COVID-19 Pandemic Associated Changes

Reviewer Comment: The changes do not significantly impact the interpretability of the data generated from study V114-031.

#### 6.2.10. Study Population and Disposition

A total of 2409 participants were enrolled in the study. Study period: December 14, 2018 (first participant, first visit) to April 9, 2021 (last participant, last visit).

#### *Populations Enrolled/Analyzed*

Refer to [Section 6.1.10](#) for definitions of enrolled/analyzed populations.

#### *Demographics*

Among all vaccinated participants, there were more males (51.3%) than females. The median chronological age at enrollment was 9 weeks (range: 6 to 12 weeks). Participants born at less than 37 weeks EGA accounted for 4.1% of all participants (n=99). The median EGA at birth of participants born at <37 weeks EGA was 36 weeks (range: 32 to 37 weeks).

The majority of participants (48.9%) were white followed by Asian (36.6%), Multiple (7.7%), and Black or African American (3%). 15.3% identified as Hispanic/Latino. The demographic characteristics of participants were similar between study groups and are shown in [Table 19](#).

**Table 19. Study V114-031: Demographic Characteristics**

<b>Characteristic</b>	<b>PCV15 N=1,967</b>	<b>PCV13 N=436</b>	<b>Total N=2,403</b>
Sex, n (%)	--	--	--
Male	1,022 (52.0)	210 (48.2)	1,232 (51.3)
Female	945 (48.0)	226 (51.8)	1,171 (48.7)
Age at enrollment, weeks	--	--	--
Mean (SD)	8.7 (1.5)	8.8 (1.5)	8.7 (1.5)
Minimum, maximum	6, 12	6, 12	6, 12



<b>Characteristic</b>	<b>PCV15 N=1,967</b>	<b>PCV13 N=436</b>	<b>Total N=2,403</b>
Racial origin, n (%)	--	--	--
American Indian/Alaska Native	64 (3.3)	20 (4.6)	84 (3.5)
Asian	728 (37.0)	152 (34.9)	880 (36.6)
Black/African American	54 (2.7)	19 (4.4)	73 (3.0)
Multiple	154 (7.8)	31 (7.1)	185 (7.7)
American Indian/Alaska Native, Asian	1 (0.1)	0 (0.0)	1 (0.0)
American Indian/Alaska Native, white	100 (5.1)	22 (5.0)	122 (5.1)
Black/African American, Asian	1 (0.1)	0 (0.0)	1 (0.0)
Black/African American, Native Hawaiian/other Pacific Islander	2 (0.1)	0 (0.0)	2 (0.1)
Black/African American, white	27 (1.4)	5 (1.1)	32 (1.3)
Native Hawaiian/other Pacific Islander, white	2 (0.1)	0 (0.0)	2 (0.1)
White, Asian	21 (1.1)	4 (0.9)	25 (1.0)
Native Hawaiian or other Pacific Islander	2 (0.1)	1 (0.2)	3 (0.1)
White	963 (49.0)	213 (48.9)	1,176 (48.9)
Missing	2 (0.1)	0 (0.0)	2 (0.1)
Ethnicity, n (%)	--	--	--
Hispanic and/or Latino	293 (14.9)	74 (17.0)	367 (15.3)
Non-Hispanic or Latino	1,673 (85.1)	361 (82.8)	2,034 (84.6)
Not reported	1 (0.1)	1 (0.2)	2 (0.1)
EGA at birth, n (%)	--	--	--
<37 weeks	51 (2.6)	48 (11.0)	99 (4.1)
≥37 weeks	1,916 (97.4)	388 (89.0)	2,304 (95.9)

Source: Adapted from STN 125741.6, V114-031 Clinical Study Report: Table 10-5

Abbreviations: N=number of vaccinated participants for each cohort (participants with at least 1 vaccination of either PCV15 or PCV13);

n=number of participants with indicated characteristic; SD=standard deviation

For Sex, Racial Origin, Ethnicity and Gestational Age at birth: n indicates number of subjects fulfilling the item in each category, (%) indicates % of vaccinated participants represented in each category

**Reviewer Comment:** Premature infants (i.e., those born at less than 37 weeks gestational age) accounted for 4.1% of the overall study population.

### *Participant Disposition*

A list of prespecified protocol deviations is provided in [Section 6.1.10](#) of this review memo. Of the 2409 study participants, 168 (7%) had at least one important protocol deviation. 43 (1.8%) participants had clinically important protocol deviations. Most of these clinically important protocol deviations were due to Trial Procedure deviations including administration of the study vaccine outside of the protocol defined window (30 participants, 1.2% of total), collection of the immunogenicity blood sample outside of the protocol defined window (15 participants, 0.5% of total), and immunogenicity blood samples that were not drawn or could not be tested (15 participants, 0.5% of total) during a protocol-prohibited period. The dispositions of the study participants are shown in [Table 20](#).

**Table 20. Study V114-031: Summary of Participant Disposition**

Overall Participants	PCV15 N=1,972	PCV13 N=437	Total N=2,409
Enrolled, n (%)	1,972 (100.0)	437 (100.0)	2,409 (100.0)
Vaccinated, n (%)	1,967 (99.7)	436 (99.8)	2,403 (99.8)
Completed, n (%)	1,847 (93.7)	400 (91.5)	2,247 (93.3)
APaT* - Safety, n (%)	1,965 (99.6)	433 (99.1)	2,398 (99.5)
≥1 important protocol deviation	121 (6.1)	47 (10.8)	168 (7.0)
PIIS	N=51	N=48	N=99
FAS**, n (%)	43 (84.3)	44 (91.7)	87 (87.9)
PP*** (IgG)	--	--	--
30 Days Postdose 3, n (%)	38 (74.5)	35 (72.9)	73 (73.7)
Prior to Dose 4, n (%)	38 (74.5)	40 (83.3)	78 (78.8)
30 Days Postdose 4, n (%)	34 (66.7)	39 (81.3)	73 (73.7)
PP*** (OPA)	--	--	--
30 Days Postdose 3, n (%)	36 (70.6)	35 (72.9)	71 (71.7)
Prior to Dose 4, n (%)	37 (72.5)	37 (77.1)	74 (74.7)
30 Days Postdose 4, n (%)	33 (64.7)	37 (77.1)	70 (70.7)

Source: Adapted from STN 125741.6, V114-031 Clinical Study Report: Table 10-1, Table 10-3, Table 10-4, Table 12-1, Table 14.1-5

Abbreviations: APaT=All Participants as Treated; FAS=full analysis set; IgG=immunoglobulin G; N: number of participants enrolled; n=number of participants fulfilling the item for each cohort; OPA=opsonophagocytic activity; PIIS=Premature Infant Immunogenicity Subset; PP=per-protocol population

\* All randomized participants who received at least one dose of study vaccination for the time point of interest, and participants were included in the group corresponding to the study vaccine they actually received. Participants who inadvertently received both PCV15 and PCV13 during the study were excluded from the APaT population.

≥1 important protocol deviation: participants with 1 or more important protocol deviations

\*\* All randomized participants who received all study vaccinations required at the timepoint for the analysis and have at least 1 serology result for the timepoint for the analyses.

\*\*\* All randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s)

**Reviewer Comment:** The frequencies and types of clinically important protocol deviations were generally comparable across study groups as discussed above and in [Section 6.2.12](#). They did not significantly impact the interpretability of study results.

### 6.2.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints but did include secondary serologic immune endpoints in a subset of preterm infants that included 51 participants who received PCV15 and 48 participants who received PCV13. (PIIS PP as discussed in [Section 6.2.1](#)).

*Secondary Analyses (Descriptive): GMCs and Seroresponse Rates ≥0.35 µg/mL PD3,*

In the subset of preterm infants included in the secondary analyses, the GMCs and seroresponse rates ≥0.35 µg/mL after dose 3 were generally comparable across study groups for the 13 shared serotypes. In addition, the GMCs and seroresponse rates for the two unique serotypes (22F and 33F) after dose 3 were higher in the PCV15 group as compared to PCV13 recipients. These results are shown in [Table 21](#).

**Table 21. Study V114-031: Anti-PnP IgG GMCs and % Anti-PnP IgG Concentrations  $\geq 0.35$   $\mu\text{g/mL}$  Post Dose 3, PIIS PP**

Serotype	PCV15	PCV13
	N=38	N=35
	GMC (95% CI)	GMC (95% CI)
	% $\geq 0.35$ $\mu\text{g/mL}$ (95% CI)	% $\geq 0.35$ $\mu\text{g/mL}$ (95% CI)
1	1.15 (0.88, 1.52) 97.4% (86.2%, 99.9%)	1.61 (1.25, 2.09) 97.1% (85.1%, 99.9%)
3	0.86 (0.65, 1.13) 89.5% (75.2%, 97.1%)	0.58 (0.45, 0.76) 74.3% (56.7%, 87.5%)
4	1.41 (1.01, 1.99) 94.7% (82.3%, 99.4%)	1.27 (0.96, 1.68) 97.1% (85.1%, 99.9%)
5	1.48 (1.04, 2.10) 97.4% (86.2%, 99.9%)	1.66 (1.09, 2.53) 88.6% (73.3%, 96.8%)
6A	1.37 (0.95, 1.96) 97.4% (86.2%, 99.9%)	3.19 (2.31, 4.43) 97.1% (85.1%, 99.9%)
6B	1.69 (1.15, 2.48) 92.1% (78.6%, 98.3%)	2.53 (1.64, 3.89) 94.3% (80.8%, 99.3%)
7F	1.95 (1.46, 2.62) 97.4% (86.2%, 99.9%)	2.92 (2.21, 3.87) 100% (90.0%, 100.0%)
9V	1.47 (1.08, 2.00) 97.4% (86.2%, 99.9%)	1.5 (1.07, 2.12) 94.3% (80.8%, 99.3%)
14	4.38 (3.18, 6.03) 100% (90.7%, 100.0%)	6.52 (4.35, 9.77) 97.1% (85.1%, 99.9%)
18C	1.46 (1.08, 1.96) 97.4% (86.2%, 99.9%)	1.54 (1.16, 2.04) 94.3% (80.8%, 99.3%)
19A	1.63 (1.25, 2.13) 94.7% (82.3%, 99.4%)	3.00 (2.18, 4.11) 97.1% (85.1%, 99.9%)
19F	2.03 (1.53, 2.68) 97.4% (86.2%, 99.9%)	2.78 (2.17, 3.58) 100% (90.0%, 100.0%)
23F	1.17 (0.81, 1.70) 89.5% (75.2%, 97.1%)	1.18 (0.82, 1.68) 94.3% (80.8%, 99.3%)
22F	4.33 (3.18, 5.90) 97.4% (86.2%, 99.9%)	0.05 (0.03, 0.07) 2.9% (0.1%, 14.9%)
33F	1.58 (0.93, 2.69) 86.8% (71.9%, 95.6%)	0.05 (0.04, 0.08) 2.9% (0.1%, 14.9%)

Source: Adapted from STN 125741.6, V114-031 Clinical Study Report: Table 11-1, Table 11-2

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in  $\mu\text{g/mL}$ ; IgG=immunoglobulin G; N=number of participants in the PP for each specified cohort; PIIS=Premature Infant Immunogenicity Subset; PnP=pneumococcal polysaccharide; PP=per-protocol population

**Reviewer Comment:** IgG GMCs and response rates  $\geq 0.35$   $\mu\text{g/mL}$  30 days PD3 in preterm infants were generally comparable across study groups for the 13 shared serotypes and were higher in the PCV15 group for the 2 serotypes unique to PCV15. The immune responses observed in pre-term infants who received PCV15 were similar to those reported for full-term infants who received PCV15 in Study V114-029, that included formal statistical testing for these endpoints.

*Secondary Analyses (Descriptive): IgG GMCs Pre-Dose 4 and Post Dose 4*

In the subset of preterm infants, IgG GMCs were generally comparable across groups for the 13 shared serotypes pre-dose 4 and post dose 4. GMCs for the two unique serotypes (22F and 33F) were higher at these time points in PCV15 recipients as compared to PCV13 recipients as shown in [Table 22](#).

**Table 22 Study V114-031: Anti-PnP IgG GMCs Pre-Dose 4 and Post Dose 4, PIIS PP**

Serotype	PCV15	PCV13
	N=34-38	N=37-40
	Pre-D4 GMC (95% CI) PD4 GMC (95% CI)	Pre-D4 GMC (95% CI) PD4 GMC (95% CI)
1	0.30 (0.24, 0.38)	0.47 (0.38, 0.59)
	1.56 (1.19, 2.06)	1.96 (1.54, 2.50)
3	0.22 (0.16, 0.29)	0.13 (0.10, 0.17)
	1.04 (0.80, 1.36)	0.79 (0.60, 1.06)
4	0.24 (0.19, 0.31)	0.31 (0.24, 0.38)
	1.55 (1.11, 2.16)	1.61 (1.21, 2.15)
5	0.77 (0.60, 1.01)	0.89 (0.65, 1.22)
	3.3 (2.34, 4.65)	3.6 (2.53, 5.13)
6A	0.32 (0.24, 0.43)	0.72 (0.52, 0.99)
	4.18 (3.17, 5.49)	6.38 (4.69, 8.68)
6B	0.59 (0.47, 0.75)	0.61 (0.43, 0.87)
	6.62 (5.24, 8.37)	6.75 (4.43, 10.28)
7F	0.57 (0.44, 0.73)	0.95 (0.74, 1.21)
	4.01 (2.98, 5.40)	5.10 (3.76, 6.90)
9V	0.40 (0.32, 0.51)	0.46 (0.35, 0.62)
	3.10 (2.36, 4.08)	3.09 (2.31, 4.12)
14	1.14 (0.84, 1.54)	2.22 (1.73, 2.84)
	5.4 (3.89, 7.49)	7.15 (5.33, 9.61)
18C	0.35 (0.28, 0.45)	0.36 (0.27, 0.49)
	3.21 (2.32, 4.45)	2.77 (1.99, 3.85)
19A	0.38 (0.29, 0.51)	0.81 (0.52, 1.24)
	4.96 (3.85, 6.39)	6.47 (4.46, 9.40)
19F	0.41 (0.31, 0.53)	0.69 (0.52, 0.90)
	4.48 (3.51, 5.73)	4.83 (3.66, 6.38)
23F	0.33 (0.24, 0.45)	0.37 (0.26, 0.52)
	2.38 (1.76, 3.20)	3.04 (2.16, 4.27)
22F	1.24 (0.98, 1.58)	0.05 (0.04, 0.07)
	9.83 (7.47, 12.92)	0.08 (0.07, 0.11)
33F	1.09 (0.82, 1.45)	0.05 (0.04, 0.07)
	5.46 (4.29, 6.96)	0.1 (0.07, 0.13)

Source: Adapted from STN 125741.6, V114-031 Clinical Study Report: Table 11-1

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; IgG=immunoglobulin G; N=number of participants in the PP for each specified cohort; PIIS=Premature Infant Immunogenicity Subset; PnP=pneumococcal polysaccharide; PP=per-protocol population

**Reviewer Comment:** IgG GMCs prior to dose 4 and 30 days PD4 in preterm infants were generally comparable across study groups for the 13 shared serotypes and were higher in the PCV15 group for the 2 serotypes unique to PCV15. The PD4 immune responses observed in pre-term infants who received PCV15 were similar to those reported for full term infants who received PCV15 in Study V114-029, that included formal statistical testing for this endpoint.

*Exploratory Immunogenicity Analyses (Descriptive): OPA Responses*

OPA GMTs were evaluated in a subset of the PIIS (approximately 30 participants per study group) 30 days after dose 3, prior to dose 4 and 30 days after dose 4. OPA responses were generally comparable between study groups for the 13 shared serotypes and higher in the PCV15 group for the two unique serotypes as shown in [Table 23](#).

**Table 23. Study V114-031: OPA GMTs 30 Days PD3, Pre-D4, and 30 Days PD4, OPA Subset PIIS PP**

Serotype	PCV15	PCV13
	N=32-37	N=31-36
	PD3 GMT (95%CI)	PD3 GMT (95%CI)
	Pre-D4 GMT (95%CI)	Pre-D4 GMT (95%CI)
	PD4 GMT (95%CI)	PD4 GMT (95%CI)
1	32.2 (17.6, 58.9) 9.1 (6.1, 13.5) 143.3 (78.3, 262.3)	84.4 (52.0, 136.8) 10.2 (6.6, 16.0) 215.5 (139.3, 333.3)
3	204.9 (141.7, 296.2) 70.4 (48.4, 102.2) 347.8 (253.2, 477.8)	183.2 (140.1, 239.7) 42.6 (28.7, 63.3) 401.0 (315.8, 509.2)
4	1230.1 (831.7, 1819.3) 161.2 (93.0, 279.3) 2805.5 (1667.2, 4721.1)	1915.4 (1339.7, 2738.6) 269.1 (151.2, 479.0) 4773.8 (3148.9, 7237.0)
5	393.1 (243.4, 634.9) 74.1 (45.0, 122.1) 953.1 (533.6, 1702.2)	467.7 (297.4, 735.4) 87.7 (53.2, 144.7) 193.5 (773.1, 1842.5)
6A	2446.3 (1563.6, 3827.5) 508.3 (343.7, 751.6) 4725.6 (3053.5, 7313.5)	4177.2 (2860.6, 6099.8) 640.8 (419.3, 979.2) 10632.9 (6858.1, 16485.5)
6B	1570.7 (988.4, 2496.0) 361.4 (211.2, 618.4) 4395.9 (3259.4, 5928.7)	2671.1 (1551.3, 4599.1) 323.2 (175.4, 595.7) 6659.0 (3708.1, 11958.1)
7F	4287.0 (2639.7, 6962.5) 1340.4 (860.1, 2088.9) 10573.5 (6948.2, 16090.3)	9007.4 (6646.8, 12206.2) 3425.5 (2515.9, 4663.9) 20026.0 (14154.4, 28333.5)
9V	894.2 (610.1, 1310.6) 211.5 (154.5, 289.6) 1862.8 (1365.8, 2540.7)	1171.4 (771.6, 1778.2) 292.7 (196.4, 436.3) 3976.6 (2462.0, 6423.1)
14	1586.6 (1041.9, 2416.1) 586.2 (372.3, 922.9) 2725.5 (1574.2, 4718.9)	2965.7 (1670.1, 5266.5) 847.8 (504.6, 1424.4) 2939.0 (1920.8, 4496.8)
18C	1111.1 (701.4, 1760.1) 239.0 (162.2, 352.1) 2952.3 (1787.0, 4877.5)	1555.5 (1134.8, 2132.1) 266.6 (166.4, 427.3) 3640.2 (2659.3, 4982.9)
19A	779.2 (496.9, 1222.0) 158.2 (91.2, 274.2) 3236.5 (2066.2, 5069.8)	2609.8 (1916.1, 3554.7) 481.4 (267.9, 864.8) 8761.8 (5857.1, 13107.2)
19F	601.2 (405.7, 890.8) 124.6 (91.5, 169.7) 1691.3 (1128.2, 2535.5)	1144.7 (875.2, 1497.2) 200.8 (135.9, 296.7) 2322.3 (1625.5, 3317.7)
23F	2570.7 (1682.0, 3929.2) 422.9 (228.7, 782.0) 3616.0 (1974.2, 6623.2)	7368.1 (4187.5, 12964.4) 1355.1 (708.1, 2593.4) 20486.1 (12375.8, 33911.3)
22F	1997.9 (1445.5, 2761.4) 432.9 (262.6, 713.8) 3483.1 (2399.5, 5056.2)	8.8 (6.3, 12.3) 13.8 (8.1, 23.6) 10.4 (6.8, 16.0)
23F	7720.8 (4266.0, 13973.4) 4496.6 (3290.1, 6145.6) 10617.1 (7851.4, 14357.0)	96.7 (39.4, 237.6) 1248.5 (780.7, 1996.7) 1275.7 (737.3, 2207.2)

Source: Adapted from STN 125741.6, V114-031 Clinical Study Report: Table 11-3

Abbreviations: CI=confidence interval; GMT=geometric mean titer, in µg/mL; N=number of participants in the PP for each specified cohort; OPA=opsonophagocytic activity; PD=post-dose; PIIS=Premature Infant Immunogenicity Subset; PP=per-protocol population

Reviewer Comment: Study V114-031 OPA GMTs in pre-term infants were generally comparable between study groups for the 13 shared serotypes and higher in the PCV15 group for the two unique serotypes. OPA GMTs were generally supportive of the secondary analyses in pre-term infants evaluating IgG GMCs. This provides direct evidence of functional antibody responses to all vaccine serotypes after the 3<sup>rd</sup> and 4<sup>th</sup> doses of PCV15 when administered to pre-term infants.

### Subpopulation Analyses:

For subgroup comparison of primary immunogenicity endpoints (IgG response rates/IgG GMCs post-dose 3 and IgG GMCs post-dose 4) based on EGA (<37 weeks vs ≥37 weeks), please see [Section 6.1.11](#) for Study V114-029, that included formal evaluations of these endpoints in health infants (term <37 weeks and pre-term ≥37 weeks).

### 6.2.12 Safety Analyses

#### Methods

Refer to [Section 6.1.9](#).

### Overview of Adverse Events

The following table provides an overview of the AEs of all types occurring during the study period. Solicited ARs were more commonly reported in the PCV15 group in the 14 days following any vaccination dose, although the difference across groups was not great. Rates of SAEs and unsolicited AEs were generally comparable across study groups. There was one death in each group that the study investigator did not consider related to the study product.

**Table 24. Study V114-031: Proportion of Participants Reporting at Least One Adverse Event Following Any Vaccination Dose, APaT**

AE Type	V114	PCV13
	N=1,965	N=433
	%	%
	(x participants/n)	(x participants/n)
Immediate AE: 30 minutes	4.3 (85/1,965)	4.6 (20/433)
Solicited injection site: 14 days	68.2 (1,341/1,965)	61.2 (265/433)
Solicited systemic: 14 days	83.8 (1,647/1,965)	80.1 (347/433)
Unsolicited AE: 14 days	32.1 (631/1,965)	33.0 (143/433)
AEs leading to vaccine discontinuation: entire study period	0.0 (0/1,965)	0.0 (0/433)
SAEs: entire study period	9.8 (192/1,965)	10.4 (45/433)
Deaths: entire study period	0.1 (1/1,965)	0.2 (1/433)

Source: Adapted from STN125741/6, Study V114-031 Clinical Study Report including Table 12-1, Table 12-3

Abbreviations: AE=adverse event; APaT=All Participants as Treated; n=#subjects with available data for relevant endpoint; SAE=serious adverse event; x participants=#subjects who experienced the event

### Subpopulation Analyses

Safety results were reported for all subpopulations that contained ≥5% of the total number participants for the study group. Safety results were generally comparable with those of the overall population for each of the following subpopulations: male vs. female participants, race (Black, White, Asian, and multiple races), ethnicity (Hispanic or Latino, not Hispanic or Latino).

*Analyses in Pre-Term Infants and as compared to Term Infants*

The frequencies of reported solicited ARs, unsolicited AEs, and SAEs in pre-term participants (studies V114-029, -031, and -027) following any of 4 doses of PCV15 or any of 4 doses of PCV13 were generally comparable. There were no vaccine-related SAEs or deaths in either group. The frequencies of reported solicited ARs, unsolicited AEs, and SAEs were also generally comparable between pre-term participants and full-term participants following any of 4 doses of PCV15 in the same 3 studies.

Reviewer Comment: Rates of ARs, and SAEs were generally comparable between PCV15 recipients who were either pre-term or full-term gestational age at birth.

**Solicited ARs**

[Table 25](#) provides an overview of the rates of reported ARs in the 14 days following each study dose. The most commonly reported injection site reactions in the PCV15 group were pain, erythema, and swelling. Pain and injection site swelling were most commonly reported following dose 1 and the reported occurrences were generally comparable following doses 2 through 4. The reported occurrences of erythema were generally comparable across all 4 doses. Most (~81.5%) of the solicited ARs for which intensity grading was available were graded as mild or moderate. For those reported ARs for which a maximum size was recorded (i.e., erythema, induration, and swelling), most (~91.8%) had a maximum size less than 5.08cm.

The most commonly reported systemic ARs in the PCV15 group were irritability, somnolence, and decreased appetite. Irritability was most commonly reported after dose 1 (56.4%) with decreasing frequencies reported after doses 2, 3, and 4. Somnolence was most commonly reported after dose 1 (40.6%). Reported occurrences were generally comparable following doses 2, 3, and 4. Decreased appetite was most commonly reported following doses 1 and 4. Reported occurrences were lower and generally comparable following doses 2 and 3.

**Table 25. Study V114-031: Comparison of Participants with Adverse Reactions From Day 1 Through Day 14 Following Each Study Dose, APaT**

Adverse Reaction	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3	Dose 4	Dose 4
	PCV15 N=1965	PCV13 N=433	PCV15 N=1930	PCV13 N=419	PCV15 N=1911	PCV13 N=414	PCV15 N=1854	PCV13 N=398
Injection site reactions, n (%)	--	--	--	--	--	--	--	--
Swelling	275 (14.0)	43 (9.9)	216 (11.2)	45 (10.7)	183 (9.6)	39 (9.4)	224 (12.1)	33 (8.3)
Erythema	374 (19.0)	56 (12.9)	396 (20.5)	70 (16.7)	331 (17.3)	71 (17.1)	397 (21.4)	68 (17.1)
Pain	523 (26.6)	91 (21.0)	340 (17.6)	63 (15.0)	304 (15.9)	59 (14.3)	368 (19.8)	63 (15.8)
Induration	223 (11.3)	48 (11.1)	205 (10.6)	57 (13.6)	207 (10.8)	50 (12.1)	209 (11.3)	43 (10.8)

Adverse Reaction	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3	Dose 4	Dose 4
	PCV15 N=1965	PCV13 N=433	PCV15 N=1930	PCV13 N=419	PCV15 N=1911	PCV13 N=414	PCV15 N=1854	PCV13 N=398
Systemic reactions, n (%)	--	--	--	--	--	--	--	--
Irritability	1,108 (56.4)	222 (51.3)	983 (50.9)	191 (45.6)	869 (45.5)	157 (37.9)	849 (45.8)	162 (40.7)
Somnolence	798 (40.6)	178 (41.1)	549 (28.4)	112 (26.7)	415 (21.7)	90 (21.7)	415 (22.4)	93 (23.4)
Decreased appetite	354 (18.0)	61 (14.1)	301 (15.6)	62 (14.8)	284 (14.9)	56 (13.5)	408 (22.0)	69 (17.3)
Urticaria	20 (1.0)	4 (0.9)	26 (1.3)	8 (1.9)	31 (1.6)	6 (1.4)	49 (2.6)	16 (4.0)

Source: Adapted from STN 125741.6, V114-031 Clinical Study Report: Table 14.3-22, Table 14.3-23, Table 14.3-24, Table 14.3-25  
Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n (%) =number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort

**Reviewer Comment:** The 14-day solicited AR data suggest increased reactogenicity following PCV15 versus PCV13, particularly following dose 1, although the difference across groups was not large.

*Maximum Body Temperatures: within 7 days post-vaccination*

Rates of reported fever (i.e., body temperature  $\geq 38.0^\circ$ ) were generally comparable between PCV15 and PCV13 recipients as shown in [Table 26](#).

**Table 26. Study V114-031: Maximum Body Temperature of Participants From Day 1 (Day of Vaccination) Through Day 7 Following Each Dose, APaT**

Temperature	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3	Dose 4	Dose 4
	PCV15 N=1963	PCV13 N=431	PCV15 N=1922	PCV13 N=418	PCV15 N=1906	PCV13 N=414	PCV15 N=1846	PCV13 N=395
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<38.0°C	1639 (83.5)	374 (86.8)	1527 (79.4)	333 (79.7)	1,555 (81.6)	333 (80.4)	1530 (82.9)	321 (81.3)
$\geq 38.0^\circ\text{C}$ - 39.0°C	310 (15.8)	50 (11.6)	354 (18.4)	77 (18.4)	300 (15.7)	74 (17.9)	260 (14.1)	63 (15.9)
$\geq 39.0^\circ\text{C}$ - 40.0°C	14 (0.7)	7 (1.6)	41 (2.1)	6 (1.4)	49 (2.6)	6 (1.4)	46 (2.5)	9 (2.3)
$\geq 40.0^\circ\text{C}$	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.1)	1 (0.2)	10 (0.5)	2 (0.5)

Source: Adapted from response to IR received June 2, 2022: Tables 5 - 8  
Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort with at least 1 temperature measurement from Day 1 through Day 7 following the indicated vaccination; n (%) = number of participants experiencing a maximum temperature within the indicated range during the 7-day period post vaccine in each cohort and % of the APaT belonging to that cohort which experienced a maximum temperature within that range.  
Data presented for participants with available temperature measurements reported as measured and includes participants who may have received non-US licensed vaccines concomitantly  
Of the maximum temperature measurements, ~46% to ~54% were rectal measurements and ~46% to ~54% were axillary measurements

*Unsolicited AEs within 14 days post-vaccination*

Unsolicited AEs were documented by the participant's legally acceptable representative in the eVRC and reviewed by the investigator at 15 days following each vaccine dose. Rates of unsolicited AEs were generally comparable between study groups (PCV15: 69.9%, PCV13: 69.3%). The most frequently reported events, by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, were: General disorders and administration site conditions



(PCV15: 43.0%, PCV13: 42.5%); Infections and infestations (PCV15: 29.3%, PCV13: 33.3%); and Gastrointestinal disorders (PCV15: 22.5%, PCV13: 22.9%).

**Reviewer Comment:** The reported rates and types of unsolicited adverse events are comparable across study groups and represent medical conditions that are common in children.

### Deaths

There were two participant deaths during the study (one in the PCV15 group and one in the PCV13 group). Both deaths were considered by the investigators to be unrelated to the study intervention. The participant in the PCV15 group died from cerebral injury following a car accident on Day 110 following study dose 4. The participant in the PCV13 group died due to sudden unexplained infant death on day 25 following study dose 1. The investigator did not consider either of the reported deaths to be related to the study vaccinations.

**Reviewer Comment:** The clinical reviewer agrees with the investigator’s assessments that none of the reported deaths were related to the study vaccines

### Nonfatal Serious Adverse Events

The reported occurrences of SAEs were generally comparable across groups and were reported by 2.1% of the PCV15 group (n=41) and 2.5% of the PCV13 group (n=11). The most frequently reported SAEs were classified under the SOC *Infections and infestations* and were predominantly related to viral respiratory tract infections (e.g., bronchiolitis). The majority of SAEs were considered to be serious due to the requirement for hospitalization for monitoring and/or treatment. SAEs for the study are summarized in [Table 27](#).

**Table 27. Study V114-031: Participants Reporting SAEs\* (PTs) Following Any Dose During the Study, APaT**

SAE	PCV15 N=1965	PCV13 N=433
Bronchiolitis	27 (1.4)	7 (1.6)
Gastroenteritis	15 (0.8)	0 (0.0)
Pneumonia	12 (0.6)	4 (0.9)
Bronchitis	8 (0.4)	2 (0.5)
Escherichia pyelonephritis	8 (0.4)	1 (0.2)
Pyrexia	8 (0.4)	1 (0.2)
Pneumonia viral	7 (0.4)	0 (0.0)
Exanthema subitum	7 (0.4)	1 (0.2)
Escherichia urinary tract infection	6 (0.3)	1 (0.2)
Gastroenteritis viral	5 (0.3)	1 (0.2)
Pneumonia respiratory syncytial viral	5 (0.3)	2 (0.5)
Upper respiratory tract infection	5 (0.3)	1 (0.2)
Viral infection	4 (0.2)	0 (0.0)
Febrile convulsion	4 (0.2)	1 (0.2)
Influenza	4 (0.2)	3 (0.7)
Gastroenteritis salmonella	4 (0.2)	0 (0.0)
Diarrhea infectious	3 (0.2)	0 (0.0)
Herpangina	3 (0.2)	1 (0.2)
Nasopharyngitis	3 (0.2)	0 (0.0)
Tonsillitis	3 (0.2)	0 (0.0)
Hand-foot-and-mouth disease	3 (0.2)	0 (0.0)

SAE	PCV15 N=1965	PCV13 N=433
Vomiting	2 (0.1)	0 (0.0)
Diarrhea	2 (0.1)	0 (0.0)
Croup infectious	2 (0.1)	0 (0.0)
Gastroenteritis norovirus	2 (0.1)	0 (0.0)
Pneumonia influenza	2 (0.1)	0 (0.0)
Respiratory syncytial virus infection	2 (0.1)	0 (0.0)
Urinary tract infection bacterial	2 (0.1)	1 (0.2)

Source: Adapted from STN 125741.6, V114-031 Clinical Study Report: Table 12-9

\* SAEs reported by greater than 1 participant during the study

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort receiving the indicated dose; n (%) =number of participants experiencing any SAE within 30 days of vaccine dose in each cohort and % of the APaT belonging to that cohort receiving the indicated dose; PT=preferred term; SAE=serious adverse event

A similar pattern of SAEs (primarily viral respiratory illnesses with generally comparable incidence between study groups) were seen within 7 and 30 days of vaccination.

Reviewer Comment: The clinical reviewer agrees with the applicant's assessment that the rates of SAEs were generally comparable between the two study groups.

#### **SAE of Interest: Autoimmune Hemolytic Anemia (AIHA)**

A 5.3-month-old male participant in the PCV15 group developed AIHA approximately 1 month after PCV15 dose 2 (also received diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, and rotavirus vaccines) developed fever (maximum temperature 38.0°C) and anemia (hemoglobin of 3.0 g/dL) with a positive direct antiglobulin test. He received two blood transfusions and was treated with intravenous methylprednisolone. He was discharged with oral prednisone therapy. He received vaccination 3 without recurrence of the anemia. AIHA resolved without sequelae. The investigator did not consider the AIHA to be related to the study vaccine.

Reviewer Comment: The clinical reviewer agrees with the investigator's assessment that the episode of AIHA was probably not related to the study vaccine given the interval between study vaccination and SAE onset and the lack of recurrence at rechallenge, although concomitant corticosteroid therapy may have masked this.

#### **SAEs of Interest: Pyrexia**

Two participants in the PCV15 group experienced pyrexia considered to be related to the study vaccine. A 52-day old male reported a maximum body temperature of 38.0°C that developed a few hours after PCV15 dose 1. The participant also reported injection site erythema (7.6cm), induration (2.5cm), irritability and somnolence. The participant received multiple concomitant vaccines (rotavirus, diphtheria vaccine toxoid, hepatitis b vaccine, acellular pertussis acellular 3-component, inactivated polio, tetanus vaccine toxoid, Hib vaccine conjugate). The patient was admitted to the hospital for evaluation due to the participant's age. A chest x-ray was interpreted as consistent with a viral pneumonia or reactive airways disease. No definite etiology for the fever was determined and the patient was discharged after 3 days of hospitalization when the participant became afebrile. The investigator considered the SAE as related to the study vaccine.

Another participant, a 6.8 month of age male reported a maximum body temperature of 39.4°C along with irritability, chills, and drawing up of the arms and legs on the day he received PCV15

dose 3. Concomitant vaccines included: diphtheria vaccine, hepatitis b vaccine, Hib vaccine, pertussis vaccine, and tetanus vaccine This participant was admitted to the hospital for evaluation after receiving a dose of cefotaxime. Laboratory tests (including complete blood count, serum chemistries, and blood culture) were unrevealing of a diagnosis. He continued to have fevers accompanied by irritability and emesis until Day 3 post-vaccination, after which his symptoms resolved. He was discharged without a definitive diagnosis. The investigator considered the SAE as related to the study vaccine.

Reviewer Comment: This clinical reviewer agrees with the investigators that these two SAEs could be related to the vaccine. The two vaccine-related episodes of pyrexia may reflect an increased reactogenicity of PCV15 as compared to PCV13.

### SAEs of Interest: Febrile seizures

A total of 4 febrile seizure events were reported in the PCV15 group. These events occurred a median of 135 days (range 97 to 178 days) following the most recent dose of PCV15. All were considered by the primary investigators as unrelated to the study intervention.

Reviewer Comment: This clinical reviewer agrees with the investigators assessments that the reported cases of febrile seizures are not related to the study vaccine given the time of onset. Participants reporting febrile seizures were more common in the PCV13 group (PCV15: N= 4 [0.2%] and PCV13: N=2 [0.46%], one PCV13 participant with febrile seizure in the setting of pneumonia [reported PT]).

### Dropouts and/or Discontinuations

A total of 162 discontinuations (6.7% of the study population) occurred during the study, 6.3% (n=125) of the PCV15 group and 8.5% (n=37) in the PCV13 group. Most discontinuations were due to withdrawal by parent/guardian and lost to follow-up as shown in [Table 28](#).

**Table 28. Study V114-031: Participant Dropouts and/or Discontinuations During the Study**

Reason*	PCV15 N=1972	PCV13 N=437	Total N=2409
All Discontinued, n (%)	125 (6.3)	37 (8.5)	162 (6.7)
Withdrawal**, n (%)	77 (6.9)	20 (9.9)	97 (4.0)
Lost to follow-up, n (%)	24 (1.2)	9 (2.1)	33 (1.4)
Physician decision, n (%)	22 (1.1)	7 (1.6)	29 (1.2)
Death, n (%)	1 (0.1)	0 (0.0)	1 (0.1)

Abbreviations: N=all randomized participants; n=number of discontinued participants; %= % of all randomized participants

\* Reason for discontinuation

\*\* Withdrawal by parent or guardian

There were no discontinuations due to adverse events in either study group.

### 6.2.13 Study Summary and Conclusions

Study V114-031 was included in the PCV15 clinical development plans to increase the overall safety database to support licensure of PCV15 when administered as a 4-dose series to infants at 2, 4, 6m, 12-15 months of age. The study included ~2000 PCV15 recipients who received the 4-dose series, which included ~50 pre-term infants (<37 weeks) for whom serotype specific-IgG GMCs, including seroresponse rates  $\geq 0.35$   $\mu\text{g/mL}$ , and anti-*S. pneumoniae* OPAs were assessed

compared to pre-term infants who received PCV13. The data generated from this study support the safety of a 4-dose series of PCV15 when administered to healthy full-term and pre-term infants. The immune responses to PCV15 in pre-term infants were generally comparable to those elicited in full-term infants who received PCV15 and support its use in pre-term infants.

### **6.3 Trial #3: V114-027**

**NCT 03620162:** A Study to Evaluate the Interchangeability of PCV15 and PCV13 in Healthy Infants (PNEU-DIRECTION)

**Study Overview:** The purpose of this phase 3 study was to evaluate the safety and immunogenicity of PCV15 when interchanged with PCV13 to complete the 4-dose primary pneumococcal conjugate vaccine infant series when initiated with PCV13. The study also evaluated the non-inferiority of the rotavirus and hepatitis B vaccines when administered concomitantly with PCV15 compared to when administered concomitantly with PCV13. The study enrolled 900 participants and was conducted at 31 sites in Puerto Rico, Thailand, Turkey, and the United States

#### **6.3.1 Objectives (as stated in study protocol V114-027, Amendment 0)**

##### **Primary Objectives**

1. To evaluate the safety and tolerability of complete PCV15 (Group 5) and mixed PCV15/PCV13 dosing schedules (Groups 2, 3, and 4) compared with a complete dosing schedule of PCV13 (Group 1) with respect to the proportion of participants with AEs
  - Endpoints: Refer to [Section 6.1.1](#)
  - Descriptive analyses: Refer to [Section 6.1.8](#)
2. To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days following dose 4 for participants administered mixed dosing schedules of PCV13/PCV15 (Groups 2, 3, and 4) compared with participants administered a complete dosing schedule of Prevnar 13™ (Group 1).
  - Anti-PnP serotype-specific IgG responses for the 13 serotypes shared by PCV15 and PCV13 at 30 days PD4
    - i. Descriptive analysis without formal hypothesis testing

##### **Secondary Objectives**

1. To compare the proportion of participants with anti-hepatitis B surface antigen (HBsAg) concentration  $\geq 10$  mIU/mL at 30 days PD3 for participants administered a complete primary infant series dosing schedule of PCV15 (Group 5) concomitantly with Recombivax HB versus participants administered a complete primary infant series dosing schedule of PCV13 (Groups 1 and 2) concomitantly with Recombivax HB™.
  - Hypothesis 1 (H1): Recombivax HB administered concomitantly with V114 was non-inferior to Recombivax HB administered concomitantly with PCV13
    - i. Difference in proportion of participants with anti- HBsAg concentration  $\geq 10$  mIU/mL at 30 days PD3 (PCV15-PCV13)

1. The statistical success criterion for non-inferiority required the lower bound of the 2-sided 95% CI to be greater than -10%
2. To compare the anti-rotavirus IgA GMT at 30 days PD3 for participants administered a complete primary infant series dosing schedule of PCV15 (Group 5) concomitantly with RotaTeq versus participants administered a complete primary infant series dosing schedule of PCV13 (Groups 1 and 2) concomitantly with RotaTeq
  - Hypothesis 2 (H2): RotaTeq administered concomitantly with PCV15 was non-inferior to RotaTeq administered concomitantly with PCV13
    - i. Anti-rotavirus IgA GMT ratio (PCV15/PCV3) at 30 days PD3
      1. The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI to be greater than 0.50
3. To evaluate the anti-PnPs serotype-specific IgG GMCs and the anti- PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of  $\geq 0.35$   $\mu\text{g/mL}$ ) at 30 days PD3 for each vaccination group (Groups 1, 2, 3, 4, and 5)
  - Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in PCV15
    - i. Descriptive analysis without formal hypothesis testing
4. To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days PD4 for participants administered a complete dosing schedule of PCV15 (Group 5) compared with participants administered a complete dosing schedule of PCV13 (Group 1)
  - Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in PCV15 and PCV13
    - i. Descriptive analysis without formal hypothesis testing

### **Tertiary/Exploratory Objectives**

1. To evaluate the anti-PnPs serotype-specific IgG GMCs prior to dose 4 separately for each vaccination group (Groups 1, 2, 3, 4, and 5)
  - Endpoints: Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 prior to dose 4
    - i. Descriptive analysis without formal hypothesis testing
2. To evaluate the anti-HBsAg GMCs at 30 days PD3 for participants administered a complete primary infant series dosing schedule of PCV15 (Group 5) concomitantly with Recombivax HB versus participants administered a complete primary infant series dosing schedule of PCV13 (Groups 1 and 2) concomitantly with Recombivax HB™
  - Anti-HBsAg response at 30 days PD3 of PCV15 or PCV13
    - i. Descriptive analysis without formal hypothesis testing

### **6.3.2 Design Overview**

Study V114-027 was a phase 3, multicenter, randomized, double blind study in children 2 months of age (range 6 weeks through 3 months) at enrollment. A total of 900 healthy infants were enrolled in 5 study groups. All groups received a 4-dose pneumococcal vaccine regimen

with doses administered at 2 months, 4 months, 6 months, and 12-15 months. Group 1 was the comparator arm and participants in this arm received 4 doses of PCV13. The other groups received a combination of PCV13 and PCV15, as shown in [Table 29](#).

**Table 29. Study V114-027: Dosing Regimen**

<b>Group</b>	<b>Dose 1 2 Months of Age</b>	<b>Dose 2 4 Months of Age</b>	<b>Dose 3 6 Months of Age</b>	<b>Dose 4 12-15 Months of Age</b>
1	PCV13	PCV13	PCV13	PCV13
2	PCV13	PCV13	PCV13	PCV15
3	PCV13	PCV13	PCV15	PCV15
4	PCV13	PCV15	PCV15	PCV15
5	PCV15	PCV15	PCV15	PCV15

Source: CBER clinical reviewer-generated table

### 6.3.3 Population

Inclusion and exclusion criteria as described in [Section 6.1.3](#)

### 6.3.4 Study Treatments or Agents Mandated by the Protocol

PCV15: 15-valent pneumococcal conjugate vaccine

- Dose, Schedule of Administration, Composition, and Presentation as described in [Section 6.1.4](#)
- Lot # W L00068289, WL00068572, WL00068941

PCV13: 13-valent pneumococcal conjugate vaccine (diphtheria CRM197 protein)

- Dose, Schedule of Administration, Composition, and Presentation as described in [Section 6.1.4](#)
- Lot #s: 0000867885, 0000956034 (European Union)
- Lot #s: 0000840839, 0001043617 (United States)

Routine Infant Vaccines

- Dose, Schedule of Administration, Composition, and Presentation as described in [Section 6.1.4](#)
- M-M-R II 0.5mL dose: Lot # 0000982739
- Rotateq 1mL dose: Lot # 0000866598, 0000994218
- Hiberix 0.5mL dose (US): Lot # 0000974549, 0001088213
- Hiberix 0.5mL dose (EU): Lot # 0000916327, 0000916333
- Pentavac 0.5mL: Lot# 0000890862, 0000974006, 0000995761
- Pentacel 0.5mL Lot # 0000856844, 0000955089
- Recombivax HB: Lot # 0000836888

### 6.3.5 Directions for Use

As described in [Section 6.1.4](#).

### 6.3.6 Sites and Centers

Study V114-027 was conducted at 31 sites in Puerto Rico, Thailand, Turkey, and the United States, with 487 (54%) participants enrolled in the United States sites.

### 6.3.7 Surveillance/Monitoring

Refer to [Section 6.1.7](#) for Pn ECL assay.

#### Non-Pneumococcal Immunogenicity Monitoring:

- Hepatitis B (b) (4) measured total antibody to human plasma-derived HBsAg subtypes ad and ay. (b) (4) internally prepared control serum pools, consisting of a (b) (4) were used to monitor the performance of the assay. Additionally, there were anti-HBs positive and negative manufacturer-supplied controls, which were prepared from (b) (4) (b) (4). The hepatitis B (b) (4) reference standard at (b) (4) mIU/mL was also run as a control in every assay. LLOQ: (b) (4) mIU/mL. Laboratory: (b) (4) (b) (4)
- Rotavirus Serum IgA (b) (4) measured IgA antibody to Rotavirus. This assay was run in a standard (b) (4) format. All serum samples were run (b) (4). A cut-off of (b) (4) units/mL was derived during the assay validation. Laboratory: (b) (4) (b) (4)

### 6.3.8 Endpoints and Criteria for Study Success

Refer to [Section 6.3.1](#)

### 6.3.9 Statistical Considerations & Statistical Analysis Plan

#### *Primary Immunogenicity Objective* (descriptive analyses only)

Comparison of anti-PnP serotype-specific IgG response rates for the 13 serotypes shared by PCV15 and PCV13 at 30 days PD4

- Estimation of the IgG GMC ratios and computation of the corresponding 95% confidence intervals (CIs) will be calculated using analysis of covariance (ANCOVA) model with vaccination group and stratification factor (hepatitis B vaccination status before enrollment = Yes, No) as covariates. The pairwise comparisons included Group 2 vs Group 1; Group 3 vs Group 1; and Group 4 vs Group 1.

#### Secondary Hypothesis #1 (H1)

H1 evaluated the noninferiority of Recombivax HB in the PCV15 group as compared to the PCV13 group 30 days PD3 using the following criteria:

- $H_0: p_1 - p_2 \leq -0.1$  vs.  $H_1: p_1 - p_2 > 0.1$
- $p_1$  was the proportion of participants with anti-HBsAg concentration  $\geq 10$  mIU/mL for Group 5 and  $p_2$  was the proportion of participants with anti-HBsAg concentration  $\geq 10$  mIU/mL for Group 1 + Group 2
- The Miettinen and Nurminen method was used for these analyses ([Miettinen and Nurminen, 1985](#))
- Hepatitis B vaccination status prior to enrollment was the stratification factor

### Secondary Hypothesis #2 (H2)

Hypotheses #2 evaluated the noninferiority of ROTATEQ™ in the PCV15 group as compared to the PCV13 group 30 days PD3 using the following noninferiority criteria:

- H0:  $GMT1/GMT2 \leq 0.50$  vs. H1:  $GMT1/GMT2 > 0.50$
- GMT1 was the anti-rotavirus IgA GMT for Group 5 and GMT2 was the anti-rotavirus IgA GMT for Group 1 + Group 2.
- A ratio of 0.50 corresponds to a 2.0-fold decrease of anti-rotavirus IgA GMT in the PCV15 as compared with the PCV13
- The confidence limits for GMTs are the exponentiated confidence limits for the mean natural log concentrations, based on 1-sample t-distributions.
- Additionally, anti-rotavirus IgA GMT ratios [V114 (Group 5)/PCV13 (Group 1 + Group 2)] along with 2-sided 95% CIs will be computed. The 95% CI for the ratio will be calculated using the ANCOVA model utilizing the log-transformed antibody titers as the response with vaccination group and Hepatitis B vaccination status prior to enrollment as covariates

### Other Secondary and Tertiary/Exploratory Endpoints (descriptive analyses only)

For the 15 pneumococcal serotypes in PCV15 comparative analyses across study groups were performed for:

- anti-PnPs serotype-specific IgG GMCs at 30 days PD3 and pre-D4
- anti-HBsAg GMCs at 30 days PD3

The point estimates were calculated by exponentiating the estimates of the mean of the natural log values and the within-group CIs were derived by exponentiating the CIs of the mean of the natural log values based on the 1-sample t-distribution. For the dichotomous endpoints that immune responses meet threshold value as defined in the objectives, the within-group CIs will be calculated based on the exact method proposed by Clopper and Pearson ([Collett, 2002](#)).

*Protocol Amendments:* There were no protocol amendments for this study

### *Significant Changes in the Conduct of the Study & Planned Analyses:*

There were no changes in study conduct by amendment. Refer to [Section 6.1.9](#) for COVID-19 Pandemic-Associated Changes

Reviewer Comment: The changes due to the COVID-19 pandemic do not significantly impact the interpretability of the data generated from study V114-027.

### 6.3.10 Study Population and Disposition

A total of 900 participants were enrolled in the study. Study period: October 18, 2018 (first participant, first visit) to December 14, 2020 (last participant, last visit).

#### **6.3.10.1 Populations Enrolled/Analyzed**

Refer to [Section 6.1.10](#) for definitions of enrolled and analyzed populations.

#### *Demographics*

The demographic characteristics of participants were similar across study groups and are shown in [Table 30](#). Among all vaccinated participants, there were more males (52.8%) than females.



The median chronological age at enrollment was 9.0 weeks. Ten percent of participants were born at less than 37 weeks gestational age. Most participants were White, followed by Asian, Multiple, and Black or African American. Nearly one quarter identified as Hispanic/Latino.

**Table 30. Study V114-027: Demographic Characteristics**

Characteristic	Group 1 N=179	Group 2 N=181	Group 3 N=178	Group 4 N=179	Group 5 N=179	Total N=896
Sex, n (%)	--	--	--	--	--	--
Male	103 (57.5)	90 (49.7)	94 (52.8)	94 (52.5)	92 (51.4)	473 (52.8)
Female	76 (42.5)	91 (50.3)	84 (47.2)	85 (47.5)	87 (48.6)	423 (47.2)
Age at enrollment (weeks)	--	--	--	--	--	--
Median	8.0	9.0	8.5	9.0	9.0	9.0
Range (Min, max)	6, 12	6, 12	6, 12	6, 12	6, 12	6, 12
Gestational age at birth, n (%)	--	--	--	--	--	--
<37 weeks	20 (11.2)	19 (10.5)	21 (11.8)	14 (7.8)	17 (9.5)	91 (10.2)
≥37 weeks	159 (88.8)	162 (89.5)	157 (88.2)	165 (92.2)	162 (90.5)	805 (89.8)
Racial origin, n (%)	--	--	--	--	--	--
American Indian/Alaska Native	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Asian	36 (20.1)	34 (18.8)	37 (20.8)	32 (17.9)	38 (21.2)	177 (19.8)
Black/African American	8 (4.5)	11 (6.1)	3 (1.7)	3 (1.7)	9 (5.0)	34 (3.8)
Multiple	19 (10.6)	30 (16.6)	25 (14.0)	30 (16.8)	28 (15.6)	132 (14.7)
American Indian/Alaska Native, Black/African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
American Indian/Alaska Native, Black/African American, white	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
American Indian/Alaska Native, white	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)
Black/African American, White	19 (10.6)	29 (16.0)	25 (14.0)	27 (15.1)	24 (13.4)	124 (13.8)
Native Hawaiian/other Pacific Islander, white	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
White, Asian	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.1)	1 (0.6)	4 (0.4)
Native Hawaiian/other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.2)
White	115 (64.2)	106 (58.6)	113 (63.5)	113 (63.1)	103 (57.5)	550 (61.4)
Ethnicity, n (%)	--	--	--	--	--	--
Non-Hispanic and non-Latino	146 (81.6)	134 (74.0)	132 (74.2)	135 (75.4)	136 (76)	683 (76.2)
Hispanic or Latino	33 (18.4)	47 (26.0)	46 (25.8)	43 (24.0)	43 (24.0)	212 (23.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)

Source: Adapted from STN 125741.6, V114-027 Clinical Study Report: Table 10-6

Abbreviations: N=number of vaccinated participants for each cohort (participants with at least 1 vaccination of either PCV15 or PCV13); n=number of participants with indicated characteristic; SD=standard deviation

For Sex, Gestational Age at birth, Racial Origin and Ethnicity: n indicates number of subjects fulfilling the item in each category, (%) indicates % of All Vaccinated Participants represented in each category

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

### Participant Disposition

A list of prespecified protocol deviations is provided in [Section 6.1.10](#) of this review memo. Of the 900 enrolled study participants, 23.3% (n=210) had at least one important protocol deviation with 15.3% (n=138) having clinically important protocol deviations. Most of the reported

clinically important protocol deviations were due to immunogenicity samples drawn outside of the protocol-defined window for that time point or samples that could not be tested due to errors in processing or handling of the sample (121 participants). Participant dispositions are summarized in [Table 31](#).

**Table 31. Study V114-027: Summary of Participant Disposition**

Disposition	Group 1 N=179	Group 2 N=181	Group 3 N=180	Group 4 N=180	Group 5 N=180	Total N=900
Enrolled, n (%)	179 (100.0)	181 (100.0)	180 (100.0)	180 (100.0)	180 (100.0)	900 (100.0)
Vaccinated, n (%)	179 (100.0)	181 (100.0)	178 (98.9)	179 (99.4)	179 (99.4)	896 (99.6)
Completed, n (%)	164 (91.6)	167 (92.3)	147 (81.7)	160 (88.9)	167 (92.8)	805 (89.4)
APaT* - Safety, n (%)	179 (100.0)	181 (100.0)	178 (98.9)	179 (99.4)	179 (99.4)	896 (99.6)
FAS** - 30 Days Postdose 4, n (%)	161 (89.9)	163 (90.1)	141 (78.3)	155 (86.1)	160 (88.9)	780 (86.7)
≥1 important protocol deviation, n (%)	44 (24.6)	34 (18.8)	41 (22.8)	46 (25.6)	45 (25.0)	210 (23.3)
Pentacel recipients***	129 (72.1)	137 (75.7)	123 (68.3)	127 (70.6)	128 (68.9)	640 (71.1)
PP**** (IgG), n (%)	--	--	--	--	--	--
30 Days Postdose 3	103 (57.5)	101 (55.8)	85 (47.2)	94 (52.2)	98 (54.4)	481 (53.4)
Prior to Dose 4	113 (63.1)	116 (64.1)	99 (55.0)	108 (60.0)	110 (61.1)	546 (60.7)
30 Days Postdose 4	106 (59.2)	109 (60.2)	87 (48.3)	101 (56.1)	102 (56.7)	505 (56.1)

Source: Adapted from STN 125741.6, V114-027 Clinical Study Report: Table 10-1, Table 10-3, Table 12-1, Table 14 1-4, Table 14.2-4, and Information Request response received on March 17, 2022: Table 1

Abbreviations: APaT=All Participants as Treated; FAS=full analysis set; IgG=immunoglobulin G; N: number of participants enrolled; n indicates number of participants fulfilling the item for each cohort; PP=per-protocol population

\* All randomized participants who received at least one dose of study vaccination

\*\* All randomized participants who received all study vaccinations required at the timepoint for the analysis and have serology result

≥1 important protocol deviation: subjects with one or more important protocol deviations

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

\*\*\*Participants enrolled to receive Pentacel concomitantly with either PCV15 or PCV13 (excludes Pentavac recipients)

\*\*\*\*All randomized participants excluding Pentavac recipients without deviations from the protocol that may substantially affect the results of the IgG immunogenicity endpoint(s)

**Reviewer Comment:** The frequencies of clinically important protocol deviations were generally comparable across study groups. They do not significantly impact the interpretability of study results. The proportions of participants who received Pentacel concomitantly with PCV are generally comparable across study groups.

### 6.3.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints but did include serologic immune endpoints to assess the response to study vaccines as discussed in [Section 6.1.1](#).

#### *Primary Analyses (Descriptive): Anti-PnP IgG GMCs Post Dose 4*

The primary immunogenicity analyses evaluated serotype-specific response rates at 30 days PD4 for participants in Groups 2, 3, and 4 who received mixed doses of PCV15 and PCV13 as compared to Group 1, that received only PCV13 ([Table 32](#)). The antigen-specific responses were similar across Groups 2, 3 and 4 who received 4-dose regimens that included PCV15 for at least 1 dose as compared to Group 1 responses in participants who received only PCV13.

**Table 32. Study V114-027: PD4 Anti-PnP IgG GMCs for the 13 Shared Serotypes in Groups 1 to 4 and the PD4 IgG GMC ratios (GMCRs) for Each of Groups 2 Through 4 to Group 1, PP**

Serotype	Group 1 N=104 -106 PD4 GMC	Group 2 N= 108 - 109 PD4 GMC GMCR (95% CI)	Group 3 N= 86 - 87 PD4 GMC GMCR (95% CI)	Group 4 N= 101 PD4 GMC GMCR (95% CI)
1	1.84	1.57 0.86 (0.70, 1.05)	1.73 0.94 (0.76, 1.16)	1.51 0.82 (0.67, 1.01)
3	0.68	0.68 0.99 (0.82, 1.20)	0.61 0.89 (0.73, 1.09)	0.70 1.02 (0.84, 1.23)
4	1.75	1.47 0.84 (0.66, 1.06)	1.28 0.73 (0.57, 0.93)	1.32 0.75 (0.60, 0.95)
5	3.81	3.80 1.00 (0.79, 1.26)	3.73 0.98 (0.76, 1.25)	0.78 0.78 (0.62, 0.99)
6A	5.36	7.19 1.34 (1.07, 1.69)	6.39 1.19 (0.94, 1.52)	4.71 0.88 (0.70, 1.11)
6B	5.89	8.14 1.38 (1.11, 1.34)	6.30 1.07 (0.84, 1.35)	6.36 1.08 (0.86, 1.36)
7F	4.93	5.26 1.07 (0.85, 1.34)	5.08 1.03 (0.81, 1.31)	3.75 0.76 (0.60, 0.96)
9V	2.96	2.85 0.96 (0.78, 1.18)	2.50 0.84 (0.68, 1.05)	2.61 0.88 (0.72, 1.09)
14	6.79	9.92 1.46 (1.14, 1.86)	10.07 1.48 (1.15, 1.92)	1.00 (0.78, 1.28)
18C	2.43	4.01 1.65 (1.33, 2.06)	3.58 1.48 (1.17, 1.86)	2.67 1.10 (0.88, 1.37)
19A	5.55	5.55 1.00 (0.80, 1.25)	4.66 0.84 (0.66, 1.07)	4.64 0.84 (0.66, 1.05)
19F	4.96	5.19 1.05 (0.85, 1.28)	5.18 1.04 (0.84, 1.30)	4.44 0.90 (0.73, 1.10)
23F	3.00	2.75 0.92 (0.71, 1.18)	2.34 0.78 (0.60, 1.02)	2.26 0.75 (0.58, 0.97)

Source: Adapted from responses to Information request received March 17, 2022: Table 5

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; GMCR=geometric mean concentration ratio; N=number of participants in the PP for each specified cohort excluding Pentavac recipients; PD=post-dose; PnP=pneumococcal polysaccharide; PP=per-protocol population

a. GMC, GMC ratio, and CI are estimated from a serotype-specific ANCOVA model utilizing the natural log transformed antibody concentration as the response and vaccination group and stratification factor (hepatitis B vaccination status before enrollment) as covariates

Group 1 Ratio: ratio of the GMC of the serotype specific serotype IgG in each Group's participants to the GMC of Group 1 participants

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

**Reviewer Comment:** PD4 IgG GMCs and GMCRs were generally comparable for the 13 shared serotypes across all evaluated study groups.

### Secondary Analyses (Descriptive): Anti-PNP IgG GMCs and Seroresponse Rates $\geq 0.35$ µg/mL at 30 days PD3

These secondary immunogenicity analyses evaluated the serotype-specific anti-PnP IgG GMCs and response rates at 30 days PD3 in the each of the study groups (Table 33). The IgG GMCs and seroresponse rates were generally comparable across study groups for the 13 serotypes shared by PCV13 and PCV15. For the 2 unique serotypes (22F and 33F), receipt of more doses of PCV15 corresponded with a higher seroresponse to the two unique serotypes. Group 5 participants (those receiving a 4-dose series of only PCV15) had the highest antigen responses as compared to the those of participants who received mixed series (Groups 2 to 4).

**Table 33. Study V114-027: Anti-PnP IgG GMCs and Proportion of Participants With Anti-PnP IgG Concentrations  $\geq 0.35$   $\mu\text{g/mL}$  30 Days After Dose 3, PP**

Serotype	Group 1 N=100-103	Group 2 N=98-101	Group 3 N=83-85	Group 4 N=91-94	Group 5 N=97-98
	GMC (95% CI) % $\geq 0.35$ $\mu\text{g/mL}$ (95% CI)	GMC (95% CI) % $\geq 0.35$ $\mu\text{g/mL}$ (95% CI)	GMC (95% CI) % $\geq 0.35$ $\mu\text{g/mL}$ (95% CI)	GMC (95% CI) % $\geq 0.35$ $\mu\text{g/mL}$ (95% CI)	GMC (95% CI) % $\geq 0.35$ $\mu\text{g/mL}$ (95% CI)
1	1.62 (1.40, 1.87) 97.1% (91.7, 99.4)	1.81 (1.60, 2.04) 100% (96.4, 100.0)	1.48 (1.30, 1.69) 98.8% (93.6, 100.0)	1.11 (0.97, 1.28) 97.9% (92.5, 99.7)	1.06 (0.94, 1.19) 95.9% (89.9, 98.9)
3	0.47 (0.40, 0.55) 65.7% (55.6, 74.8)	0.63 (0.53, 0.74) 72.3% (62.5, 80.7)	0.45 (0.39, 0.51) 71.8% (61.0, 81.0)	0.61 (0.52, 0.70) 77.7% (67.9, 85.6)	0.84 (0.74, 0.94) 91.8% (84.5, 96.4)
4	1.21 (1.05, 1.39) 98.0% (93.1, 99.8)	1.35 (1.17, 1.55) 98.0% (92.8, 99.8)	0.99 (0.84, 1.16) 90.5% (82.1, 95.8)	0.9 (0.77, 1.04) 92.5% (85.1, 96.9)	1.18 (1.03, 1.34) 95.9% (89.9, 98.9)
5	1.57 (1.32, 1.86) 97.1% (91.6, 99.4)	1.98 (1.68, 2.34) 99.0% (94.6, 100.0)	1.6 (1.34, 1.91) 96.4% (89.9, 99.3)	1.44 (1.22, 1.71) 95.7% (89.5, 98.8)	1.58 (1.36, 1.83) 98.0% (92.8, 99.8)
6A	2.5 (2.14, 2.92) 99.0% (94.6, 100.0)	2.98 (2.56, 3.47) 99.0% (94.5, 100.0)	2.63 (2.20, 3.15) 98.8% (93.5, 100.0)	1.77 (1.47, 2.14) 96.8% (91.0, 99.3)	1.57 (1.33, 1.86) 98.0% (92.8, 99.8)
6B	1.79 (1.39, 2.29) 89.0% (81.2, 94.4)	2.56 (2.08, 3.17) 94.9% (88.6, 98.3)	2.13 (1.71, 2.64) 95.2% (88.1, 98.7)	2.21 (1.74, 2.80) 95.7% (89.5, 98.8)	2.08 (1.65, 2.64) 94.8% (88.4, 98.3)
7F	3.02 (2.67, 3.43) 100% (96.5, 100.0)	3.24 (2.85, 3.69) 100% (96.4, 100.0)	3 (2.61, 3.45) 100% (95.8, 100.0)	2.28 (1.98, 2.62) 100% (96.2, 100.0)	2.08 (1.84, 2.35) 100% (96.3, 100.0)
9V	1.46 (1.25, 1.70) 95.1% (89.0, 98.4)	1.64 (1.42, 1.89) 96.0% (90.2, 98.9)	1.28 (1.07, 1.52) 95.2% (88.3, 98.7)	1.31 (1.12, 1.53) 93.6% (86.6, 97.6)	1.85 (1.62, 2.11) 98.0% (92.8, 99.8)
14	5.79 (4.83, 6.95) 98.0% (93.1, 99.8)	5.55 (4.55, 6.78) 98.0% (93.0, 99.8)	7.58 (5.88, 9.77) 95.2% (88.3, 98.7)	5.88 (4.88, 7.09) 100% (96.2, 100.0)	4.9 (4.21, 5.70) 99.0% (94.4, 100.0)
18C	1.38 (1.17, 1.62) 94.2% (87.8, 97.8)	1.81 (1.60, 2.06) 100% (96.4, 100.0)	1.63 (1.41, 1.89) 98.8% (93.6, 100.0)	1.3 (1.13, 1.49) 98.9% (94.2, 100.0)	1.3 (1.14, 1.49) 99.0% (94.4, 100.0)
19A	2 (1.72, 2.33) 99.0% (94.7, 100.0)	2.32 (2.03, 2.64) 100% (96.4, 100.0)	1.84 (1.54, 2.19) 97.6% (91.8, 99.7)	1.45 (1.23, 1.69) 95.7% (89.5, 98.8)	1.41 (1.23, 1.61) 96.9% (91.3, 99.4)
19F	2.48 (2.18, 2.82) 99.0% (94.7, 100.0)	2.76 (2.42, 3.15) 99.0% (94.6, 100.0)	2.62 (2.26, 3.03) 98.8% (93.5, 100.0)	2.03 (1.77, 2.33) 100% (96.2, 100.0)	1.94 (1.70, 2.20) 100% (96.3, 100.0)

Serotype	Group 1 N=100-103	Group 2 N=98-101	Group 3 N=83-85	Group 4 N=91-94	Group 5 N=97-98
	GMC (95% CI) % ≥0.35 µg/mL (95% CI)	GMC (95% CI) % ≥0.35 µg/mL (95% CI)	GMC (95% CI) % ≥0.35 µg/mL (95% CI)	GMC (95% CI) % ≥0.35 µg/mL (95% CI)	GMC (95% CI) % ≥0.35 µg/mL (95% CI)
23F	1.17 (0.95, 1.45) 91.1% (83.8, 95.8)	1.48 (1.26, 1.74) 97.0% (91.4, 99.4)	0.92 (0.77, 1.10) 88.1% (79.2, 94.1)	1.18 (0.96, 1.44) 91.2% (83.4, 96.1)	1.19 (1.00, 1.41) 92.9% (85.8, 97.1)
22F	0.04 (0.04, 0.05) 3.0% (0.6, 8.4)	0.05 (0.04, 0.06) 2.0% (0.2, 7.1)	3.09 (2.35, 4.05) 92.9% (85.1, 97.3)	5.42 (4.63, 6.34) 100% (96.1, 100.0)	4.51 (3.83, 5.32) 98.0% (92.8, 99.8)
33F	0.05 (0.04, 0.06) 2.9% (0.6, 8.4)	0.05 (0.04, 0.06) 3.0% (0.6, 8.5)	0.21 (0.15, 0.29) 32.5% (22.6, 43.7)	0.86 (0.64, 1.16) 75.3% (65.2, 83.6)	1.86 (1.49, 2.32) 90.8% (83.3, 95.7)

Source Adapted from response to Information Request received March 24, 2022: Table 1 and Table 2

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; N=number of participants in the PP for each specified cohort; PD=post-dose; PnP=pneumococcal polysaccharide; PP=per-protocol population

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

**Reviewer Comment:** PD3 IgG GMCs and seroresponse rates to the 13 shared serotypes were comparable for groups 1 through 3 (i.e., those groups receiving 2 to 3 doses of PCV 13 prior to determination of the study end point). IgG GMCs and seroresponse rates followed different trends in participants who had received > 1 dose of PCV 15 (i.e., groups 4 and 5). The immune responses elicited to serotype 3 were higher in groups receiving more doses of PCV 15. The immune responses to other serotypes (i.e., 6A, 7F, 19 A, and 19 F) were lower in groups receiving more doses of PCV 15 although the differences were not large. IgG GMCs and seroresponse rates for the 2 unique serotypes increased with more doses received prior to endpoint determination.

### Secondary Analysis (H1) Hepatitis B Antigen Responses Post-PCV Dose 3

The response to concomitant Hepatitis B vaccination was assessed by the proportion of participants with anti-HBsAg concentration ≥10 mIU/mL at 30 days PD3 for participants administered the PCV15 series (Group 5) concomitantly with Recombivax HB compared to participants administered the PCV13 series (Groups 1 and 2) with Recombivax HB. Most (97.2%) participants received an initial non-study dose of Hepatitis B vaccine shortly after birth and then two study doses of Recombivax HB. Demonstration of noninferiority was based on the lower bound of the 2-sided 95% CI being greater than -10%. The noninferiority criterion was met as shown in [Table 34](#). Anti-HBsAg GMCs were also determined PD3 and were generally comparable in all study groups supporting the results of the antigen response rate evaluation.

**Table 34. Study V114-027: Hepatitis B Antigen Response Rates After Dose 3, PP**

Vaccine	Endpoint*	Group 5	Group 1+Group 2	Difference (95% CI)
		# of PCV15 doses: 3 N=102 % ≥CL	# of PCV13 doses: 3 N=201 % ≥CL	
Hepatitis B	% ≥10 mIU/mL	98.0	99.0	-0.9 (-6.0, 2.0)

Source: Adapted from response to Information Request received March 24, 2022: Table 4

Abbreviations: CI=confidence interval; CL=comparison level for determination of response rate to each vaccine; N=number of participants in the PP belonging to the indicated cohort included in the determination of the endpoint; PP=per-protocol population

\* Includes the proportion (%) of participants who achieved the pre-defined serologic assay threshold

% ≥CL: Percent of participants in the PP cohort who had a response rate equal to or greater than the comparison level

Difference: Difference in % of participants with a response greater than or equal to the comparison level between Group 5 participants and Group 1+Group 2 participants

**Reviewer Comment:** Three doses of hepatitis B vaccine elicited noninferior immune responses when administered concomitantly with either 3 doses of PCV 15 or 3 doses of PCV 13.

### Secondary Analysis (H2) Rotavirus Antigen Responses post-PCV Dose 3

The IgA GMTs to Rotavirus vaccine were determined after dose 3 of the pneumococcal vaccine series composed entirely of PCV15 (Group 5) as compared to series composed of PCV13 (Groups 1 and 2) are shown in [Table 35](#). The statistical criterion for non-inferiority required the lower bound of the 2-sided 95% CI to be greater than 0.50. The noninferiority criterion was met as shown in as shown in [Table 35](#).

**Table 35. Study V114-027: Anti-Rotavirus IgA GMTs 30 Days After Dose 3, PP**

Antigen	Group 5	Group 1+Group 2	Ratio (95% CI)
	3 PCV15 Doses N=102 GMT	3 of PCV13 Doses N=209 GMT	
Anti-rotavirus IgA	309.1	298.1	1.04 (0.72, 1.49)

Source: Adapted from STN 125741.6, V114-027 Clinical Study Report: Table 11-4

Abbreviations: CI=confidence interval; GMT=geometric mean titer; IgA=immunoglobulin A; N=number of participants in the PP belonging to the indicated cohort included in the determination of the endpoint; PP=per-protocol population

Ratio: ratio of the anti-rotavirus IgA GMTs in Group 5 participants to the anti-rotavirus IgA of Group 1+Group 2 participants

**Reviewer Comment:** Although the immune responses elicited by 3 doses of RotaTeq met noninferiority criteria when administered concomitantly with either 3 doses of PCV13 or three doses of PCV15, the endpoint evaluated (i.e., anti-rotavirus IgA) is not considered adequate to evaluate for immune interference impacting effectiveness of RotaTeq when administered concomitantly with PCV15.

**Exploratory Analyses (Descriptive):** Anti-PnP serotype-specific IgG GMCs, Pre-dose 4 Pre-D4 serotype specific anti-PNP IgG GMCs were generally comparable across study groups with the exception of the two unique serotypes (22F and 33F). The IgG GMCs for those study groups whose recipients received more doses of PCV15 (i.e., groups 3, 4, and 5) had higher GMCs for the two unique serotypes.

### Subpopulation Analyses

Subpopulation analyses were conducted for the primary immunogenicity endpoint for all subpopulations that were composed of ≥5% of the total number participants for the study group.

Observed serotype specific IgG GMCs and response rates for the 13 shared serotypes were consistent with those observed in the overall population for the following subgroups: male vs. female participants, race (White, Asian, and multiple races), ethnicity (Hispanic or Latino, not Hispanic or Latino), and those participants who received Hepatitis B vaccination prior to enrollment.

### 6.3.12 Safety Analyses

#### Methods

See [Section 6.1.9](#)

#### Overview of Adverse Events

[Table 36](#) provides an overview of the AEs of all types occurring during the study period. The rates of solicited ARs, SAEs and unsolicited AEs were generally comparable between study groups. No deaths occurred during the study period.

**Table 36. Study V114-027: Proportion of Participants Reporting at Least One Adverse Event Following Any Vaccination Dose, APaT Population**

AE Type	Group 1 N=179	Group 2 N=181	Group 3 N=178	Group 4 N=179	Group 5 N=179
Any adverse event, n (%)	168 (93.9)	165 (91.2)	165 (92.7)	167 (93.3)	163 (91.1)
Injection site event, n (%)	128 (71.5)	114 (63.0)	123 (69.1)	121 (67.6)	127 (70.9)
Systemic event, n (%)	161 (89.9)	160 (88.4)	156 (87.6)	161 (89.9)	156 (87.2)
Serious adverse event, n (%)	21 (11.7)	24 (13.3)	15 (8.4)	18 (10.1)	21 (11.7)
AEs leading to vaccine discontinuation, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Vaccine-related adverse reactions*</b>	<b>N=129</b>	<b>N=137</b>	<b>N=123</b>	<b>N=127</b>	<b>N=124</b>
Any adverse reaction, n (%)	118 (91.5)	125 (91.2)	116 (94.3)	119 (93.7)	112 (90.3)
Injection site	103 (79.8)	99 (72.3)	95 (77.2)	96 (75.6)	95 (76.6)
Systemic	110 (85.3)	110 (80.3)	106 (86.2)	111 (87.4)	105 (84.7)

Source: Adapted from response to Information Request received March 17, 2022: Table 7

Abbreviations: APaT=All Participants as Treated; x participants=#subjects who experienced the event; n=#subjects with available data for relevant endpoint

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

\* Vaccine-related adverse events exclude participants who received Pentavac

#### Solicited ARs

Most study participants reported an injection site (63.0% to 71.5%), or systemic (75.1% to 82.1%) AR. Rates were generally comparable for all study doses. [Table 37](#) provides an overview of reported ARs following study dose 1. Pain (27.6% to 35.7%), erythema (12.4% to 21.0%), and swelling (6.3% to 14.5%) were the 3 most reported injection site ARs. Irritability (46.0% to 58.1%), somnolence (40.9% to 54.3%), and decreased appetite (8.1%-17.8%) were the 3 most commonly reported systemic ARs.

**Table 37. Study V114-027: Comparison of Participants With Solicited Adverse Events From Day 1 Through Day 14 Post Dose 1, APaT Excluding Pentavac Recipients**

Selected Adverse Event	Group 1 N=129	Group 2 N=137	Group 3 N=123	Group 4 N=127	Group 5 N=124
Injection site reactions, n (%)	--	--	--	--	--
Swelling	13 (10.1)	11 (8.0)	15 (12.2)	8 (6.3)	18 (14.5)
Erythema	16 (12.4)	21 (15.3)	21 (17.1)	16 (12.6)	26 (21.0)
Pain	46 (35.7)	46 (33.6)	34 (27.6)	36 (28.3)	44 (35.5)
Induration	20 (15.5)	21 (15.3)	17 (13.8)	10 (7.9)	21 (16.9)
Systemic reactions, n (%)	--	--	--	--	--
Irritability	70 (54.3)	63 (46.0)	67 (54.5)	62 (48.8)	72 (58.1)
Somnolence	70 (54.3)	56 (40.9)	57 (46.3)	60 (47.2)	60 (48.4)
Decreased appetite	23 (17.8)	16 (11.7)	10 (8.1)	20 (15.7)	18 (14.5)
Urticaria	2 (1.6)	2 (1.5)	2 (1.6)	3 (2.4)	3 (2.4)

Source: Adapted from response to Information Request received March 27, 2022: Table 28

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n=number of participants experiencing indicated event

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

[Table 38](#) provides an overview of reported ARs following study dose 2. Pain (23.7% to 30.2%), erythema (19.1% to 30.0%), and induration (13.2% to 18.8%) were the 3 most reported injection site ARs. Irritability (48.9% to 58.3%), somnolence (31.9% to 43.0%), and decreased appetite (9.9% to 17.5%) were the 3 most reported systemic ARs.

**Table 38. Study V114-027: Comparison of Participants With Solicited Adverse Events From Day 1 Through Day 14 Post Dose 2, APaT Excluding Pentavac Recipients**

Selected Adverse Event	Group 1 N=128	Group 2 N=131	Group 3 N=116	Group 4 N=121	Group 5 N=120
Injection site reactions, n (%)	--	--	--	--	--
Swelling	11 (8.6)	11 (8.4)	10 (8.6)	12 (9.9)	12 (10.0)
Erythema	34 (26.6)	25 (19.1)	23 (19.8)	26 (21.5)	36 (30.0)
Pain	34 (26.6)	31 (23.7)	35 (30.2)	33 (27.3)	34 (28.3)
Induration	24 (18.8)	19 (14.5)	19 (16.4)	16 (13.2)	19 (15.8)
Systemic reactions, n (%)	--	--	--	--	--
Irritability	69 (53.9)	64 (48.9)	65 (56.0)	65 (53.7)	70 (58.3)
Somnolence	55 (43.0)	45 (34.4)	37 (31.9)	41 (33.9)	43 (35.8)
Decreased appetite	17 (13.3)	20 (15.3)	18 (15.5)	12 (9.9)	21 (17.5)
Urticaria	3 (2.3)	2 (1.5)	2 (1.7)	2 (1.7)	1 (0.8)

Source: Adapted from response to Information Request received March 27, 2022: Table 29

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n (%) =number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

[Table 39](#) provides an overview of reported ARs following study dose 3. Pain (20.8% to 38.4%), erythema (20.5% to 28.3%), and induration (13.4% to 18.9%) were the 3 most reported injection site ARs. Irritability (47.2 to 61.7%), somnolence (20.8% to 33.1%), and decreased appetite (10.8% to 17.3%) were the 3 most reported systemic ARs.



**Table 39. Study V114-027: Comparison of Participants With Solicited Adverse Events From Day 1 Through Day 14 Post Dose 3, APaT Excluding Pentavac Recipients**

Selected Adverse Event	Group 1 N=127	Group 2 N=130	Group 3 N=112	Group 4 N=119	Group 5 N=120
Injection site reactions, n (%)	--	--	--	--	--
Swelling	14 (11.0)	12 (9.2)	13 (11.6)	13 (10.9)	16 (13.3)
Erythema	36 (28.3)	27 (20.8)	23 (20.5)	25 (21.0)	25 (20.8)
Pain	27 (21.3)	27 (20.8)	43 (38.4)	28 (23.5)	38 (31.7)
Induration	24 (18.9)	20 (15.4)	15 (13.4)	16 (13.4)	21 (17.5)
Systemic reactions, n (%)	--	--	--	--	--
Irritability	60 (47.2)	62 (47.7)	62 (55.4)	61 (51.3)	74 (61.7)
Somnolence	42 (33.1)	27 (20.8)	28 (25.0)	38 (31.9)	33 (27.5)
Decreased appetite	22 (17.3)	14 (10.8)	14 (12.5)	14 (11.8)	17 (14.2)
Urticaria	1 (0.8)	0 (0)	3 (2.7)	4 (3.4)	2 (1.7)

Source: Adapted from response to Information Request received March 27, 2022: Table 30

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n (%) =number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

[Table 40](#) provides an overview of reported ARs following study dose 4. Pain (18.4% to 33.7%), erythema (16.8% to 25.2%), and induration (9.6% to 17.6%) were the 3 most commonly reported injection site ARs. Irritability (44.8% to 53.8%), somnolence (26.1% to 31.9%), and decreased appetite (13.5% to 23.5%) were the 3 most reported systemic ARs

**Table 40. V114-027: Comparison of Participants With Solicited Adverse Events From Day 1 Through Day 14 Post Dose 4, APaT Excluding Pentavac Recipients**

Selected Adverse Event	Group 1 N=119	Group 2 N=125	Group 3 N=104	Group 4 N=115	Group 5 N=117
Injection site reactions, n (%)	--	--	--	--	--
Swelling	10 (8.4)	9 (7.2)	12 (11.5)	7 (6.1)	14 (12.0)
Erythema	30 (25.2)	21 (16.8)	24 (23.1)	28 (24.3)	28 (23.9)
Pain	32 (26.9)	23 (18.4)	35 (33.7)	25 (21.7)	23 (19.7)
Induration	21 (17.6)	12 (9.6)	17 (16.3)	16 (13.9)	12 (10.3)
Systemic reactions, n (%)	--	--	--	--	--
Irritability	56 (47.1)	56 (44.8)	52 (50.0)	55 (47.8)	63 (53.8)
Somnolence	38 (31.9)	39 (31.2)	29 (27.9)	30 (26.1)	31 (26.5)
Decreased appetite	28 (23.5)	20 (16.0)	14 (13.5)	16 (13.9)	18 (15.4)
Urticaria	3 (2.5)	3 (2.4)	1 (1.0)	3 (2.6)	1 (0.9)

Source: Adapted from response to Information Request received March 27, 2022: Table 31

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n (%) =number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

**Reviewer Comment:** Overall, reported rates of solicited ARs were generally comparable across study groups following each dose. Reports of erythema and irritability following any dose were slightly more frequent in group 5 (i.e., those receiving 4 doses of PCV 15). This may be consistent with the increased reactogenicity of PCV 15 versus PCV13 observed in study V114-031.

*Maximum Body Temperatures: within 7 days post-vaccination*

Rates of reported fever belonging to the highest temperature increment (i.e., body temperature  $\geq 40.0^\circ$ ) were slightly more common following doses 3 and 4 of PCV15. Rates of fever (i.e.,

body temperature  $\geq 38.0^\circ$ ) were otherwise generally comparable across all study groups as shown in [Table 41](#)

**Table 41. V114-027: Comparison of Maximum Temperatures Reported By Participants, APaT Excluding Pentavac Recipients**

Temperature	Group 1 N=119-129 n (%)	Group 2 N=124-136 n (%)	Group 3 N=102-123 n (%)	Group 4 N=115-127 n (%)	Group 5 N=115-124 n (%)
<38.0	--	--	--	--	--
Dose 1	123 (95.3)	132 (97.1)	117 (95.1)	117 (92.1)	116 (93.5)
Dose 2	113 (88.3)	107 (81.7)	96 (84.2)	100 (83.3)	102 (87.2)
Dose 3	102 (81.0)	105 (82.7)	97 (87.4)	106 (89.1)	107 (89.9)
Dose 4	111 (93.3)	106 (85.5)	91 (89.2)	101 (87.8)	94 (81.7)
$\geq 38.0$ and <39.0	--	--	--	--	--
Dose 1	6 (4.7)	4 (2.9)	6 (4.9)	10 (7.9)	8 (6.5)
Dose 2	12 (9.4)	22 (16.8)	15 (13.2)	19 (15.8)	11 (9.4)
Dose 3	22 (17.5)	20 (15.7)	12 (10.8)	11 (9.2)	10 (8.4)
Dose 4	5 (4.2)	14 (11.3)	9 (8.8)	12 (10.4)	18 (15.7)
$\geq 39.0$ and <40.0	--	--	--	--	--
Dose 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dose 2	3 (2.3)	2 (1.5)	2 (1.8)	1 (0.8)	3 (2.6)
Dose 3	2 (1.6)	2 (1.6)	2 (1.8)	2 (1.7)	1 (0.8)
Dose 4	3 (2.5)	4 (3.2)	2 (2.0)	2 (1.7)	2 (1.7)
$\geq 40.0$	--	--	--	--	--
Dose 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dose 2	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
Dose 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Dose 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

Source: Adapted from response to IR received June 2, 2022: Tables 9-12

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each group; n = number of participants with available temperature data, n (%) = number of participants reporting temperature in indicated range after specified dose and % of participants with available temperature data

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

Data presented for participants with available temperature data that excludes Pentavac recipients and reported as measured

Of the maximum temperature measurements, ~75% to ~83% were rectal measurements, ~17% to ~25% were axillary measurements and 0.2% were temporal measurements.

**Reviewer Comment:** There was a small trend towards increased rates of reported fevers in recipients of 4 doses of PCV15, especially after doses 3 and 4, as compared to participants who received regimens that included fewer PCV 15 doses.

#### *Unsolicited AEs within 14 days post-vaccination*

Unsolicited AEs were documented by the participant's legally acceptable representative in the eVRC and reviewed by the investigator at vaccine study visits and at 15 days following each vaccine dose. Rates of unsolicited AEs were generally comparable across study groups (Group 1: 67.6%; Group 2: 66.9%; Group 3: 64.6%; Group 4: 64.2%; Group 5: 63.1%). The most frequently reported events, by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, were: General disorders and administration site conditions (32.0%-39.2%); Infections and infestations (29.8%-36.9%); and Gastrointestinal disorders (16.2%-18.2%).

Reviewer Comment: The reported rates and types of unsolicited adverse events are comparable across study groups and represent medical conditions that are common in children.

## Deaths

There were no deaths due to AEs reported for this study

## Nonfatal Serious Adverse Events

There were 99 reported SAEs in the study (~11% of study participants). The most frequently reported SAEs, as summarized in [Table 42](#), were classified under the SOC *Infections and infestations* with the most common PTs of Bronchiolitis and RSV Bronchiolitis. Reported SAE occurrences were generally comparable across study groups. The types of SAEs were similar within 30 days and 7 days of study vaccination.

**Table 42. Study V114-027: Participants Reporting SAEs\* During the Study by Preferred Term, APaT**

Preferred Term	Group 1	Group 2	Group 3	Group 4	Group 5
	N=179 n (%)	N=181 n (%)	N=178 n (%)	N=179 n (%)	N=179 n (%)
Bronchiolitis	6 (3.4)	6 (3.3)	3 (1.7)	3 (1.7)	8 (4.5)
Gastroenteritis	4 (2.2)	2 (1.1)	1 (0.6)	0 (0.0)	1 (0.6)
Respiratory syncytial virus bronchiolitis	2 (1.1)	2 (1.1)	1 (0.6)	3 (1.7)	3 (1.7)
Pneumonia	2 (1.1)	0 (0.0)	1 (0.6)	2 (1.1)	2 (1.1)
Influenza	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	3 (1.7)
Urinary tract infection	1 (0.6)	2 (1.1)	0 (0.0)	2 (1.1)	1 (0.6)
Bronchitis	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.1)	1 (0.6)
Seizure	0 (0.0)	2 (1.1)	1 (0.6)	0 (0.0)	0 (0.0)

Source: Adapted from STN 125741.6, V114-027 Clinical Study Report: Table 12-8

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort receiving the indicated dose; n (%) =number of participants reporting any SAE during the study and % of the APaT belonging to that cohort receiving the indicated dose; SAE=serious adverse event

\* Serious adverse event by PT experienced by >1 participant in any study group

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

Reviewer Comment: The rates of SAEs were generally comparable across the two study groups and no SAEs were considered related to PCV15.

## SAE of Interest – Afebrile seizure

A 4.6-month-old Asian male (Group 3) developed seizures following Dose 2 of PCV13. The participant had initially developed seizures with fever 1.8 months after dose 1 of PCV13. He was admitted to the hospital at that time and presumptively diagnosed with Dravet syndrome (a rare form of epilepsy that begins in the first year of life) along with an acute parainfluenza virus infection. His seizures resolved after he was started on levetiracetam, and he was discharged. Genetic testing later confirmed the diagnosis of Dravet syndrome, a disorder caused by a mutation in SCN1A gene which encodes a sodium voltage-gated channel protein. The investigator ruled that episode of seizures following study dose 2 was related to that study dose and that the initial episode of seizures following dose 1 was unrelated. The participant was discontinued from the study due to this SAE.

### SAEs of Interest: Febrile seizures

One participant in Group 5 (received 4 doses of PCV15) reported 2 febrile seizure events. These events occurred 78- and 118-days following doses 3 and 4 of PCV15, respectively. Another participant in Group 2 (3 doses of PCV13 followed by 1 dose of PCV15 reported a febrile seizure 50 days after PCV15. All were considered by the investigator as unrelated to the study intervention.

Reviewer Comment: This clinical reviewer agrees with the investigators assessments that the reported cases of febrile seizures were not related to the study vaccine given the time of onset and clinical features. Participants reporting febrile seizures were generally balanced across study groups (Group 1: n= 0, Group 2: n=2, Group 3: n = 1, Group 4: n=0, Group 5: n=1).

### Subpopulation Analyses

Safety results were reported for all subpopulations that contained  $\geq 5\%$  of the total number participants for the study group. Safety results were generally comparable across subpopulations and with those of the overall population for each of the following subpopulations: male vs. female participants, race (white, Asian, and multiple races), ethnicity (Hispanic or Latino, not Hispanic or Latino).

### Dropouts and/or Discontinuations

A total of 95 discontinuations occurred during the study, and the number discontinuations was generally comparable across study groups with the exception of Group 3 which had 33 discontinuations (18.3% of the study group). 89.4% of the total study participants completed the study. Most discontinuations were due to withdrawal by parent/guardian and lost to follow-up as shown [Table 43](#). There was one discontinuation due to epilepsy in a Group 3 participant following PCV13, as discussed in the *Nonfatal Serious Adverse Events* section [above](#).

**Table 43. Study V114-027: Participant Dropouts and/or Discontinuations During the Study**

Reason*	Group 1 N=129	Group 2 N=137	Group 3 N=124	Group 4 N=128	Group 5 N=125	Total N=643
All Discontinued, n (%)	15 (8.4)	14 (7.7)	33 (18.3)	20 (11.1)	13 (7.2)	95 (10.6)
Withdrawal**, n (%)	9 (5.0)	8 (4.4)	25 (13.9)	17 (9.4)	9 (5.0)	68 (7.6)
Lost to follow-up, n (%)	2 (1.1)	6 (3.3)	7 (3.9)	3 (1.7)	2 (1.1)	20 (2.2)
Physician decision, n (%)	4 (2.2)	0 (0)	0 (0)	0 (0)	2 (1.1)	7 (0.8)

Source: Adapted from STN 125741.6, V114-027 Clinical Study Report: Table 10-1, Table 10-3, Table 12-1, Table 14 1-4, Table 14.2-4

n indicates number of participants fulfilling the item for each cohort

N: number of participants enrolled

\* APaT: all randomized participants who received at least one dose of study vaccination

\*\* FAS: all randomized participants who received all study vaccinations required at the timepoint for the analysis and have serology result

\*\*\* PP: Per protocol population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the IgG immunogenicity endpoint(s)

$\geq 1$  Important Protocol Deviation: subjects with one or more important protocol deviations

Dropouts and discontinuations in the study, excluding those participants who received Pentavac, are shown in [Table 44](#). The proportions of discontinued participants were generally similar across study groups and the interpretability of the study results does not seem to be impacted.

**Table 44. Study V114-027: Participant Dropouts and/or Discontinuations During the Study excluding Pentavac Recipients**

<b>Reason*</b>	<b>Group 1 N=129</b>	<b>Group 2 N=137</b>	<b>Group 3 N=124</b>	<b>Group 4 N=128</b>	<b>Group 5 N=125</b>	<b>Total N=643</b>
All Discontinued, n (%)	11 (8.5)	13 (9.5)	23 (18.5)	14 (10.9)	9 (7.2)	70 (10.9)
Withdrawal**, n (%)	6 (4.7)	7 (5.1)	16 (12.9)	11 (8.6)	6 (4.8)	46 (7.2)
Lost to follow-up, n (%)	2 (1.6)	6 (4.4)	7 (5.6)	3 (2.3)	2 (1.6)	20 (3.1)
Physician decision, n (%)	3 (2.3)	0 (0)	0 (0)	0 (0)	1 (0.8)	4 (0.6)

Source: Adapted from response to Information Request March 4, 2022: Table 3

Abbreviations: N=all randomized participants; n=number of discontinued participants; %= % of all randomized participants

\* Reason for discontinuation

\*\* Withdrawal by parent or guardian

Group 1 received 4 doses of PCV13. Group 2 received 3 doses of PCV13 and 1 dose of PCV15. Group 3 received 2 doses of PCV13 and 2 doses of PCV15. Group 4 received 1 dose of PCV13 and 3 doses of PCV15. Group 5 received 4 doses of PCV15.

### 6.3.13 Study Summary and Conclusions

Study V114- 027 was a phase 3 study designed to evaluate the safety, tolerability, and immunogenicity of PCV15 when interchanged with PCV13 for one, two, three, or four doses of a 4-dose infant series. The study also evaluated for potential immune interference of rotavirus and hepatitis B vaccines when administered concomitantly with 3 doses of either PCV15 or PCV13.

Reported rates of solicited ARs and unsolicited AEs through 14 days following each dose, and SAEs through the study duration were comparable across groups. No obvious safety concerns were identified. The study endpoints supported the safety of PCV15 for the completion of 4-dose PCV series started with PCV13.

Primary immunogenicity endpoints (i.e., IgG GMCs PD4) and secondary immunogenicity endpoints (i.e., IgG GMCs and seroresponse rates PD3) supported the comparability of anti-PnP immune responses elicited by 4 dose regimens of PCV when varying doses of PCV15 completed a series started with PCV13.

The antibody responses elicited by hepatitis B vaccine were noninferior when the hepatitis B vaccine was co-administered with 3 doses of either PCV15 or PCV13, consistent with the immune noninterference of concomitant administration of PCV15 with Hepatitis B vaccine as compared to PCV13.

The immune responses elicited by Rotavirus vaccine, as measured by anti-rotavirus IgA GMTs, met noninferiority criteria when co-administered with 3 doses of either PCV13 or PCV15; however, CBER does not consider results using this assay sufficient to draw conclusions regarding the immune noninterference of PCV15 with Rotavirus vaccine.

Overall, this study supports the safety and effectiveness of a 4-dose infant PCV series with PCV15 when the series was initiated with one or more doses of PCV13.

### 6.4 Trial #4: V114-024

**NCT03885934:** A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of Catch-up Vaccination Regimens of PCV15 in Healthy Infants, Children, and Adolescents (PNEU-PLAN)

**Study Overview:** The purpose of this phase 3 study was to descriptively evaluate the safety and immunogenicity of PCV15 in children 7 months through 17 years of age when administered as either 3-dose, 2-dose, or 1-dose catch-up vaccination schedules, based on age at the time of enrollment. Enrolled participants <2 years of age were pneumococcal conjugate vaccine (PCV) naïve, while children  $\geq 2$  years of age were either PCV naïve, partially vaccinated with PCV (including PCV13), or fully vaccinated with a lower valency PCV (not including PCV13). The study enrolled 606 participants from 25 sites in Finland, Malaysia, Poland, Russian Federation, and Thailand.

#### 6.4.1 Objectives (as stated in study protocol V114-024, Amendment 0)

##### **Primary Safety Objective**

1. To evaluate the safety and tolerability of PCV15 with respect to the proportion of participants with adverse events:
  - Endpoints:
    - i. Solicited injection-site AEs from Day 1 through Day 14 following any vaccination with PCV15
    - ii. Solicited systemic AEs from Day 1 through Day 14 following any vaccination with PCV15
      - For participants 7 months to <3 years of age at enrollment, solicited systemic AEs include irritability, drowsiness/somnolence, appetite lost/decreased appetite, and hives or welts/urticaria
      - For participant  $\geq 3$  years to of age at enrollment, solicited systemic AEs include muscle pain/ myalgia, joint pain/arthritis, headache, tiredness/fatigue, and hives or welts/urticaria
    - iii. Vaccine-related serious adverse events (SAEs) through completion of study participation

##### **Primary Immunogenicity Objective**

1. To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days following the last because dose for each vaccination group.
  - Endpoints: Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in PCV15 at 30 days after the last dose of study vaccine

##### **Secondary Immunogenicity Objective**

1. To evaluate the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of  $\geq 0.35$   $\mu\text{g/mL}$ ) at 30 days following the last dose for each vaccination group.
  - Endpoints: Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in PCV15 at 30 days after the last dose of study vaccine

##### **Tertiary/Exploratory Immunogenicity Objective (participants $\geq 2$ years of age only)**

1. To evaluate the serotype-specific Geometric Mean Fold Rises (GMFRs) in IgG responses from pre-vaccination (Day1) to 30 days following the last dose for each vaccination group.
  - Endpoints: Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in PCV15 at 30 days after the last dose of study vaccine

## 6.4.2 Design Overview

Study V114-024 was a multicenter, randomized, double-blind phase study in healthy children who were either pneumococcal vaccine-naïve or who had previously received a partial or full series of pneumococcal vaccination (participants  $\geq 2$  years of age only). A total of 606 participants (7 months through 11 months old: n=128; 12 through 23 months old: n=126; 2 through 17 years: n=352) were randomized 1:1 between PCV13 and PCV15.

## 6.4.3 Population

### *Inclusion Criteria*

Participants were eligible for inclusion in the study if the participant:

- Is healthy (based on a review of medical history and physical examination) based on the clinical judgement of the investigator
- Is male or female, from 7 months to 17 years of age (inclusive), at the time of obtaining the informed consent/assent.
- Female participants should use contraceptives in a manner that is consistent with local regulations regarding the methods of contraception for those participating in clinical studies and:
  - Not be pregnant or breastfeeding
  - If of childbearing potential, follow contraceptive guidance during the treatment period and for at least 6 weeks after the last dose of study intervention.

### *Exclusion Criteria*

In addition to those exclusion criteria listed in [Section 6.1.3](#) (and with the exception of those criteria pertaining to concomitant routine infant vaccines), participants were excluded if a participant was:

- 7 to 23 months of age and has received a dose of a pneumococcal vaccine prior to study entry based on medical record. Participants  $\geq 2$  years of age could have received a pneumococcal vaccine at least 8 weeks prior to study entry as follows: a partial regimen of Prevnar™, Synflorix™, or Prevnar 13™ or a full regimen of Prevnar™ or Synflorix™ based on local guidelines. Participants should not have received any dose of a pneumococcal polysaccharide vaccine.

## 6.4.4 Study Treatments or Agents Mandated by the Protocol

PCV15: 15-valent pneumococcal conjugate vaccine

- See [Section 6.1.4](#) for dose, composition, and presentation
- Schedule of administration (by participant age/pneumococcal vaccine status):
  - 7 to 11 months/naïve: 3 doses - Day 0, 4 to 8 weeks after Dose 1, and 8 to 12 weeks after Dose 2
  - 12 to 23 months/naïve: 2 doses – Day 0 and 8 to 12 weeks after Dose 1
  - 2 to 17 years/naïve: 1 dose – Day 0
  - 2 to 17 years/ not naïve: 1 dose – Day 0, at least 8 weeks after previous pneumococcal vaccine dose
- Lot # WL00068572

#### PCV13: 13-valent pneumococcal conjugate vaccine

- See [Section 6.1.4](#) for dose, composition, and presentation
- Schedule of administration (by participant age/pneumococcal vaccine status):
  - 7 to 11 months/naïve: 3 doses - Day 0, 4 to 8 weeks after Dose 1, and 8 to 12 weeks after Dose 2
  - 12 to 23 months/naïve: 2 doses – Day 0 and 8 to 12 weeks after Dose 1
  - 2 to 17 years/naïve: 1 dose – Day 0
  - 2 to 17 years/ not naïve: 1 dose – Day 0, at least 8 weeks after previous pneumococcal vaccine dose
- Lot # 0000921112

#### 6.4.5 Directions for Use

See [Section 6.4.4](#)

#### 6.4.6 Sites and Centers

Study V114-024 was conducted at 25 sites in Finland, Malaysia, Poland, Russian Federation, and Thailand.

#### 6.4.7 Surveillance/Monitoring

See [Section 6.1.7](#) for general surveillance/monitoring procedures. See [Section 6.4.1](#) for solicited systemic ARs based on age.

#### 6.4.8 Endpoints and Criteria for Study Success

See [Section 6.4.1](#).

#### 6.4.9 Statistical Considerations & Statistical Analysis Plan

##### *Primary, Secondary, and Tertiary Immunogenicity Endpoints (Descriptive)*

Analyses were conducted for each of the 15 pneumococcal serotypes contained in PCV15 separately by age group (7 to 11 months of age, 12 to 23 months of age, and 2 to 17 years of age) at the time of randomization. For continuous endpoints, point estimates were calculated by exponentiating the estimates of the mean of the natural log values and the within-group confidence intervals (CIs) were derived by exponentiating the upper and lower bounds of the CI for the mean of the natural log values based on the t-distribution.

For the dichotomous endpoints for immune responses meeting threshold value as defined in the objectives, the within-group CIs will be calculated based on the exact method proposed by Clopper and Pearson ([Clopper and Pearson, 1934](#)).

##### *Significant Changes in the Conduct of the Study & Planned Analyses:*

There were no changes in study conduct by amendment. Refer to [Section 6.1.9](#) for COVID-19 Pandemic Associated Changes

Reviewer Comment: The changes due to the COVID-19 pandemic do not significantly impact the interpretability of the data generated from study V114-024.



#### 6.4.10 Study Population and Disposition

A total of 606 participants were enrolled in the study. Study period: June 25, 2019 (first participant, first visit) to December 9, 2020 (last participant, last visit).

#### Populations Enrolled/Analyzed

Per Protocol (PP) population: all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint.

Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive study vaccine (PCV15, Prevnar 13™) as per randomization schedule
- Failure to receive correct clinical material as per randomization schedule (i.e., participants who were cross treated)
- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination
- Receipt of a prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of a blood sample outside of the prespecified protocol window

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. All the immunogenicity analyses will be conducted by age (7 to 11 months of age, 12 to 23 months of age, and 2 to 17 years of age) at the time of randomization.

See [Section 6.1.10](#) for definitions of the FAS and APaT population.

#### Demographics

The percentage of male and female participants were evenly divided among all vaccinated individuals. Within stratified age ranges, there were more males among infants 7 to 11 months (51.6%) and children 2 to 17 years of age (52.3%). There were more female participants (54%) among children 12 to 23 months of age. The mean chronological ages at enrollment, by stratification group were: 8.7 months (7-to-11-month age group), 17.7 months (12-to-23-month age group), and 6.5 years (2-to-17-year age group). 455 participants (75.1% of APaT) were pneumococcal vaccination naïve. Most participants were Asian (54%) followed by White (45.9%). Almost all participants did not identify as Hispanic/Latino. The demographic characteristics of participants are shown in [Table 45](#).

**Table 45. Study V114-024: Demographic Characteristics**

Characteristic	PCV15	PCV13	Total
Participants 7 to 11 Months of Age	N=64	N=64	N=128
Sex, n (%)	--	--	--
Male	35 (54.7)	31 (48.4)	66 (51.6)
Female	29 (45.3)	33 (51.6)	62 (48.4)
Age at enrollment (months)	--	--	--
Mean (SD)	8.6 (1.4)	8.8 (1.6)	8.7 (1.5)
Minimum, maximum	7, 11	7, 11	7, 11
Racial origin, n (%)	--	--	--
Asian	53 (82.8)	53 (82.8)	106 (82.8)
White	11(17.2)	11 (17.2)	22 (17.2)

<b>Characteristic</b>	<b>PCV15</b>	<b>PCV13</b>	<b>Total</b>
Ethnicity, n (%)	--	--	--
Non-Hispanic and Non-Latino	64 (100.0)	64 (100.0)	128 (100.0)
PCV-naïve, n (%)	--	--	--
Yes	64 (100.0)	64 (100.0)	128 (100.0)
Participants 12 to 23 Months of Age	N=62	N=64	N=126
Sex, n (%)	--	--	--
Male	32 (51.6)	26 (40.6)	58 (46.0)
Female	30 (48.4)	38 (59.4)	68 (54.0)
Age at enrollment (months)	--	--	--
Mean (SD)	17.7 (3.2)	17.8 (3.3)	17.7 (3.2)
Minimum, maximum	12, 23	12, 23	12, 23
Racial origin, n (%)	--	--	--
Asian	52 (83.9)	53 (82.8)	105 (83.3)
White	10 (16.1)	11 (17.2)	21 (16.7)
Ethnicity, n (%)	--	--	--
Non-Hispanic and Non-Latino	62 (100.0)	63 (98.4)	125 (99.2)
Hispanic or Latino	0 (0.0)	1 (1.6)	1 (0.8)
PCV-naïve, n (%)	--	--	--
Yes	62 (100.0)	64 (100.0)	126 (100.0)
Participants 2 to 17 Years of Age	N=177	N=175	N=352
Sex, n (%)	--	--	--
Male	92 (52.0)	92 (52.6)	184 (52.3)
Female	85 (48.0)	83 (47.4)	168 (47.7)
Age at enrollment (years)	--	--	--
Mean (SD)	6.5 (4.7)	6.5 (4.7)	6.5 (4.7)
Minimum, maximum	2, 17	2, 17	2, 17
Racial origin, n (%)	--	--	--
Asian	60 (33.9)	56 (32.0)	116 (33.0)
Multiple	0 (0.0)	1 (0.6)	1 (0.3)
Black/African American, white	0 (0.0)	1 (0.6)	1 (0.3)
White	117 (66.1)	118 (67.4)	235 (66.8)
Ethnicity, n (%)	--	--	--
Non-Hispanic and Non-Latino	176 (99.4)	174 (99.4)	350 (99.4)
Not Reported	1 (0.6)	1 (0.6)	2 (0.6)
PCV-Naïve for Participants 2 to <6 Years of Age, n (%)	--	--	--
Yes	63 (35.6)	62 (35.4)	125 (35.5)
No	51 (28.8)	50 (28.6)	101 (28.7)
PCV-Naïve for Participants ≥6 to 17 Years of Age, n (%)	--	--	--
Yes	39 (22.0)	37 (21.1)	76 (21.6)
No	24 (13.6)	26 (14.9)	50 (14.2)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 10-6, Table 10-7, Table 10-8

Abbreviations: N=number of randomized participants for each cohort (participants with at least 1 vaccination of either PCV15 or PCV13); SD=standard deviation

For Sex, Racial Origin, Ethnicity and PCV-Naïve: n indicates number of subjects fulfilling the item in each category, (%) indicates % of APaT represented in each category or country

### *Participant Disposition*

Of the 606 study participants, 89 (14.7%) had at least one important protocol deviation. 46 participants (7.6%) had clinically important protocol deviations. Most of these clinically important protocol deviations (90.4%) were due to immunogenicity samples being drawn outside of the protocol-defined window for that time point. Participant dispositions are summarized in [Table 46](#).

**Table 46. Study V114-024: Summary of Participant Disposition**

<b>Disposition</b>	<b>PCV15 N=303</b>	<b>PCV13 N=303</b>	<b>Total N=606</b>
Enrolled, n (%)	303 (100.0)	303 (100.0)	606 (100.0)
Vaccinated, n (%)	303 (100.0)	303 (100.0)	606 (100.0)
Completed, n (%)	302 (99.7)	303 (100.0)	605 (99.8)
APaT* - Safety, n (%)	303 (100.0)	303 (100.0)	606 (100.0)
FAS**, n (%)	297 (92.1)	302 (99.7)	599 (98.8)
PP*** (IgG), n (%)	--	--	--
30 days post last dose of PCV	278 (91.7)	281 (92.7)	559 (92.2)
≥1 important protocol deviation, n (%)	48 (15.8)	41 (13.5)	89 (14.7)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 10-1, Table 10-3, Table 10-4, Table 10-5, Table 12-1, Table 12-2, Table 12-3, Table 14.1-4

Abbreviations: APaT=all participants as treated; FAS=full analysis set; IgG=immunoglobulin G; N=number of participants enrolled; n=number of participants fulfilling the item for each cohort; PP=per-protocol population

\* Participants who received at least one dose of study vaccination

\*\* Participants who received all study vaccinations required at the timepoint for the analysis and have serology result

\*\*\* Participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s) no opsonophagocytosis activity data were planned for this study

**Reviewer Comment:** The frequencies and types of clinically important protocol deviations were generally comparable across study groups as discussed above and in [Section 6.4.12](#). They do not significantly impact the interpretability of study results. Nearly all enrolled participants completed the study.

#### 6.4.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints. All efficacy endpoints were related to the serotype specific IgG responses to vaccination

##### *Primary and Secondary Analyses (Descriptive)*

The primary immunogenicity endpoints evaluated the IgG GMCs at 30 days after the final dose of either PCV15 or PCV13. IgG GMCs were generally comparable for the 13 shared serotypes for all study groups and were higher for the 2 serotypes unique to PCV15 in PCV15 recipients in all age groups.

The secondary immunogenicity endpoints evaluated the proportion of participants with anti-PnP IgG concentrations  $\geq 0.35$   $\mu\text{g/mL}$  30 days after the final dose of pneumococcal vaccination (either PCV15 or PCV13). A similar pattern of responses was observed with the response rates to the shared serotypes generally comparable for all study groups and the rates of responses to the two unique serotypes higher in PCV15 recipients. The GMCs and response rates are shown in [Table 47](#).

**Table 47. Study V114-024: Anti-PnP IgG GMCs and Proportion  $\geq 0.35\mu\text{g/mL}$  30 Days After Final Dose, PP**

Serotype	PCV15, N=60	PCV13, N=59
	GMC (95% CI) % $\geq 0.35 \mu\text{g/mL}$ (95%CI)	GMC (95% CI) % $\geq 0.35 \mu\text{g/mL}$ (95%CI)
Age	7-11 Months	7-11 Months
1	2.47 (2.09, 2.92) 100% (94.0.% 100.0%)	3.66 (2.98, 4.50) 100% (93.9%, 100.0%)
3	2.65 (2.30, 3.05) 100% (94.0.% 100.0%)	1.71 (1.40, 2.08) 96.6% (88.3%, 99.6%)
4	2.21 (1.82, 2.68) 100% (94.0.% 100.0%)	3.85 (3.12, 4.76) 100% (93.9%, 100.0%)
5	3.82 (3.14, 4.63) 100% (94.0.% 100.0%)	4.56 (3.58, 5.80) 100% (93.9%, 100.0%)
6A	2.23 (1.71, 2.91) 95% (86.1.% 99.0%)	4.3 (3.28, 5.65) 98.3% (90.9%, 100.0%)
6B	3.03 (2.41, 3.82) 96.7% (88.5.% 99.6%)	4.17 (3.25, 5.36) 100% (93.9%, 100.0%)
7F	5.16 (4.27, 6.23) 100% (94.0.% 100.0%)	6.42 (5.25, 7.85) 100% (93.9%, 100.0%)
9V	2.61 (2.09, 3.26) 98.3% (91.1.% 100.0%)	3.59 (2.86, 4.51) 100% (93.9%, 100.0%)
14	9.62 (7.94, 11.67) 100% (94.0.% 100.0%)	13.07 (10.40, 16.42) 100% (93.9%, 100.0%)
18C	3.45 (2.80, 4.24) 100% (94.0.% 100.0%)	3.5 (2.75, 4.45) 100% (93.9%, 100.0%)
19A	4.59 (3.95, 5.33) 100% (94.0.% 100.0%)	5.81 (4.92, 6.85) 100% (93.9%, 100.0%)
19F	3.49 (2.94, 4.15) 100% (94.0.% 100.0%)	4.83 (4.03, 5.79) 100% (93.9%, 100.0%)
23F	2.62 (2.02, 3.39) 98.3% (91.1.% 100.0%)	2.79 (2.10, 3.69) 100% (93.9%, 100.0%)
22F	9.04 (7.48, 10.93) 100% (94.0.% 100.0%)	0.14 (0.10, 0.19) 13.8% (6.1%, 25.4%)
33F	3.37 (2.78, 4.10) 100% (94.0.% 100.0%)	0.13 (0.10, 0.16) 11.9% (4.9%, 22.9%)
Age	12-23 Months	12-23 Months
1	3.83 (3.07, 4.77) 100% (93.6%, 100.0%)	4.20 (3.30, 5.34) 98.3% (91.1, 100.0)
3	2.96 (2.44, 3.58) 98.2% (90.4%, 100.0%)	1.68 (1.29, 2.20) 90% (79.5, 96.2)
4	3.46 (2.67, 4.50) 100% (93.6%, 100.0%)	4.89 (3.76, 6.36) 96.7% (88.5, 99.6)
5	3.39 (2.65, 4.34) 98.2% (90.4%, 100.0%)	3.12 (2.52, 3.88) 98.3% (91.1, 100.0)
6A	2.05 (1.30, 3.23) 83.9% (71.7%, 92.4%)	3.73 (2.64, 5.29) 95% (86.1, 99.0)
6B	2.69 (1.70, 4.25) 89.3% (78.1%, 96.0%)	2.87 (1.92, 4.30) 88.3% (77.4, 95.2)
7F	4.80 (3.63, 6.34) 98.2% (90.4%, 100.0%)	5.42 (4.30, 6.82) 100% (94.0, 100.0)
9V	2.48 (1.97, 3.11) 98.2% (90.4%, 100.0%)	2.89 (2.21, 3.78) 96.7% (88.5, 99.6)
14	8.23 (6.19, 10.94) 98.2% (90.4%, 100.0%)	8.30 (6.56, 10.51) 100% (94.0, 100.0)

Serotype	PCV15, N=60	PCV13, N=59
	GMC (95% CI) % ≥0.35 µg/mL (95%CI)	GMC (95% CI) % ≥0.35 µg/mL (95%CI)
18C	5.09 (3.98, 6.52) 96.4% (87.7%, 99.6%)	3.68 (2.85, 4.75) 98.3% (91.1, 100.0)
19A	6.74 (5.29, 8.60) 98.2% (90.4%, 100.0%)	5.87 (4.85, 7.11) 100% (94.0, 100.0)
19F	5.90 (4.69, 7.43) 100% (93.6%, 100.0%)	5.92 (4.93, 7.11) 100% (94.0, 100.0)
23F	2.85 (1.99, 4.07) 94.6% (85.1%, 98.9%)	2.18 (1.54, 3.07) 88.3% (77.4, 95.2)
22F	15.90 (12.16, 20.78) 100% (93.6%, 100.0%)	0.12 (0.09, 0.16) 6.7% (1.8, 16.2)
33F	5.17 (3.96, 6.74) 94.6% (85.1%, 98.9%)	0.15 (0.12, 0.19) 15.0% (7.1, 26.6)
Age	2-17 Years	2-17 Years
1	3.00 (2.60, 3.46) 99.4% (96.6%, 100.0%)	3.99 (3.48, 4.58) 100% (97.7%, 100.0%)
3	1.37 (1.19, 1.58) 95.7% (91.3%, 98.2%)	1.03 (0.88, 1.21) 87.7% (81.6%, 92.3%)
4	2.53 (2.17, 2.96) 98.8% (95.6%, 99.9%)	5.22 (4.52, 6.03) 100.0% (97.7%, 100.0%)
5	3.43 (2.89, 4.07) 99.4% (96.6%, 100.0%)	4.24 (3.46, 5.20) 99.4% (96.6%, 100.0%)
6A	9.03 (7.07, 11.53) 98.1% (94.7%, 99.6%)	8.81 (6.96, 11.14) 98.1% (94.7%, 99.6%)
6B	13.55 (10.52, 17.46) 98.1% (94.7%, 99.6%)	10.51 (8.01, 13.78) 96.9% (92.9%, 99.0%)
7F	4.03 (3.46, 4.70) 99.4% (96.6%, 100.0%)	4.63 (3.92, 5.46) 100.0% (97.7%, 100.0%)
9V	3.60 (3.06, 4.24) 100.0% (97.7%, 100.0%)	4.35 (3.65, 5.20) 98.8% (95.6%, 99.9%)
14	9.21 (7.11, 11.92) 99.4% (96.6%, 100.0%)	8.04 (6.24, 10.36) 98.1% (94.7%, 99.6%)
18C	7.16 (6.03, 8.52) 100.0% (97.7%, 100.0%)	4.46 (3.76, 5.30) 100.0% (97.7%, 100.0%)
19A	10.99 (9.12, 13.26) 100.0% (97.7%, 100.0%)	14.9 (12.23, 18.16) 100.0% (97.7%, 100.0%)
19F	8.95 (7.45, 10.76) 99.4% (96.6%, 100.0%)	12.28 (10.07, 14.97) 100.0% (97.7%, 100.0%)
23F	5.36 (4.41, 6.50) 99.4% (96.6%, 100.0%)	5.12 (4.12, 6.37) 95.7% (91.3%, 98.2%)
22F	14.99 (12.73, 17.66) 100% (97.7%, 100.0%)	0.31 (0.24, 0.38) 37.7% (30.2%, 45.8%)
33F	4.89 (4.12, 5.80) 99.4% (96.6%, 100.0%)	0.27 (0.22, 0.32) 37.5% (30.0%, 45.5%)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 11-1, Table 11-2, Table 11-3, Table 11-4, Table 11-5, Table 11-6  
Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; IgG=immunoglobulin G; N=number of participants in the PP for each specified cohort; PnP=pneumococcal polysaccharide; PP=per-protocol population

### *Tertiary/Exploratory Analyses (Descriptive)*

The tertiary/exploratory endpoints of study V114-024 evaluated the serotype-specific geometric fold rises (GMFRs) from pre-vaccination to 30 days after the final pneumococcal vaccine dose. GMFRs from baseline were generally comparable for the 13 shared serotypes for PCV15 and

PCV13 recipients and were higher for the two unique serotypes for PCV15 recipients as compared to PCV13 recipients. Serotype-specific GMFRs are shown in [Table 48](#).

**Table 48. Study V114-024: Anti-PnP IgG GMFRs Day 1 to 30 Days PD, Age  $\geq$  2 Years, PP**

Serotype	PCV15	PCV13
	N=161-162 GMFR (95% CI)	N=159-162 GMFR (95% CI)
1	16.6 (14.1, 19.6)	23.6 (20.2, 27.6)
3	9.2 (7.5, 11.3)	7.3 (6.0, 9.0)
4	16.1 (13.3, 19.6)	33.2 (27.8, 39.7)
5	4.2 (3.6, 4.9)	5.1 (4.3, 6.1)
6A	24.9 (19.1, 32.3)	28.1 (22.1, 35.7)
6B	26.6 (20.6, 34.3)	21.8 (17.3, 27.4)
7F	19.7 (16.4, 23.7)	21.5 (17.9, 25.8)
9V	16.5 (13.9, 19.6)	18.4 (15.2, 22.1)
14	13.8 (10.6, 17.9)	16.1 (12.6, 20.4)
18C	23.3 (18.7, 29.1)	18.5 (15.4, 22.4)
19A	10.6 (8.4, 13.5)	14.2 (11.2, 18.0)
19F	15.3 (12.0, 19.5)	20.9 (16.3, 26.9)
23F	16.9 (13.2, 21.7)	15 (12.0, 18.8)
22F	66.3 (51.4, 85.5)	1.2 (1.1, 1.3)
33F	20.0 (16.2, 24.5)	1.3 (1.1, 1.4)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 14.2-10

Abbreviations: CI=confidence interval; GMFR=geometric mean fold rise; IgG=immunoglobulin G; N=number of participants in the PP for each specified cohort; PD=post-dose; PnP=pneumococcal polysaccharide; PP=per-protocol population

### Subpopulation Analyses

Subpopulation analyses were conducted for the primary immunogenicity endpoints for all subpopulations that were composed of  $\geq$ 5% of the total number participants for the study group. Observed serotype-specific IgG GMCs and response rates for the serotypes were consistent with those observed in the overall population for the following subgroups: male vs. female participants, race (Asian and White), ethnicity (Hispanic or Latino, not Hispanic or Latino). Participants in the 2 to 6 years and  $\geq$ 6 to 17 years age groups had serotype-specific IgG GMCs that were generally consistent with the results of the overall population of participants ages 2 to 17 years.

#### 6.4.12 Safety Analyses

##### Methods

See [Section 6.1.9](#), safety analyses were conducted by age (7 to 11 months of age, 12 to 23 months of age, and 2 to 17 years of age) at the time of randomization.

##### Overview of Adverse Events

Safety data were provided for the PCV15 and PCV13 groups by age cohort and overviews are shown in [Table 49](#), [Table 50](#), and [Table 51](#). Reported rates of SAEs, solicited ARs, and unsolicited AEs were generally comparable between study groups for all age cohorts. There were no deaths reported during the study period.

**Table 49. Study V114-024: Safety Overview, Proportion of Participants Reporting at Least One Adverse Event; Participants 7 to 11 Months of Age, APaT Population**

AE Type	V114	PCV13
	N=64 %	N=64 %
	(x participants/n)	(x participants/n)
Immediate AE: 30 minutes	3.1 (2/64)	3.1 (2/64)
Solicited injection site: 14 days	39.1 (25/64)	40.6 (26/64)
Solicited systemic: 14 days	46.9 (30/64)	50.0 (32/64)
Unsolicited AE: 14 days	23.4 (15/64)	32.8 (21/64)
AEs leading to vaccine discontinuation: entire study period	0.0 (0/64)	0.0 (0/64)
SAEs: entire study period	10.9 (7/64)	7.8 (5/64)
Deaths: entire study period	0.0 (0/64)	0.0 (0/64)

Source: Adapted from STN125741/6, Study V114-024 Clinical Study Report including Table 12-1, Table 12-4

Abbreviations: AE=adverse event; APaT=All Participants as Treated; N=number of subjects in the cohort; n=number of subjects with available data for relevant endpoint; SAE=serious adverse event; x participants: number of subjects who experienced the event

**Table 50. Study V114-024: Proportion of Participants Reporting at Least One Adverse Event; Participants 12 to 23 Months of Age Following Any Vaccination Dose, APaT Population**

AE Type	V114	PCV13
	N=62 %	N=64 %
	(x participants/n)	(x participants/n)
Immediate AE: 30 minutes	0.0 (0/62)	0.0 (0/64)
Solicited injection site: 14 days	51.6 (32/62)	37.5 (24/64)
Solicited systemic: 14 days	48.4 (30/62)	32.8 (21/64)
Unsolicited AE: 14 days	32.3 (20/62)	26.6 (17/64)
AEs leading to vaccine discontinuation: entire study period	0.0 (0/62)	0.0 (0/64)
SAEs: entire study period	6.5 (4/62)	6.3 (4/64)
Deaths: entire study period	0.0 (0/62)	0.0 (0/64)

Source: Adapted from STN125741/6, Study V114-024 Clinical Study Report including Table 12-2, Table 12-5

Abbreviations: AE=adverse event; APaT=All Participants as Treated; N=number of subjects in the cohort; n=number of subjects with available data for relevant endpoint; SAE=serious adverse event; x participants: number of subjects who experienced the event

**Table 51. Study V114-024: Proportion of Participants Reporting at Least One Adverse Event; Participants 2 to 17 Years of Age Following PCV, APaT Population**

AE Type	V114	PCV13
	N=177 %	N=175 %
	(x participants/n)	(x participants/n)
Immediate AE: 30 minutes	1.1 (2/177)	1.1 (2/175)
Solicited injection site: 14 days	66.7 (118/177)	68.0 (119/175)
Solicited systemic: 14 days	40.7 (72/177)	38.9 (68/175)
Unsolicited AE: 14 days	28.2 (50/177)	32.0 (56/175)
SAEs: entire study period	2.3 (4/177)	2.3 (4/175)
Deaths: entire study period	0.0 (0/177)	0.0 (0/175)

Source: Adapted from STN125741/6, Study V114-024 Clinical Study Report including Table 12-3, Table 12-6

Abbreviations: AE=adverse event; APaT=All Participants as Treated; N=number of subjects in the cohort; n=number of subjects with available data for relevant endpoint; SAE=serious adverse event; x participants: number of subjects who experienced the event

**Reviewer Comment:** Proportions of participants reporting at least 1 AE were generally comparable between study groups for all AE types within each age cohort.

### Solicited Adverse Reactions (ARs)

[Table 52](#), [Table 53](#), and [Table 54](#) provide overviews of the rates of solicited adverse events in the 14 days following each study dose for each age cohort.

For Participants ages 7 through 11 months, local and systemic adverse events were generally comparable between study groups with the exception of injection site swelling and pain, which were more common in PCV15 recipients following doses 2 and 3.

**Table 52. Study V114-024: Comparison of Participants 7 to 11 Months of Age With Solicited Adverse Events From Day 1 Through Day 14 by Dose, APaT**

Adverse Event	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3
	PCV15 N=64	PCV13 N=64	PCV15 N=63	PCV13 N=64	PCV15 N=63	PCV13 N=64
Injection site reactions, n (%)	--	--	--	--	--	--
Swelling	6 (9.4)	9 (14.1)	9 (14.3)	4 (6.3)	8 (12.7)	4 (6.3)
Erythema	13 (20.3)	20 (31.3)	8 (12.7)	9 (14.1)	7 (11.1)	6 (9.4)
Pain	5 (7.8)	4 (6.3)	9 (14.3)	1 (1.6)	5 (7.9)	1 (1.6)
Induration	9 (14.1)	5 (7.8)	4 (6.3)	6 (9.4)	5 (7.9)	5 (7.8)
Systemic reactions, n (%)	--	--	--	--	--	--
Irritability	14 (21.9)	17 (26.6)	11 (17.5)	12 (18.8)	9 (14.3)	9 (14.1)
Somnolence	8 (12.5)	8 (12.5)	5 (7.9)	5 (7.8)	7 (11.1)	1 (1.6)
Decreased appetite	4 (6.3)	8 (12.5)	6 (9.5)	5 (7.8)	3 (4.8)	3 (4.7)
Urticaria	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.1)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 14.3-28, Table 14.3-29, Table 14.3-30  
 Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n (%) =number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort

For Participants ages 12 through 23 months, local and systemic adverse events were generally comparable between study groups PD1. Local and systemic AEs were more common in PCV15 recipients PD2 as shown in [Table 53](#).

**Table 53. Study V114-024: Comparison of Participants 12 to 23 Months of Age With Solicited Adverse Events From Day 1 Through Day 14 by Dose, APaT**

Adverse Event	Dose 1	Dose 1	Dose 2	Dose 2
	PCV15 N=62	PCV13 N=64	PCV15 N=62	PCV13 N=64
Injection site reactions, n (%)	--	--	--	--
Swelling	7 (11.3)	6 (9.4)	4 (6.5)	2 (3.1)
Erythema	7 (11.3)	10 (15.6)	7 (11.3)	6 (9.4)
Pain	11 (17.7)	8 (12.5)	15 (24.2)	9 (14.1)
Induration	4 (6.5)	6 (9.4)	3 (4.8)	2 (3.1)
Systemic reactions, n (%)	--	--	--	--
Irritability	18 (29.0)	9 (14.1)	10 (16.1)	9 (14.1)
Somnolence	13 (21.0)	8 (12.5)	10 (16.1)	3 (4.7)
Decreased appetite	10 (16.1)	9 (14.1)	6 (9.7)	6 (9.4)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 14.3-36, Table 14.3-37  
 Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n (%) =number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort

For Participants ages 2 through 17 years, local and systemic adverse events were generally comparable between study groups except for myalgias, which were reported more frequently by PCV15 recipients as shown in [Table 54](#).



**Table 54. Study V114-024: Participants 2 to 17 Years of Age With Solicited Adverse Events, APaT**

Adverse Event	PCV15 N=177	PCV13 N=175
Injection site reactions, n (%)	--	--
Swelling	37 (20.9)	42 (24.0)
Erythema	34 (19.2)	37 (21.1)
Pain	97 (54.8)	99 (56.6)
Induration	12 (6.8)	26 (14.9)
Systemic reactions*, n (%)	--	--
Irritability	5 (2.8)	7 (4.0)
Somnolence	5 (2.8)	5 (2.9)
Decreased appetite	4 (2.3)	5 (2.9)
Urticaria	2 (1.1)	2 (1.1)
Arthralgia	0 (0.0)	3 (1.7)
Fatigue	28 (15.8)	30 (17.1)
Headache	21 (11.9)	24 (13.7)
Myalgia	42 (23.7)	29 (16.6)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 12-6

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort; n (%) =number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort

\*Different systemic adverse events were solicited for participants 2 to <3 years of age, than for participants ≥3 to 17 years of age. For participants <3 years of age (Vaxneuvance N=32, Prevnar 13 N=28), decreased appetite, irritability, somnolence, and urticaria were solicited from Day 1 through Day 14 following vaccination. For participants ≥3 to 17 years of age, arthralgia, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination

**Reviewer Comment:** The frequencies of reported solicited ARs were generally comparable between study groups within each age cohort. Solicited ARs were more frequently reported among those ages 2 through 17 years than in the younger age cohorts. As discussed in *Subpopulation Analyses*, this difference was likely driven by the increased solicited ARs reported by those 6 through 17 years of age. There were no significant safety concerns identified.

*Maximum Body Temperatures within 7 days post-vaccination*

Rates of reported fever belonging to the highest 2 temperature increments (i.e., body temperature ≥39.0°C and ≥40.0°C ) in the 7 days following vaccination were higher in PCV15 recipients ages 7 months to 11 months, particularly after doses 2 and 3 as shown in [Table 55](#).

**Table 55. Study V114-024: Maximum Body Temperature of Participants 7 to 11 Months of Age From Day 1 (Day of Vaccination) Through Day 7 Following Each Dose, APaT**

Temperature	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3
	PCV15 N=64	PCV13 N=64	PCV15 N=63	PCV13 N=64	PCV15 N=63	PCV13 N=64
n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<38.0°C	59 (92.2)	59 (92.2)	55 (87.3)	60 (93.8)	59 (93.7)	62 (96.9)
≥38.0°C-39.0°C	3 (4.7)	3 (4.7)	6 (9.5)	3 (4.7)	2 (3.2)	2 (3.1)
≥39.0°C-40.0°C	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
≥40.0°C	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	2 (3.2)	0 (0.0)

Source: Adapted from IR response received June 2, 2022: Tables 13 - 15

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort with at least 1 temperature measurement from Day 1 through Day 7 following the indicated vaccination; n (%) =number of participants experiencing a maximum temperature within the indicated range during the 7-day period post vaccine in each cohort and % of the APaT belonging to that cohort which experienced a maximum temperature within that range

Data presented for participants with available temperature measurements reported as measured

Of the maximum temperature measurements, ~13% to ~17% were rectal measurements and ~83% to ~87% were axillary measurements

Rates of reported fever (i.e., body temperature  $\geq 38.0^{\circ}\text{C}$ ) in the 7 days following vaccination were generally comparable between study groups for participants ages 12 through 23 months of age as shown in [Table 56](#).

**Table 56. Study V114-024: Maximum Body Temperature of Participants 12 to 23 Months of Age From Day 1 (Day of Vaccination) Through Day 7 Following Any Dose, APaT**

Temperature	Dose 1 PCV15 N=62		Dose 1 PCV13 N=64		Dose 2 PCV15 N=62		Dose 2 PCV13 N=64	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<38.0°C	56 (90.3)	60 (93.8)	60 (96.8)	62 (96.9)	60 (96.8)	62 (96.9)	60 (96.8)	62 (96.9)
$\geq 38.0^{\circ}\text{C}$ -39.0°C	5 (8.1)	3 (4.7)	0 (0.0)	2 (3.1)	0 (0.0)	2 (3.1)	0 (0.0)	2 (3.1)
$\geq 39.0^{\circ}\text{C}$ -40.0°C	1 (1.6)	1 (1.6)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)
$\geq 40.0^{\circ}\text{C}$	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)

Source: Adapted from IR response received June 2, 2022: Table 17

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort with at least 1 temperature measurement from Day 1 through Day 7 following the indicated vaccination; n (%) =number of participants experiencing a maximum temperature within the indicated range during the 7-day period post vaccine in each cohort and % of the APaT belonging to that cohort which experienced a maximum temperature within that range

Data presented for participants with available temperature measurements reported as measured

Of the maximum temperature measurements, ~17% were rectal measurements and ~83% were axillary measurements.

Rates of reported fever reported in the 7 days following vaccination were higher in the PCV15 group for participants ages 2 through 17 years of age as shown in [Table 57](#). No participants reported fever in the highest temperature increment.

**Table 57. Study V114-024: Maximum Body Temperature of Participants 2 through 17 Years of Age From Day 1 (Day of Vaccination) Through Day 7 Following Any Dose, APaT**

Temperature	Dose 1 PCV15 N=177		Dose 1 PCV13 N=175	
	n (%)	n (%)	n (%)	n (%)
<38.0°C,	170 (96.0)	172 (98.3)	170 (96.0)	172 (98.3)
$\geq 38.0^{\circ}\text{C}$ -39.0°C	5 (2.8)	3 (1.7)	5 (2.8)	3 (1.7)
$\geq 39.0^{\circ}\text{C}$ -40.0°C,	2 (1.1)	0 (0.0)	2 (1.1)	0 (0.0)
$\geq 40.0^{\circ}\text{C}$	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from IR response received June 2, 2022: Table 18

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort with at least 1 temperature measurement from Day 1 through Day 7 following the indicated vaccination; n (%) =number of participants experiencing a maximum temperature within the indicated range during the 7-day period post vaccine in each cohort and % of the APaT belonging to that cohort which experienced a maximum temperature within that range

Data presented for participants with available temperature measurements reported as measured

The percentage of participants 2 to <3 years of age with rectal temperature measurements was 5.0% and with axillary temperature measurements was 95.0%.

The percentage of participants  $\geq 3$  to 17 years of age with oral temperature measurements was 65.4% and with axillary temperature measurements was 34.6%.

**Reviewer Comment:** Although the reported rate of fever was higher in the PCV15 group for participants 2 through 17 years of age, there were no fevers  $\geq 40.0^{\circ}\text{C}$  reported.

#### *Unsolicited AEs within 14 days post-vaccination*

Unsolicited AEs were documented by the participant or a legally acceptable representative in the eVRC and reviewed by the investigator at vaccine study visits and at 15 days following each vaccine dose. Rates of reported unsolicited AEs were generally comparable between study groups for each age cohort. The rates and most frequently reported events, by age cohort and Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, were:

- 7 through 11 months: PCV15 - 10.2% (n=31); PCV13 – 13.2% (n=40)
  - General disorders and administration site conditions (PCV15: 6.3%, PCV13: 6.9%)
  - Infections and infestations (PCV15: 4.6%, PCV13: 7.3%)
- 12 through 23 months: PCV15 – 6.6% (n=20); PCV13 – 9.2% (n=28)
  - Infections and infestations (PCV15: 4.3%, PCV13: 5.3%)
  - General disorders and administration site conditions (PCV15: 3.0%, PCV13: 4.0%)
- 2 through 17 years: PCV15 – 18.8% (n=57); PCV13 – 17.2% (n=52)
  - General disorders and administration site conditions (PCV15: 7.9%, PCV13: 6.3%)
  - Infections and infestations (PCV15: 5.9%, PCV13: 7.3%)
  - Gastrointestinal disorders (PCV15: 3.3%, PCV13: 2.0%)

**Reviewer Comment:** The reported rates and types of unsolicited adverse events were comparable across study groups and represent medical conditions that are common in children.

## Deaths

There were no deaths reported in the study.

## Nonfatal Serious Adverse Events (SAEs)

Fifteen SAEs were reported in PCV15 recipients during the study across all age groups. These SAEs are summarized in [Table 58](#), [Table 59](#), and [Table 60](#). None of these were considered vaccine-related and the incidences were generally comparable between study groups. Non-vaccine related infections and infestations were the most common SAE for all age groups and were generally normal childhood illnesses. The occurrences and distributions of SAEs were similar within 7 and 30 days of vaccination.

**Table 58. Study V114-024: Participants 7 to 11 Months of Age with Any SAE During the Study by System Organ Class and Preferred Term, APaT**

Serious Adverse Event	PCV15 N=64	PCV13 N=64
Infections and infestations, n (%)	7 (10.9)	5 (7.8)
Bacteremia	0 (0.0)	1 (1.6)
Bronchiolitis	1 (1.6)	1 (1.6)
Croup infectious	1 (1.6)	0 (0.0)
Exanthema subitem	0 (0.0)	1 (1.6)
Gastroenteritis	2 (3.1)	0 (0.0)
Gastroenteritis salmonella	1 (1.6)	0 (0.0)
Pharyngitis	1 (1.6)	0 (0.0)
Pneumonia bacterial	1 (1.6)	0 (0.0)
Pneumonia respiratory syncytial viral	0 (0.0)	1 (1.6)
Tracheobronchitis	0 (0.0)	1 (1.6)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 12-19

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort receiving the indicated dose; n (%) =number of participants experiencing any serious AE (SAE) during the study and % of the APaT belonging to that cohort receiving the indicated dose; SAE=serious adverse event

**Table 59. Study V114-024: Participants 12 to 23 Months of Age in APaT With Any SAE During the Study by System Organ Class and Preferred Term**

Serious Adverse Event	PCV15 N=62	PCV13 N=64
Infections and infestations, n (%)	3 (4.8)	4 (6.3)
Bronchiolitis	0 (0.0)	1 (1.6)
Chikungunya virus infection	1 (1.6)	0 (0.0)
Gastroenteritis	0 (0.0)	1 (1.6)
Gastroenteritis viral	1 (1.6)	0 (0.0)
Nasopharyngitis	0 (0.0)	1 (1.6)
Pharyngitis	0 (0.0)	1 (1.6)
Pneumonia viral	1 (1.6)	0 (0.0)
Pyelonephritis acute	0 (0.0)	1 (1.6)
Injury, poisoning and procedural complications, n (%)	1 (1.6)	0 (0.0)
Limb injury	1 (1.6)	0 (0.0)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 12-20

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort receiving the indicated dose; n (%) =number of participants experiencing any serious AE (SAE) during the study period and % of the APaT belonging to that cohort receiving the indicated dose; SAE=serious adverse event

**Table 60. Study V114-024: Participants 2 to 17 Years of Age in APaT With Any SAE During the Study by System Organ Class and Preferred Term**

Serious Adverse Event	PCV15 N=177	PCV13 N=175
Infections and infestations, n (%)	4 (2.3)	3 (1.7)
Gastroenteritis	1 (0.6)	1 (0.6)
Influenza	1 (0.6)	0 (0.0)
Pneumonia	1 (0.6)	1 (0.6)
Tonsillitis	0 (0.0)	1 (0.6)
Tuberculosis	1 (0.6)	0 (0.0)
Wound abscess	0 (0.0)	1 (0.6)
Injury, poisoning and procedural complications, n (%)	0 (0.0)	1 (0.6)
Concussion	0 (0.0)	1 (0.6)

Source: Adapted from STN 125741.6, V114-024 Clinical Study Report: Table 12-21

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort receiving the indicated dose; n (%) =number of participants experiencing any serious AE (SAE) during the study period and % of the APaT belonging to that cohort receiving the indicated dose; SAE=serious adverse event

### Subpopulation Analyses

Safety results were reported for all subpopulations that contained  $\geq 5\%$  of the total number participants for the study group. Safety results were generally comparable across subpopulations and with those of the overall population for each of the following subpopulations: male vs. female participants and race (Asian and white).

Participants who were 6 through 17 years of age more commonly reported solicited ARs than those who were less than 6 years of age (Older age group with 1 or more AR: 95.2% [n=60]; Younger age group with 1 or more AR: 57.9% [n=66]). Pain (n=54), myalgias (n=21), and fatigue (n=21) were the most commonly reported ARs in this older age group.

Reviewer Comment: The increased occurrence of reported solicited ARs in children and adolescents 6 through 17 years of age may be the result of increased recognition of

symptoms in older individuals rather than increased reactogenicity, especially given the types of ARs that were predominantly responsible for the higher AR frequency in this age group.

### **Dropouts and/or Discontinuations**

There was 1 participant in the 7-month to 11-month-old PCV15 group who was withdrawn from the study by their parent/guardian. There were no AE-related discontinuations in the study.

#### **6.4.13 Study Summary and Conclusions**

Study V114- 024 was a phase 3 study evaluating the safety, tolerability, and immunogenicity of 1 to 3 dose regimens of PCV15 as compared to PCV13 for catch-up vaccination of children who were: pneumococcal-vaccine naïve (7 months through 17 years of age), previously vaccinated with a partial series of any lower valency PCV, or previously vaccinated with a full series of a lower valency PCV not including PCV13 (2 years through 17 years of age).

Reported rates of solicited ARs, unsolicited AEs, and SAEs were generally comparable between study groups within each age cohort and there were no concerning safety findings.

The immune responses elicited by PCV15 were generally comparable to those elicited by PCV13 for each of the 13 shared serotypes, as measured by IgG GMCs and seroresponse rates  $\geq 0.35$   $\mu\text{g/mL}$  30 days following the final series dose.

The safety and immunogenicity results from this study support the use of PCV15 for catch-up pneumococcal vaccination of children who are either pneumococcal vaccine-naïve, incompletely vaccinated, or vaccinated with a PCV series of a lower valency (not including PCV13).

### **6.5 Trial #5: V114-030**

**NCT03921424:** 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 Children Infected With Human Immunodeficiency Virus (HIV) (PNEU-WAY PED)

Study Overview: V114- 030 is a phase 3 study evaluating the safety, tolerability, and immunogenicity of PCV15 followed by PPSV23 eight weeks later in children 6 years through 17 years of age infected with HIV. The study was conducted at 12 sites in South Africa, Thailand, and the Ukraine.

#### **6.5.1 Objectives (as stated in protocol V114-030, Amendment 0)**

##### **Primary Safety Objective**

1. To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).
  - Endpoints: Refer to [Section 6.1.1](#)

### **Primary Immunogenicity Objective**

1. To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination (Day 30) with PCV15 or Prevnar 13™ by each vaccination group.
  - Endpoint: Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in PCV15 at Day 30
    - i. Descriptive analyses

### **Secondary Safety Objective**

1. To evaluate the safety and tolerability of PPSV23 administered 8 weeks following PCV15 with respect to the proportion of participants with AEs
  - Endpoints:
    - i. Solicited injection-site AEs from Day 1 through Day 14 postvaccination
    - ii. Solicited systemic AEs from Day 1 through Day 14 postvaccination

### **Secondary Immunogenicity Objectives**

1. To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination (Day 30) with PCV15 or Prevnar 13 by each vaccination group.
  - Endpoints: Anti-PnPs serotype-specific OPA responses for the 15 serotypes contained in PCV15 at Day 30
    - i. Descriptive analyses
2. To evaluate the anti-PnPs serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with PPSV23 (Week 12) by each vaccination group
  - Endpoints: Anti-PnPs Serotype-specific OPA and IgG responses for the 15 serotypes contained in PCV15 at Week 12
    - i. Descriptive analyses

### **Tertiary/Exploratory**

1. To evaluate the Anti-PnPs serotype-specific Geometric Mean Fold Rises (GMFRs) from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) with V114 or Prevnar 13™ for both OPA and IgG responses by each vaccination group.
  - Endpoints: Anti-PnPs serotype-specific OPA and IgG responses for the 15 serotypes contained in V114 at Day 1 and Day 30
    - i. Descriptive analyses

#### **6.5.2 Design Overview**

Study V114-030 was a phase 3, multicenter, randomized, double-blind, active-controlled study in otherwise healthy children with HIV infection from 6 through 17 years of age who were either pneumococcal vaccine (either PCV or PPSV23) naïve or who had received a PCV  $\geq 3$  years prior to study enrollment or PPSV23  $\geq 5$  years prior to study enrollment. A total of 407 participants were enrolled and were randomized 1:1 to receive either a single dose of PCV15 or PCV13 followed by PPSV23 approximately 8 weeks later.

### 6.5.3 Population

#### *Inclusion*

The study enrolled male and female children and adolescents 6 through 17 years of age who:

1. Was infected with HIV and has a CD4+ T-cell count  $\geq 200$  cells/ $\mu$ L and plasma HIV RNA  $< 50,000$  copies/mL tested at Screening (Visit 1).
2. Was PCV naïve, previously vaccinated with a  $< 13$ -valent PCV, partially vaccinated with PCV13, or has a history of previous PCV13 vaccination  $\geq 3$  years before study day 1
3. Was PPSV23 vaccine naïve or has a history of one previous PPSV23 vaccination  $\geq 5$  years before study day 1
4. Not pregnant or breastfeeding, and not a woman of childbearing potential (WOCBP) or a WOCBP who agreed to follow the pre-specified contraceptive guidance

#### *Exclusion*

Participants were excluded if they had a history of (or were):

1. World Health Organization (WHO) HIV classification of clinical Stage 4 disease within the past 12 months before study enrollment
2. Active hepatitis with elevation in pretreatment aspartate transaminase or alanine transaminase values  $> 5$  times the upper limit of normal within 6 months before the first vaccination at Visit 2 (Day 1).
3. History of IPD (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 of Visit 2 (Day 1).
4. Known hypersensitivity to any component of PnPs vaccine, PCV, or any diphtheria toxoid-containing vaccine.
5. Known or suspected congenital immunodeficiency (other than HIV infection), functional or anatomic asplenia, or history of autoimmune disease
6. Bleeding disorder contraindicating intramuscular vaccinations.
7. Recent febrile illness (defined as oral temperature  $\geq 38.1^{\circ}\text{C}$  [ $\geq 100.5^{\circ}\text{F}$ ]; axillary temperature  $\geq 37.8^{\circ}\text{C}$  [ $\geq 100.0^{\circ}\text{F}$ ]) occurring within 72 hours prior to receipt of study vaccine
8. Malignancy  $\leq 5$  years prior to signing informed consent/assent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer
9. A woman of child-bearing potential with a positive urine or serum pregnancy test before the first vaccination

### 6.5.4 Study Treatments or Agents Mandated by the Protocol

PCV15: 15-valent pneumococcal conjugate vaccine

- See [Section 6.1.4](#) for dose, composition, and presentation
- Schedule of administration: Study visit 1
- Lot #0000957291

PCV13: 13-valent pneumococcal conjugate vaccine (diphtheria CRM197 protein)

- See [Section 6.1.4](#) for dose, composition, and presentation
- Schedule of administration: Study visit 1
- Lot #: 0000940410

PNEUMOVAX 23 (PPSV23): 23- valent pneumococcal polysaccharide vaccine

- Dose: 0.5mL administered SC
- Schedule of administration: Study visit 4 (week 8)
- Composition: Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F

#### 6.5.5 Directions for Use

See [Section 6.5.4](#)

#### 6.5.6 Sites and Centers

Study V114-030 was conducted at 12 sites in South Africa, Thailand, and the Ukraine.

#### 6.5.7 Surveillance/Monitoring

See [Section 6.1.7](#) for details of study surveillance and monitoring with the exception of the pre-defined solicited systemic ARs which, for study V114-030, were:

- muscle pain, joint pain, headache, tiredness, and hives or welts

#### 6.5.8 Endpoints and Criteria for Study Success

See [Section 6.5.1](#).

#### 6.5.9 Statistical Considerations & Statistical Analysis Plan

*Primary, Secondary and Tertiary Immunogenicity Endpoints (Descriptive)*

Evaluations of the primary and secondary endpoints for each of the 15 pneumococcal serotypes contained in PCV15 were performed separately. Evaluation of the serotype-specific IgG GMCs at 30 days post-vaccination with PCV15 or PCV13 (Day 30) included descriptive summaries and within-group 95% CIs for each vaccination group.

Point estimates for the IgG GMCs were calculated by exponentiating the estimates of the mean of the natural log values. The within-group CIs were derived by exponentiating the CIs of the mean of the natural log values based on the t distribution.

A similar statistical approach was used to evaluate serotype-specific OPA responses at Study Day 30, and IgG and OPA responses at 30 days postvaccination with PPSV23 (Week 12) for each vaccination group. Point estimates of serotype-specific GMFR and its associated 95% CI were calculated based on the t-distribution of natural log-transformed fold rise.

#### *Significant Changes in the Conduct of the Study & Planned Analyses:*

There were no changes in study conduct by amendment. Refer to [Section 6.1.9](#) for COVID-19 Pandemic Associated Changes

Reviewer Comment: The changes due to the COVID-19 pandemic do not significantly impact the interpretability of the data generated from study V114-030.



### 6.5.10 Study Population and Disposition

#### Populations Enrolled/Analyzed

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint. Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive study vaccine at Visit 2 (Day 1)
- Failure to receive correct clinical material as per randomization schedule (i.e., participants who were cross-treated)
- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination
- Failure to receive Pneumovax23 at Visit 4 (Week 8)
- Receipt of a prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of a blood sample outside of the pre-specified window (as described in Section 1.3)

See [Section 6.1.10](#) for definitions of the FAS and APaT population.

#### Demographics

Among all vaccinated participants, there was a small male predominance in the study (52.1%). The median age was 13 years (range 6 to 17 years). Most participants (91.6%) had a CD4+ T cell count  $\geq 500$  cells/ $\mu$ L at screening.

As shown in [Table 61](#), most participants were Black or African American (40.8%) followed by Asian (31.4%) and White (21.9%). Almost all participants identified as Not Hispanic or Latino.

**Table 61. Study V114-030: Demographic Characteristics for All Vaccinated Participants**

Characteristic	PCV15 N=203	PCV13 N=204	Total N=407
Sex, n (%)	--	--	--
Male	107 (52.7)	105 (51.5)	212 (52.1)
Female	96 (47.3)	99 (48.5)	195 (47.9)
Age at enrollment (years)	--	--	--
Mean (SD)	12.7 (2.7)	12.6 (3.0)	12.7 (2.9)
Minimum, maximum	6, 17	6, 17	6, 17
CD4 count, n (%)	--	--	--
$\geq 200$ to $< 500$ cells/ $\mu$ L	17 (8.4)	17 (8.3)	34 (8.4)
$\geq 500$ cells/ $\mu$ L	186 (91.6)	187 (91.7)	373 (91.6)
Racial origin, n (%)	--	--	--
White	40 (19.7)	49 (24.0)	89 (21.9)
Black/African American	88 (43.3)	78 (38.2)	166 (40.8)
Asian	62 (30.5)	66 (32.4)	128 (31.4)
Multiple	12 (5.9)	9 (4.4)	21 (5.2)
Black/African American, White	10 (4.9)	9 (4.4)	19 (4.7)
Missing	2 (1.0)	0 (0.0)	2 (0.5)
Missing	1 (0.5)	2 (1.0)	3 (0.7)

<b>Characteristic</b>	<b>PCV15 N=203</b>	<b>PCV13 N=204</b>	<b>Total N=407</b>
Ethnicity, n (%)	--	--	--
Not Hispanic or Latino	201 (99.0)	203 (99.5)	404 (99.3)
Hispanic or Latino	0 (0.0)	1 (0.5)	1 (0.2)
Not Reported	2 (1.0)	0 (0.0)	2 (0.5)

Source: Adapted from STN 125741.6, V114-030 Clinical Study Report: Table 10-5

Abbreviations: CD=cluster of differentiation; N=number of vaccinated participants for each cohort (participants with at least 1 vaccination of either PCV15 or PCV13); SD=standard deviation

For Sex, Racial Origin and Ethnicity: n indicates number of participants fulfilling the item in each category, (%) indicates % of vaccinated participants represented in each category

**Reviewer Comment:** The severity of HIV infection, as assessed by CD4 count, of participants enrolled in the study was balanced between study groups. Other demographic characteristics were also balanced across groups.

### *Participant Disposition*

Of the 407 study participants, 46 (11.3%) had at least one important protocol deviation. 42 (10.3% of total participants) had at least one clinically important protocol deviations. The occurrences were comparable by study group. Most of these clinically important protocol deviations (31, 7.6% of total participants) were due to Trial Procedure deviations such as immunogenicity samples drawn outside of the protocol-defined window for that time point. Participant dispositions are summarized in [Table 62](#).

**Table 62. Study V114-030: Summary of Participant Disposition**

<b>Disposition</b>	<b>PCV15 N=203</b>	<b>PCV13 N=204</b>	<b>Total N=407</b>
Enrolled, n (%)	203 (100.0)	204 (100.0)	407 (100.0)
Vaccinated with	--	--	--
PCV (Day 1)	203 (100.0)	204 (100.0)	407 (100.0)
PPV23 (Week 8)	203 (100.0)	202 (99.0)	405 (99.5)
Completed, n (%)	203 (100.0)	201 (98.5)	404 (99.3)
APaT* - Safety, n (%)	--	--	--
Following PCV	203 (100.0)	204 (100.0)	407 (100.0)
Following PPV23	203 (100.0)	202 (99.0)	405 (99.5)
FAS** (IgG), n (%)	202 (99.5)	204 (100.0)	406 (99.8)
PP*** (IgG), n (%)	--	--	--
Day 1	202 (99.5)	204 (100.0)	406 (99.8)
Day 30	194 (95.6)	196 (96.1)	390 (95.8)
Week 12	192 (94.6)	183 (89.7)	375 (92.1)

<b>Disposition</b>	<b>PCV15 N=203</b>	<b>PCV13 N=204</b>	<b>Total N=407</b>
PP*** (OPA), n (%)	--	--	--
Day 1	200 (98.5)	202 (99.0)	402 (98.8)
Day 30	164 (80.8)	160 (78.4)	324 (79.6)
Week 12	165 (81.3)	162 (79.4)	327 (80.3)
≥1 important protocol deviation, n (%)	20 (9.9)	26 (12.7)	46 (11.3)

Source: Adapted from STN 125741.6, V114-030 Clinical Study Report: Table 10-1, Table 10-3, Table 10-4, Table 14 1-4

Abbreviations: APaT=All Participants as Treated; FAS=full analysis set; IgG=immunoglobulin G; N=number of participants enrolled n=number of participants fulfilling the item for each cohort; OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine (PCV15 or PCV13); PP=per-protocol population; PPV23=pneumococcal polysaccharide vaccine (Pneumovax23)

\* Participants who received the relevant study vaccination for the timepoint of interest (i.e., a participant must have received a single dose of PCV15 or PCV13 at Day 1 to be included in the safety analyses following PCV; a participant must have received a single dose of PPV23 at Week 8 to be included in the safety analyses following PPV23)

\*\* Participants who received all study vaccinations required at the timepoint for the analysis (i.e., Day 30) and have at least 1 serology result for the timepoint for the analysis

\*\*\* Participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s)

≥1 important protocol deviation: participants with 1 or more important protocol deviations

Day 30 is 30 days postvaccination with PCV; Week 12 is 30 days postvaccination with PPV23

**Reviewer Comment:** The types and frequencies of protocol deviations were balanced across study groups and do not significantly impact the interpretability of study results.

### 6.5.11 Immunogenicity Analyses

*Analyses Post-PCV (Descriptive): Primary [IgG GMCs], Secondary [OPA GMTs] and Tertiary Analyses [IgG GMFRs] (Descriptive)*

The primary immunogenicity endpoints evaluated the serotype-specific IgG GMCs and GMFRs at 30 days after either PCV15 or PCV13 as shown in Table 63. IgG GMCs and GMFRs for serotype 1 and serotype 4 were higher in the PCV13 group. IgG GMCs and GMFRs to serotype 6B were higher in the PCV15 group. IgG GMCs and GMFRs to the other shared serotypes were generally comparable between study groups and higher in the PCV15 group for the 2 serotypes unique to PCV15.

OPA GMTs (shown in [Table 63](#)) were comparable between study groups for serotype 1. For serotype 4, OPA GMTs were lower in the PCV15 group but the % with a 4-fold rise in OPA titers were similar (PCV15: 83.5%, PCV13: 85.4%, not shown in Table 63). OPA GMTs were generally comparable for the other shared serotypes and were higher in the PCV15 group for the two unique serotypes.

**Table 63. Study V114-030: Anti-PnP IgG GMCs, IgG GMFRs, and OPA GMTs 30 Days After Pneumococcal Conjugate Vaccine, PP**

Serotype	PCV15	PCV13
	N=192	N=183
	IgG GMC (95% CI)	IgG GMC (95% CI)
	IgG GMFR (95% CI)	IgG GMFR (95% CI)
	OPA GMT (95% CI)	OPA GMT (95% CI)
1	2.17 (1.89, 2.48)	3.26 (2.82, 3.77)
	13.9 (12.1, 15.9)	20.8 (17.9, 24.2)
	353.4 (278.4, 448.7)	398.3 (313.5, 506.1)
3	1.05 (0.93, 1.19)	0.84 (0.73, 0.97)
	3.9 (3.4, 4.6)	3.9 (3.4, 4.5)
	330.0 (284.4, 383.0)	301.5 (255.5, 355.7)
4	2.59 (2.23, 3.00)	4.27 (3.57, 5.11)
	15.1 (12.6, 18.1)	25.1 (20.9, 30.2)
	6078.3 (5106.1, 7235.4)	9172.8 (7582.8, 11096.1)
5	2.94 (2.44, 3.54)	2.78 (2.30, 3.37)
	4.1 (3.5, 4.9)	4.0 (3.4, 4.8)
	847.6 (671.1, 1070.4)	642.1 (490.9, 839.9)
6A	7.98 (6.30, 10.11)	7.56 (6.06, 9.45)
	30.8 (25.0, 37.9)	27.4 (22.2, 33.8)
	14274.6 (12014.1, 16960.4)	11915.4 (10160.9, 13973.0)
6B	11.44 (9.07, 14.43)	6.92 (5.45, 8.79)
	32.7 (26.5, 40.2)	21.0 (17.1, 25.8)
	17636.5 (14728.7, 21118.3)	15052.9 (12719.6, 17814.2)
7F	4.84 (4.10, 5.71)	5.00 (4.29, 5.83)
	21.4 (18.1, 25.2)	22.2 (18.8, 26.2)
	17574.4 (15234.2, 20274.0)	18519.3 (16010.9, 21420.8)
9V	4.15 (3.56, 4.85)	4.78 (4.03, 5.66)
	15.3 (13.0, 18.0)	18.3 (15.4, 21.6)
	4800.0 (4201.0, 5484.4)	5879.7 (4853.9, 7122.2)
14	20.38 (16.39, 25.35)	18.29 (14.43, 23.17)
	23.9 (18.7, 30.4)	20.9 (16.7, 26.3)
	18444.3 (15257.3, 22297.0)	17920.8 (14874.4, 21591.2)
18C	5.18 (4.32, 6.20)	5.15 (4.29, 6.18)
	15.5 (12.7, 18.9)	17.2 (14.0, 21.0)
	4556.2 (3794.1, 5471.5)	3543.0 (2919.6, 4299.5)
19A	14.20 (11.81, 17.07)	14.78 (12.45, 17.54)
	7.8 (6.6, 9.2)	9.0 (7.6, 10.6)
	8176.4 (6778.3, 9862.8)	8690.2 (7382.3, 10229.8)
19F	9.76 (8.03, 11.85)	8.61 (7.28, 10.18)
	10.6 (8.8, 12.9)	10.4 (8.7, 12.5)
	3711.8 (3178.0, 4335.2)	3277.6 (2833.1, 3791.8)
23F	6.71 (5.42, 8.31)	6.35 (5.14, 7.85)
	20.0 (16.1, 24.8)	20.3 (16.5, 24.9)
	11693.1 (9483.8, 14417.1)	11933.8 (9597.5, 14838.8)

Serotype	PCV15 N=192	PCV13 N=183
	IgG GMC (95% CI) IgG GMFR (95% CI) OPA GMT (95% CI)	IgG GMC (95% CI) IgG GMFR (95% CI) OPA GMT (95% CI)
22F	9.28 (7.76, 11.09)	0.24 (0.20, 0.29)
	49.1 (38.6, 62.5)	1.2 (1.1, 1.4)
	10791.3 (9157.2, 12716.9)	503.1 (330.1, 766.8)
33F	4.53 (3.80, 5.39)	0.29 (0.25, 0.33)
	17.9 (15.1, 21.3)	1.2 (1.2, 1.3)
	36357.0 (31146.2, 42439.6)	5520.6 (4659.5, 6540.9)

Source: Adapted from STN 125741.6, V114-030 Clinical Study Report: Table 14.2-3

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; GMFR=geometric mean fold rise; GMT=geometric mean titer; IgG=immunoglobulin G; N=number of participants in the PP for each specified cohort; OPA=opsonophagocytic activity; PnP=pneumococcal polysaccharide; PP: per-protocol population

Post-PCV: 30 Days After Initial Study Dose of PCV15 or PCV13

**Reviewer Comment:** The immune responses, as measured by serotype-specific IgG GMCs and OPA GMTs, were generally comparable between study groups for the 12 of the 13 shared serotypes, with a slightly smaller absolute IgG and OPA responses elicited to serotype 4 (but with similar proportions achieving a 4-fold rise from baseline). The immune responses to the 2 unique serotypes were higher in PCV15 recipients. Overall, the immune responses support the effectiveness of PCV15 in this population.

*Analyses Post-PPSV23 (Descriptive): Primary [IgG GMCs], Secondary [OPA GMTs] and Tertiary Analyses [IgG GMFRs]*

IgG GMCs were lower in the PCV15 group for serotypes 4 (a shared serotype) and 33F (a serotype unique to PCV15), as shown in [Table 64](#). They were generally comparable for all other serotypes. IgG GMFRs followed the same pattern as the GMCs. OPA GMTs, shown in [Table 64](#), and GMFRs were generally comparable between groups for all 15 serotypes.

**Table 64. Study V114-030: Serotype-Specific IgG GMCs and OPA GMTs 30 Days After PPSV23**

Serotype	PCV15 IgG N=192 OPA N=163-165	PCV13 IgG N=182-183 OPA N=161-162
	IgG GMC (95% CI) OPA GMT (95% CI)	IgG GMC (95% CI) OPA GMT (95% CI)
1	2.58 (2.31, 2.88)	3.33 (2.95, 3.75)
	326.4 (267.0, 399.0)	337.0 (272.3, 417.1)
3	1.10 (0.97, 1.24)	1.08 (0.94, 1.24)
	327.2 (278.9, 383.9)	384.8 (333.0, 444.6)
4	2.36 (2.08, 2.69)	3.61 (3.09, 4.23)
	5445.7 (4663.7, 6358.8)	7526.8 (6309.7, 8978.7)
5	3.01 (2.58, 3.52)	3.24 (2.75, 3.82)
	985.6 (813.6, 1193.8)	939.5 (737.3, 1197.3)
6A	4.67 (3.74, 5.84)	4.91 (3.94, 6.11)
	10208.7 (8703.8, 11973.7)	10699.8 (9010.5, 12705.7)
6B	7.12 (5.75, 8.81)	4.96 (3.96, 6.22)
	13774.8 (11661.6, 16271.0)	12745.8 (10887.3, 14921.6)
7F	4.10 (3.55, 4.72)	4.27 (3.71, 4.92)
	17415.9 (15091.4, 20098.5)	19140.5 (16778.5, 21835.0)
9V	3.69 (3.20, 4.25)	4.52 (3.89, 5.24)

	5135.9 (4328.2, 6094.3)	6152.2 (5219.6, 7251.4)
14	18.88 (15.43, 23.09) 17207.5 (14074.5, 21037.9)	19.89 (16.00, 24.72) 16461.2 (13695.1, 19785.9)
18C	3.75 (3.18, 4.43) 3635.1 (3103.0, 4258.5)	4.11 (3.48, 4.85) 3369.0 (2844.0, 3990.9)
19A	11.23 (9.48, 13.31) 7613.7 (6414.6, 9036.9)	12.19 (10.38, 14.32) 8838.0 (7592.6, 10287.6)
19F	8.56 (7.26, 10.08) 3694.8 (3212.9, 4248.9)	7.98 (6.83, 9.33) 3904.4 (3382.3, 4507.1)
23F	4.40 (3.63, 5.34) 10216.7 (8465.7, 12329.8)	4.83 (3.96, 5.88) 10086.0 (8334.0, 12206.2)
22F	8.18 (7.10, 9.42) 8756.1 (7419.0, 10334.1)	10.32 (8.67, 12.29) 6958.0 (5941.5, 8148.5)
33F	3.76 (3.23, 4.38) 34173.6 (29554.9, 39514.0)	6.18 (5.23, 7.30) 30651.0 (26240.5, 35802.8)

Source: Adapted from STN 125741.6, V114-030 CI Table 14.2-3

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; GMT=geometric mean titer;

IgG=immunoglobulin G; N=number of participants in the PP for each specified cohort; OPA=opsonophagocytic activity;

PnP=pneumococcal polysaccharide; PP: per-protocol population

Post-PPV23: 30 Days After PPV23; PPV23: Pneumovax23

**Reviewer Comment:** Although IgG GMCs 30 days after PPSV23 were slightly lower in the PCV15 group for serotypes 4 and 33F, functional assay data (OPA GMTs) support the general comparability of the immune responses to PPSV23 between groups. IgG GMCs and OPA GMTs to the remaining serotypes were generally comparable between study groups.

#### *Additional post-hoc analyses*

Additional analyses evaluated the proportion of participants with at least a 4-fold rise in IgG and OPA responses following PCV. The proportions of participants with 4-fold rises in serotype-specific IgG concentration and OPA titers were generally comparable across study groups for the shared serotypes higher for the 2 unique serotypes in the PCV15 group.

#### **Subpopulation Analyses**

Subpopulation analyses were conducted for the primary immunogenicity endpoints for all subpopulations that were composed of ≥5% of the total number participants for the study group.

#### Sex

Serotype-specific IgG GMCs were consistent with those observed in the overall population for male vs. female participants.

#### Race

Serotype-specific IgG GMCs at 30 days postvaccination with PCV in black/African American and Asian participants were comparable with those observed in the overall study population. In white participants, serotype specific IgG GMCs were generally lower than those observed in the overall study population, especially for serotypes 5 and 19F. Immune responses were generally comparable between the PCV15 and PCV13 groups for all shared serotypes.

**Reviewer Comment:** Although the point estimates of serotype-specific IgG GMCs were generally lower in white participants than in the overall study population, the differences

were not large with CIs that overlapped, except for serotypes 5 and 19F. The difference was not specific to PCV15 as comparably decreased immune responses were also observed in the PCV13 group.

#### Age

Participants in the 6 to 9 years, 10 to 14 years, and 15 to 17 years age groups had serotype-specific IgG GMCs that were generally comparable with the results of the overall study population.

#### CD4+ T cell count

In participants with CD4+ T cell counts from 200 to <500 cells/ $\mu$ L, serotype-specific IgG GMCs at 30 days post PCV were lower than those observed in the overall study population, although the differences were not large and were consistent between the PCV15 and PCV13 study groups. IgG GMCs in those with CD4+ T cell counts  $\geq$ 500 cells/ $\mu$ L were consistent with overall study population.

Reviewer Comment: The lower IgG GMCs observed in participants with CD4+ T cell counts <500 cells/ $\mu$ L are likely a result of a greater immune suppression in these individuals.

#### Prior PCV status

In PCV-naïve participants, serotype-specific IgG GMCs were generally comparable with the results observed in the overall population at 30 days post-PCV. Serotype-specific IgG GMCs were generally higher than those observed in the overall population in both intervention groups, although there were only 15 participants in this subpopulation in each study group.

### 6.5.12 Safety Analyses

#### **Methods**

See [Section 6.1.9](#).

#### **Overview of Adverse Events**

Safety data were provided for the PCV15 and PCV13 groups following PCV and PPSV. More participants reported Immediate AEs and Solicited ARs following PCV15 than PCV13, shown in [Table 65](#). The reported occurrences of unsolicited AEs and SAEs were similar between groups.

**Table 65. Study V114-030: Safety Overview, Proportion of Participants Reporting at Least One Adverse Event Following PCV, APaT**

AE Type	PCV15	PCV13
	N=203	N=204
	% (x participants/n)	% (x participants/n)
Immediate AE: 30 minutes	4.4 (9/203)	1.5 (3/204)
Solicited injection site: 14 days	71.4 (145/203)	59.8 (122/204)
Solicited systemic: 14 days	49.8 (101/203)	38.2 (78/204)
Unsolicited AE: 14 days	9.4 (19/203)	11.3 (23/204)
AEs leading to vaccine discontinuation: following PCV	0.0 (0/203)	0.5 (1/204)
SAEs: Following PCV	0.5 (1/203)	0.5 (1/204)
Deaths: Following PCV	0.0 (0/203)	0.0 (0/204)

Source: Adapted from STN125741/6, Study V114-030 Clinical Study Report including Table 12-1, Table 12-5

Abbreviations: AE=adverse event; APaT=All Participants as Treated; n=number of subjects with available data for relevant endpoint; PCV=Pneumococcal Conjugate Vaccine (V114 or Prevnar 13™); SAE=serious adverse event; x participants= number of subjects who experienced the event

Following PCV: Adverse events that occurred from Day 1 (following vaccination with PCV) through Week 8 (prior to vaccination with PPV23)

**Reviewer Comment:** Solicited ARs and immediate AEs were more commonly reported in the PCV15 group while SAEs were generally comparable between groups. This observation is consistent with the trend of increased non-serious reactogenicity following PCV15 observed in the 4-dose infant studies. No serious safety concerns were identified.

Following PPSV23, the occurrence of immediate AEs, solicited ARs, and SAEs were generally comparable between study groups as shown in [Table 66](#).

**Table 66. Study V114-030: Safety Overview, Proportion of Participants Reporting at Least One Adverse Event Following PPSV23, APaT**

AE Type	PCV15	PCV13
	N=203	N=202
	% (x participants/n)	% (x participants/n)
Immediate AE: 30 minutes	4.9 (10/203)	4.5 (9/202)
Solicited injection site: 14 days	72.9 (148/203)	72.3 (146/202)
Solicited systemic: 14 days	54.7 (111/203)	49.5 (100/202)
Unsolicited AE: 14 days	0.0 (0/203)	0.0 (0/202)
SAEs: Following PPSV23	1.0 (2/203)	1.0 (2/202)
Deaths: Following PPSV23	0.0 (0/203)	0.0 (0/202)

Source: Adapted from STN125741/6, Study V114-030 Clinical Study Report including Table 12-2, Table 14.3-9

Abbreviations: AE=adverse event; APaT=All Participants as Treated; n=number of subjects with available data for relevant endpoint; PPV23=Pneumococcal Polysaccharide Vaccine (Pneumovax23); SAE=serious adverse event; x participants=number of subjects who experienced the event

Following PPV23: Adverse events that occurred from Week 8 (following vaccination with PPV23) through completion of study participation

**Reviewer Comments:** The comparability of the occurrences of AEs and ARs between study groups supports the safety of PPSV23 administration following PCV15 in individuals with HIV infection.

### Subpopulation Analyses

Safety results were reported for all subpopulations that contained  $\geq 5\%$  of the total number participants for the study group. Safety results were generally comparable with those of the overall population based on age (6 through 9 years, 10 through 14 years, and 15 through 17



years), sex (male vs. female), CD4+ T cell count (200 cells/ $\mu$ L through <500 cells/ $\mu$ L and  $\geq$ 500 cells/ $\mu$ L), and prior pneumococcal vaccine status.

### Race

Lower proportions of white participants had systemic AEs as compared with overall population. A lower proportion of Asian participants in the PCV15 group reported 1 or more AEs as compared to black or African American and white participants.

### Solicited ARs

[Table 67](#) provides an overview of the rates of reported ARs in the 14 days following either PCV or PPSV23. The most common injection site ARs following PCV were pain (PCV15: 55.2%, PCV13: 28.6%), swelling (PCV15: 28.6%, PCV13: 21.6%), and induration (PCV15: 10.3%, PCV13: 6.4%) and these ARs were more commonly reported in the PCV15 group.

The most common systemic ARs following PCV were myalgia (PCV15: 34.0%, PCV13: 25.5%), headache (PCV15: 14.8%, PCV13: 10.8%), and arthralgia (PCV15: 9.4%, PCV13: 10.3%). Myalgias and headaches were more commonly reported in the PCV15 group.

Most (~96.8%) of the solicited ARs after PCV for which intensity grading was available were graded as mild or moderate. For those reported ARs for which a maximum size was recorded (i.e., erythema, induration, and swelling), most (~77%) had a maximum size less than 5.08cm. The severities of ARs were generally comparable between study groups. Most (~84%) of the reported ARs lasted 3 days or less.

Following PPSV23, the most commonly reported injection site ARs were pain, swelling, and induration. Swelling and induration were more commonly reported in the PCV15 group while pain was more commonly reported in the PCV13 group. Myalgia, arthralgia, and fatigue were the most commonly reported systemic ARs. The reported rates of systemic ARs were generally comparable between study groups, see [Table 67](#).

Most (~87%) of the solicited ARs after PPSV23 for which intensity grading was available were graded as mild or moderate. For those reported ARs for which a maximum size was recorded (i.e., erythema, induration, and swelling), ~56% had a maximum size less than 5.08cm, ~27% had a maximum size from >5.08cm to 7.62cm. The severities of ARs were generally comparable between study groups.

**Table 67. Study V114-030: Proportions of Participants With Solicited ARs From Day 1 Through Day 14 Following Either PCV or PPSV**

Adverse Reaction	Post-PCV	Post-PCV	Post-PPSV23	Post-PPSV23
	PCV15 Group N=203	PCV13 Group N=204	PCV15 Group N=203	PCV13 Group N=202
Injection site reactions, n (%)	--	--	--	--
Swelling	58 (28.6)	44 (21.6)	96 (47.3)	70 (34.7)
Erythema	19 (9.4)	12 (5.9)	21 (10.3)	25 (12.4)
Pain	112 (55.2)	110 (53.9)	105 (51.7)	111 (55.0)
Induration	21 (10.3)	13 (6.4)	37 (18.2)	27 (13.4)

<b>Adverse Reaction</b>	<b>Post-PCV PCV15 Group N=203</b>	<b>Post-PCV PCV13 Group N=204</b>	<b>Post-PPSV23 PCV15 Group N=203</b>	<b>Post-PPSV23 PCV13 Group N=202</b>
Systemic reactions, n (%)	--	--	--	--
Arthralgia	19 (9.4)	21 (10.3)	26 (12.8)	17 (8.4)
Fatigue	16 (7.9)	17 (8.3)	25 (12.3)	23 (11.4)
Headache	30 (14.8)	22 (10.8)	21 (10.3)	19 (9.4)
Myalgia	69 (34.0)	52 (25.5)	88 (43.3)	79 (39.1)
Urticaria	1 (0.5)	3 (1.5)	0 (0.0)	1 (0.5)

Source: Adapted from STN 125741.6, V114-030 Clinical Study Report: Table 12-5, Table 14.3-9

Abbreviations: APaT=All Participants as Treated; AR=adverse reaction; N=number of participants in APaT belonging to each cohort; n (%)=number of participants experiencing indicated solicited local reactions in each cohort and % of the APaT belonging to that cohort; PCV=pneumococcal conjugate vaccine; PPSV=Pneumococcal Polysaccharide Vaccine

**Reviewer Comment:** The 14-day solicited AR data suggest increased reactogenicity following PCV15 as has been observed in other studies in for varying dosing regimens of PCV15. The comparability of reported occurrences of ARs after a subsequent dose of PPSV23 support the safety of PPSV23 administered after PCV15. No serious safety concerns were identified.

#### *Maximum Body Temperatures within 7 days post-vaccination*

The reported rates of fever (i.e., body temperature  $\geq 38.0^{\circ}\text{C}$ ) were generally comparable between groups following PCV and PPSV23 as shown in [Table 68](#).

**Table 68. Study V114-030: Maximum Body Temperatures Day 1 Through Day 7 Following PCV and PPSV23, APaT**

<b>Temperature</b>	<b>Post-PCV PCV15 Group N=203</b>	<b>Post-PCV PCV13 Group N=204</b>	<b>Post-PPSV23 PCV15 Group N=203</b>	<b>Post-PPSV23 PCV13 Group N=201</b>
<38.0°C,	195 (96.1)	194 (95.1)	193 (95.1)	196 (97.5)
$\geq 38.0^{\circ}\text{C}$ -39.0°C	5 (2.5)	4 (2.0)	7 (3.4)	2 (1.0)
$\geq 39.0^{\circ}\text{C}$ -40.0°C,	1 (0.5)	2 (1.0)	3 (1.5)	2 (1.0)
$\geq 40.0^{\circ}\text{C}$	0 (0.0)	4 (2.0)	0 (0.0)	1 (0.5)

Source: Adapted from IR response received June 2, 2022: Table 20 and IR response received June 6, 2022: Table 1

Abbreviations: APaT=All Participants as Treated; N=number of participants in APaT belonging to each cohort with at least 1 temperature measurement from Day 1 through Day 7 following the indicated vaccination; n (%)=number of participants experiencing a maximum temperature within the indicated range during the 7-day period postvaccination in each cohort and % of the APaT belonging to that cohort which experienced a maximum temperature within that range; PCV=pneumococcal conjugate vaccine; PPSV23=Pneumococcal Polysaccharide Vaccine  
Data presented for participants with available temperature measurements reported as measured  
Of the maximum temperature measurements, ~59% to ~77% were oral measurements and ~23% to ~41% were axillary measurements.

**Reviewer Comment:** The reported rates of fever support the safety of PCV15 and subsequent administration of PPSV23 for individuals with HIV infection.

#### *Unsolicited AEs within 14 days post-vaccination*

Unsolicited AEs were documented by the participant's legally acceptable representative in the eVRC and reviewed by the investigator at 15 days following each study dose. Rates of unsolicited AEs were generally comparable between study groups following PCV (PCV15: 11.3%, PCV13: 9.4%) and PPSV23 (PCV15: 6.9%, PCV13: 9.4%).

The most frequently reported events after PCV, by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, were: General disorders and administration site conditions

(PCV15: 3.0%, PCV13: 3.9%); Gastrointestinal disorders (PCV15: 1.5%, PCV13: 3.4%); and Infections and Infestations (PCV15: 1.5%, PCV13: 1.0%).

No MedDRA SOC contained >1.0% of the unsolicited AEs in the PCV15 group following PPSV23.

Reviewer Comment: The reported rates and types of unsolicited adverse events are comparable across study groups and generally represent medical conditions that are common in children/adolescents.

### **Deaths**

There were no deaths in the study.

### **Nonfatal Serious Adverse Events**

There were no SAEs that were considered related to the study intervention. No SOC contained >1 SAE and SAEs were equally reported between the PCV13 and PCV15 groups. Only 3 SAEs were reported in the PCV15 group.

### **Dropouts and/or Discontinuations**

There were 3 discontinuations in the PCV13 group and none in the PCV15 group. One of the discontinuations in the PCV13 group was considered related to the study vaccine and was due to erythema, swelling, and induration on day 2-3 post-vaccination. The other 2 discontinuations were not considered related to the study product.

#### **6.5.13 Study Summary and Conclusions**

Study V114-030 was a phase 3 study designed to evaluate descriptively the safety and immunogenicity of PCV15 followed by PPSV23 in HIV-positive participants. Comparative rates of solicited ARs through 14 days post vaccination, unsolicited AEs through 14 days post vaccination, and SAEs through study completion support the safety of PCV15 followed by PPSV23 in individuals with HIV infection. There were no SAEs considered related to PCV15.

Anti-PnP IgG GMCs and OPA GMTs 30 days after PCV supported the overall comparability of the immune response to the 13 shared serotypes in PCV15 recipients vs. PCV13 recipients. Anti-PnP IgG GMCs and OPA GMTs 30 days after PPSV23 supported the comparability of the immune responses elicited by PPSV23 when administered after either PCV15 or PCV13. Subgroup analyses supported the immunogenicity in individuals with mild and moderate immunocompromise due to HIV infection.

Overall, this study supports the safety and immunogenicity of PCV15 for use in HIV-infected individuals and the comparability of the antibody responses elicited by subsequent administration of PPSV23.

### **6.6 Trial #6: V114-023**

**NCT03731182:** A Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children With Sickle Cell Disease (PNEU-SICKLE)

Overview: Study V114-023 evaluated the safety and immunogenicity of a single dose of PCV15 in children 5 through 17 years of age with sickle cell disease (SCD). The study enrolled 104 participants from 19 sites in Brazil, Columbia, Dominican Republic, Greece, Italy, Panama, and the US.

#### 6.6.1 Objectives (as stated in study protocol V114-023, Amendment 0)

##### **Primary Safety Objective**

1. To evaluate the safety and tolerability of PCV15 with respect to the proportion of participants with adverse events (AEs)
  - a. Endpoints: Refer to [Section 6.1.1](#)
    - i. Descriptive analyses

##### **Primary Immunogenicity Objective**

1. To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination (Day 30) for each vaccination group.
  - a. Endpoints: Anti-PnPs serotype specific IgG responses for the 15 serotypes contained in PCV15 at day 30
    - i. Descriptive analyses

##### **Secondary Immunogenicity Objectives**

1. To evaluate the anti-PnPs serotype specific OPA GMTs at 30 days post vaccination for each vaccination group
  - a. Endpoints: Anti-PnPs serotype specific OPA responses for the 15 serotypes contained in PCV15 at day 30
    - i. Descriptive analyses
2. To evaluate the anti-PnPs serotype specific GMFRs from pre-vaccination (day one) to 30 days post vaccination for both OPA and IgG responses for each vaccination group
  - a. Endpoints: Anti-PnPs serotype specific OPA and IgG responses for the 15 serotypes contained in PCV15 at day 1 and Day 30
    - i. Descriptive analyses

#### 6.6.2 Design Overview

Study V114-023 was a phase 3 randomized active-controlled, multisite, double-blind study of PCV15 in participants 5 through 17 years of age with SCD. A total of 103 participants were randomized in a 2:1 ratio to receive a single dose of either PCV15 or PCV13.

#### 6.6.3 Population

##### **Inclusion Criteria**

Study V114-023 enrolled otherwise healthy males and females 5 through 17 years of age who:

1. Had a documented diagnosis of SCD
2. Not pregnant or breastfeeding, and not a woman of childbearing potential (WOCBP) or a WOCBP who agreed to follow the pre-specified contraceptive guidance

### Exclusion Criteria

1. Had a history of IPD (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 of Visit 1 (Day 1).
2. Had a known hypersensitivity to any component of pneumococcal conjugate vaccine (PCV), or any diphtheria toxoid-containing vaccine.
3. Had a known or suspected impairment of immunological function.
4. Had a history of congenital or acquired immunodeficiency.
5. Had a documented human immunodeficiency virus (HIV) infection.
6. Had a history of autoimmune disease (including but not limited to systemic lupus erythematosus, antiphospholipid syndrome, Bechet's disease, autoimmune thyroid disease, polymyositis and dermatomyositis, scleroderma, or type 1 diabetes mellitus).
7. Had a known coagulation disorder contraindicating intramuscular vaccination.
8. Had had a recent febrile illness (defined as oral or tympanic temperature  $\geq 38.1^{\circ}\text{C}$  [ $\geq 100.5^{\circ}\text{F}$ ]; axillary or temporal temperature  $\geq 37.8^{\circ}\text{C}$  [ $\geq 100.0^{\circ}\text{F}$ ]) or received antibiotic therapy for any acute illness occurring within 72 hours before receipt of study vaccine. Had a history of malignancy  $\leq 5$  years prior to signing informed consent/assent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
9. Was a WOCBP who Had a positive urine or serum pregnancy test before the first vaccination at Visit 1 (Day 1).
10. Had received any PCV or PnPs vaccine  $< 3$  years before Visit 1 (Day 1).
11. Was 5 years of age and had received  $< 3$  doses of PCV.
12. Had received systemic corticosteroids (prednisone equivalent of  $\geq 20$  mg/day) for  $\geq 14$  consecutive days and had not completed treatment at least 30 days before study vaccination.
13. Had received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) within 14 days before study vaccination.
14. Was expected to require systemic corticosteroids within 30 days after study vaccination.
15. Was 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 not including hydroxyurea.
16. Had received any non-live vaccine within the 14 days before receipt of the study vaccine or was scheduled to receive any non-live vaccine within 30 days following receipt of the study vaccine. Exceptions: Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of the study vaccine or at least 15 days after receipt of the study vaccine. PNEUMOVAX23 may be administered after the blood draw at Visit 2 (Day 30).
17. Had received any live vaccine within 30 days before receipt of the study vaccine or was scheduled to receive any live vaccine within 30 days following receipt of the study vaccine.
18. Had received immunoglobulin within 6 months before receipt of study vaccine.
19. Had participated in another clinical study of an investigational product within 2 months before the beginning or anytime during the duration of the current clinical study. Participants enrolled in observational studies may be included; these will be reviewed on a case-by-case basis for approval by the Applicant.
20. Had a recent history (within the last year) of more than 3 inpatient hospitalizations.

21. Was, at the time of signing informed consent/assent, a user of recreational or illicit drugs or had had a recent history (within the last year) of drug or alcohol abuse or dependence as assessed by the study investigator.
22. Had a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might expose the participant to risk by participating in the study, confound the results of the study, or interfere with the participant's participation for the full duration of the study in the opinion of the Investigator.
23. Was or had an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who was investigational site or Applicant staff directly involved with this study.

#### 6.6.4 Study Treatments or Agents Mandated by the Protocol

##### PCV15: 15-valent pneumococcal conjugate vaccine

- See [Section 6.1.4](#) for dose, composition, and presentation
- Schedule of administration: Study visit 1
- Lot # WL00068289, WL00068572

##### PCV13: 13-valent pneumococcal conjugate vaccine (diphtheria CRM197 protein)

- See [Section 6.1.4](#) for dose, composition, and presentation
- Schedule of administration: Study visit 1
- Lot #: 0000867885 (EU)
- Lot #: 0000840839 (US)
- Lot #: 00000965616 (BR)

#### 6.6.5 Directions for Use

See [Section 6.6.4](#)

#### 6.6.6 Sites and Centers

Study V114-023 was conducted at 19 sites in Brazil, Columbia, Dominican Republic, Greece, Italy, Panama, and the US. Six study sites were in the US and accounted for ~24% of study participants.

#### 6.6.7 Surveillance/Monitoring

See [Section 6.1.7](#) for details of study surveillance and monitoring with the exception of the pre-defined solicited systemic ARs which, for study V114-023, were:

- muscle pain, joint pain, headache, tiredness, and hives or welts

#### 6.6.8 Endpoints and Criteria for Study Success

See [Section 6.6.1](#). Analyses were descriptive without protocol-defined success criteria.

#### 6.6.9 Statistical Considerations & Statistical Analysis Plan

##### **Primary and Secondary Immunogenicity Endpoints (Descriptive)**

Serotype-specific IgG GMCs were descriptively evaluated for each of the 15 pneumococcal serotypes contained in PCV15 at 30 days post-vaccination with PCV15 or PCV13. These point estimates were calculated by exponentiating the estimates of the mean of the natural log values

and the within-group CIs were derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

A similar statistical approach was used to evaluate the OPA GMTs at 30 days postvaccination with PCV15 or PCV13.

*Significant Changes in the Conduct of the Study & Planned Analyses:*

There were no changes in study conduct by amendment. Refer to [Section 6.1.9](#) for COVID-19 Pandemic-Associated Changes

Reviewer Comment: The changes due to the COVID-19 pandemic do not significantly impact the interpretability of the data generated from study V114-023

#### 6.6.10 Study Population and Disposition

A total of 104 participants were randomized in the study. 103 participants (69 participants in the PCV15 group and 34 participants in the PCV13 group) were vaccinated.

#### Populations Enrolled/Analyzed

##### Per Protocol (PP):

The PP population consisted of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint. Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses included:

- Failure to receive any study vaccine at Visit 1 (Day 1)
- Failure to receive correct clinical material as per randomization schedule
- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination
- Receipt of a prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of a blood sample outside of the protocol pre-specified window

See [Section 6.1.10](#) for definitions of the FAS and APaT population.

##### Demographics

Among all vaccinated participants, the median age was 11 years old with a range of 5 to 17 years of age. 54.4% of participants (n=56) were male. 60.2% (n=62) or black or African American, 16.5% (n=17) or multiple races, and 11.7% (n=12) were either American Indian/Alaska native or white. Most participants (66%, n=68) identified as Hispanic or Latino. Study demographics are summarized in [Table 69](#).

**Table 69. Study V114-030: Demographic Characteristics for All Vaccinated Participants**

Characteristic	PCV15 N=69	PCV13 N=34	Total N=103
Sex, n (%)	--	--	--
Male	36 (52.2)	20 (48.8)	56 (54.4)
Female	33 (47.8)	14 (41.2)	47 (45.6)

<b>Characteristic</b>	<b>PCV15 N=69</b>	<b>PCV13 N=34</b>	<b>Total N=103</b>
Age at enrollment (years)	--	--	--
Median	11.0	11.0	11.0
Minimum, maximum	5, 17	5, 16	5, 17
Racial origin, n (%)	--	--	--
White	10 (14.5)	2 (5.9)	12 (11.7)
Black/African American	37 (53.6)	25 (73.5)	62 (60.2)
Multiple	12 (5.9)	9 (4.4)	21 (5.2)
American Indian or Alaska Native, Black, or African American	1 (1.4)	0 (0.0)	1 (1.4)
American Indian or Alaska Native, White	1 (1.4)	0 (0.0)	1 (1.4)
Black or African American, White	11 (15.9)	4 (11.8)	15 (4.6)
Ethnicity, n (%)	--	--	--
Hispanic or Latino	44 (63.8)	24 (70.6)	68 (66.0)
Not Hispanic or Latino	25 (36.2)	10 (29.4)	35 (34.0)

Source: Adapted from STN 125741.6, V114-030 Clinical Study Report: Table 10-5

Abbreviations: N=number of vaccinated participants for each cohort (participants with at least 1 vaccination of either PCV15 or PCV13); n=number of participants with indicated characteristic

For Sex, Racial Origin and Ethnicity: n indicates number of participants fulfilling the item in each category, (%) indicates % of vaccinated participants represented in each category

**Reviewer Comment:** Participant demographic characteristics were generally balanced across groups.

### *Participant Disposition*

Of the 104 study participants, 4.9% (n=5) had clinically important protocol deviations. Most clinically important deviations were due to Trial Procedure deviations including immunogenicity samples drawn outside of the protocol-defined window for that time point. The dispositions of study participants are shown in [Table 70](#).

**Table 70. Study V114-023: Summary of Participant Disposition**

<b>Disposition</b>	<b>PCV15 N=70</b>	<b>PCV13 N=34</b>	<b>Total N=103</b>
Enrolled, n (%)	70(100.0)	34 (100.0)	104(100.0)
Vaccinated	69 (98.7)	34(100.0)	103 (99.0)
Completed, n (%)	65 (100.0)	34(100.0)	99 (95.2)
APaT* - Safety, n (%)	69 (98.7)	34 (100.0)	103 (99.0)
FAS** (IgG), n (%)	69 (98.7)	34 (100.0)	103 (99.0)
PP*** (IgG), n (%)	--	--	--
Day 1	68 (97.1)	32 (94.1)	100 (96.2)
Day 30	66 (94.3)	32 (94.1)	98 (94.2)
Both Day 1 and Day 30 timepoints	66 (94.3)	30 (88.2)	96 (92.3)



<b>Disposition</b>	<b>PCV15 N=70</b>	<b>PCV13 N=34</b>	<b>Total N=103</b>
PP*** (OPA), n (%)	--	--	--
Day 1	66 (94.3)	32 (94.1)	98 (94.2)
Day 30	51 (72.9)	22 (64.7)	73 (70.2)
Both Day 1 and Day 30 timepoints	50 (71.4)	21 (61.8)	71 (68.3)
≥1 important protocol deviation, n (%)	10 (14.3)	4 (11.8)	14 (13.5)

Source: Adapted from STN 125741.6, V114-023 Clinical Study Report: Table 10-1, Table 10-3, Table 10-4, Table 14 1-3

Abbreviations: APaT=All Participants as Treated; FAS=full analysis set; IgG=immunoglobulin G; N=number of participants enrolled; n=number of participants fulfilling the item for each cohort; OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine (PCV15 or PCV13); PP=per-protocol population

\* Participants who received the relevant study vaccination for the timepoint of interest (i.e., a participant must have received a single dose of PCV15 or PCV13 at Day 1)

\*\* Participants who received all study vaccinations required at the timepoint for the analysis (i.e., Day 30) and have at least 1 serology result for the timepoint for the analysis

\*\*\* Participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s)

≥1 important protocol deviation

**Reviewer Comment:** The types and frequencies of protocol deviations were balanced across study groups and do not impact on the interpretability of study results.

### 6.6.11 Immunogenicity Analyses

*IgG Analyses (Descriptive): Primary - IgG GMCs; Secondary - IgG GMFRs; and Post-hoc - Proportion ≥4-fold Rise 30 days Post-dose*

Serotype-specific IgG GMCs were generally comparable between study groups for all 13 shared serotypes. IgG GMCs for the two serotypes unique to PCV15 were higher among the PCV15 cohort as compared to the PCV13 cohort. These results are shown in [Table 71](#).

**Table 71. Study V114-023: Anti-PnP IgG GMCs, GMFRs, and Proportion ≥4-Fold Rise 30 Days Post-Dose, PP**

<b>Serotype</b>	<b>PCV15 N=66-68</b>	<b>PCV13 N=29-32</b>
	<b>GMC (95%CI) GMFR (95%CI) %≥4-Foldrise (95%CI)</b>	<b>GMC (95%CI) GMFR (95%CI) %≥4-Foldrise (95%CI)</b>
1	2.12 (1.63, 2.75)	2.76 (1.95, 3.91)
	6.2 (4.6, 8.5)	6 (3.7, 9.9)
	62.10% (49.3, 73.8)	60.00% (40.6, 77.3)
3	1.09 (0.87, 1.38)	1.07 (0.70, 1.65)
	4.8 (3.5, 6.6)	4.1 (2.6, 6.7)
	53.00% (40.3, 65.4)	48.30% (29.4, 67.5)
4	1.58 (1.18, 2.10)	2.9 (2.00, 4.20)
	6 (4.3, 8.3)	9.3 (5.4, 16.2)
	56.10% (43.3, 68.3)	72.40% (52.8, 87.3)
5	4.44 (3.19, 6.17)	6.56 (4.09, 10.52)
	5.3 (3.8, 7.4)	6.4 (3.8, 10.8)
	53.00% (40.3, 65.4)	58.60% (38.9, 76.5)
6A	23.29 (17.22, 31.52)	15.97 (8.82, 28.91)
	54.7 (37.9, 78.9)	40.6 (22.9, 71.9)
	93.90% (85.2, 98.3)	93.10% (77.2, 99.2)
6B	38.38 (28.53, 51.64)	22.94 (13.60, 38.71)
	37.2 (25.8, 53.6)	25 (13.8, 45.3)
	93.90% (85.2, 98.3)	89.70% (72.6, 97.8)

Serotype	PCV15 N=66-68	PCV13 N=29-32
	GMC (95%CI) GMFR (95%CI) %≥4-Foldrise (95%CI)	GMC (95%CI) GMFR (95%CI) %≥4-Foldrise (95%CI)
7F	5.81 (4.42, 7.64)	4.65 (3.06, 7.06)
	11.6 (8.3, 16.0)	9.8 (6.3, 15.3)
	74.20% (62.0, 84.2)	83.30% (65.3, 94.4)
9V	4.46 (3.44, 5.78)	5.36 (3.45, 8.33)
	7.4 (5.3, 10.3)	8.1 (4.9, 13.2)
	62.10% (49.3, 73.8)	60.00% (40.6, 77.3)
14	16.03 (11.23, 22.90)	20.53 (12.39, 34.03)
	10.8 (6.8, 17.2)	7.2 (3.5, 14.8)
	63.10% (50.2, 74.7)	55.20% (35.7, 73.6)
18C	6.11 (4.47, 8.35)	4.2 (2.66, 6.62)
	10.8 (7.7, 15.1)	7.6 (4.5, 12.8)
	71.20% (58.7, 81.7)	60.00% (40.6, 77.3)
19A	19.86 (14.77, 26.70)	21.65 (14.45, 32.44)
	8.2 (5.4, 12.4)	8.6 (5.0, 14.9)
	57.60% (44.8, 69.7)	63.30% (43.9, 80.1)
19F	13.88 (9.96, 19.35)	12.8 (9.10, 18.01)
	8.3 (5.6, 12.3)	7.6 (4.5, 12.8)
	65.20% (52.4, 76.5)	66.70% (47.2, 82.7)
23F	5.38 (3.88, 7.46)	6.88 (4.01, 11.83)
	9.3 (6.1, 14.2)	13.1 (7.4, 23.4)
	69.80% (57.0, 80.8)	72.40% (52.8, 87.3)
22F	7.3 (5.68, 9.36)	0.49 (0.33, 0.73)
	15 (10.1, 22.1)	1.1 (0.9, 1.3)
	78.80% (67.0, 87.9)	0.00% (0.0, 12.3)
33F	4.46 (3.38, 5.87)	0.97 (0.62, 1.51)
	9 (6.7, 12.1)	1.3 (1.0, 1.7)
	75.80% (63.6, 85.5)	6.70% (0.8, 22.1)

Source: Adapted from STN 125741.6, V114-023 CSR Table 14.2-4

Abbreviations: CI=confidence interval; GMC=geometric mean concentration, in µg/mL; GMFR=geometric mean fold rise; IgG=immunoglobulin G; N=number of participants in the PP for each specified cohort with IgG data; OPA=opsonophagocytic activity; PnP=pneumococcal polysaccharide; PP=per-protocol population

% ≥4-foldrise: Proportion of participants with a 4-fold rise in GMC from Day 1 (pre-vaccination) to Day 30 post-vaccination

*OPA Analyses (Descriptive): Primary - OPA GMTs; Secondary - OPA GMFRs; and Post-hoc - Proportion ≥4-fold Rise 30 days post-dose*

Serotype specific OPA GMTs were generally comparable between study groups for all 13 shared serotypes. OPA GMTs for the two serotypes unique to PCV15 were higher among the PCV15 cohort as compared to the PCV13 cohort. These results are shown in [Table 72](#).

**Table 72. Study V114-023: Anti-PnP OPA GMTs, GMFRs, and Proportion  $\geq$ 4-Fold Rise 30 Days Post-Dose, PP**

Serotype	PCV15	PCV13
	N=45-51	N=19-22
	GMT (95% CI)	GMT (95% CI)
	GMFR (95% CI)	GMFR (95% CI)
	% $\geq$ 4-Foldrise (95% CI)	% $\geq$ 4-Foldrise (95% CI)
1	484 (327.5, 715.4) 24.1 (14.9, 39.1) 79.6% (39/49) (65.7, 89.8)	504 (254.8, 997.0) 13.3 (5.1, 34.2) 70.0% (14/20) (45.7, 88.1)
3	264.8 (193.4, 362.4) 4.9 (3.5, 7.0) 62.0% (31/50) (47.2, 75.3)	234.3 (133.0, 412.6) 3.1 (1.8, 5.6) 42.9% (9/21) (21.8, 66.0)
4	4670.8 (2965.9, 7355.6) 10.2 (6.3, 16.6) 65.3% (32/49) (50.4, 78.3)	7015.5 (3994.0, 12322.6) 18.5 (8.8, 38.9) 81.0% (17/21) (58.1, 94.6)
5	1383.9 (957.1, 2000.9) 23.7 (15.0, 37.5) 81.6% (40/49) (68.0, 91.2)	1198.2 (638.1, 2250.0) 13.8 (6.6, 28.6) 76.2% (16/21) (52.8, 91.8)
6A	27305.7 (19797.6, 37661.2) 20.7 (13.3, 32.1) 85.1% (40/47) (71.7, 93.8)	20277.1 (11740.2, 35021.7) 11.2 (4.8, 26.2) 66.7% (14/21) (43.0, 85.4)
6B	31560.4 (24134.1, 41272.1) 21.7 (12.7, 36.9) 83.0% (39/47) (69.2, 92.4)	18531 (11024.7, 31148.1) 13.7 (6.8, 27.7) 84.2% (16/19) (60.4, 96.6)
7F	19411.5 (15195.9, 24796.5) 5.4 (3.8, 7.7) 58.0% (29/50) (43.2, 71.8)	16928.1 (11107.4, 25799.0) 5.4 (3.2, 9.1) 52.4% (29.8, 74.3)
9V	4561.8 (3240.7, 6421.4) 4.4 (3.0, 6.5) 43.8% (21/48) (29.5, 58.8)	3941.7 (2659.6, 5841.7) 6.1 (3.6, 10.4) 55.0% (11/20) (31.5, 76.9)
14	6597.6 (4706.8, 9248.0) 6.9 (4.3, 11.1) 56.0% (28/50) (41.3, 70.0)	8112.2 (4827.2, 13632.8) 4.6 (2.1, 10.2) 38.1% (8/21) (18.1, 61.6)
18C	9684.6 (6642.1, 14120.7) 14 (8.9, 22.0) 75.6% (34/45) (60.5, 87.1)	5685.1 (3329.4, 9707.6) 4.8 (2.5, 9.3) 40.0% (8/20) (19.1, 63.9)
19A	14067.7 (9972.8, 19843.9) 9 (5.4, 15.0) 64.0% (32/50) (49.2, 77.1)	9224.9 (5015.5, 16967.1) 7.8 (4.4, 14.0) 66.7% (14/21) (43.0, 85.4)
19F	4931.8 (3387.8, 7179.7) 6.4 (4.3, 9.7) 56.0% (28/50) (41.3, 70.0)	3313.3 (2039.4, 5383.1) 6.6 (3.3, 12.9) 55.0% (11/20) (31.5, 76.9)
23F	17190.9 (12066.0, 24492.4) 10.4 (5.8, 18.4) 58.3% (28/48) (43.2, 72.4)	19197.1 (10511.1, 35061.1) 18.1 (8.8, 37.1) 85.0% (17/20) (62.1, 96.8)

Serotype	PCV15 N=45-51	PCV13 N=19-22
	GMT (95% CI) GMFR (95% CI) % $\geq$ 4-Foldrise (95% CI)	GMT (95% CI) GMFR (95% CI) % $\geq$ 4-Foldrise (95% CI)
22F	7257.5 (5278.5, 9978.3) 6.5 (3.7, 11.3) 58.3% (28/48) (43.2, 72.4)	1013.2 (477.4, 2150.1) 0.9 (0.7, 1.2) 0.0% (0/17) (0.0, 19.5)
33F	24013.6 (17612.4, 32741.4) 3.8 (2.7, 5.2) 42.0% (21/50) (28.2, 56.8)	4824.8 (3216.3, 7237.9) 0.8 (0.7, 1.0) 0.0% (0/21) (0.0, 16.1)

Source: Adapted from STN 125741.6, V114-023 CSR Table 14.2-5

Abbreviations: CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; N=number of participants in the PP for each specified cohort with IgG data; OPA=opsonophagocytic activity; PnP=pneumococcal polysaccharide; PP=per-protocol population  
 %  $\geq$ 4-foldrise: Proportion of participants with a 4-fold rise in GMC from Day 1 (pre-vaccination) to Day 30 post-vaccination

Post-hoc immunogenicity analyses evaluated the proportions of participants with a  $\geq$ 4-fold rise from pre-vaccination to 30 days postvaccination for both IgG and OPA responses. The proportions of participants with 4-fold rises to the shared serotypes were generally comparable between the two study groups and higher in participants in the PCV15 groups for the two unique serotypes.

Reviewer Comment: Serotype-specific IgG GMCs and OPA GMTs 30 days after the study dose support the comparability of the immune responses to the 13 shared serotypes in PCV15 and PCV13 recipients and provide evidence of higher immune responses to the 2 unique serotypes in PCV15 recipients who have SCD.

### Subpopulation Analyses

Subpopulation analyses were made for all groups which contained  $\geq$ 10 participants in each vaccination group within that subgroup. Primary immunogenicity endpoints were generally consistent with the results of the overall population for age (5 to 9 years and 10 to 14 years), male vs. female participants, Black/African American, and for participants identifying as Hispanic/Latino.

#### 6.6.12 Safety Analyses

##### Methods

See [Section 6.1.9](#).

##### Overview of Adverse Events

Safety data were provided for the PCV15 and PCV13 groups. Rates of reported Immediate AEs, ARs within 14 days, Unsolicited AEs within 14 days, SAEs for the entire study were generally comparable between study groups, [Table 73](#).

**Table 73. Study V114-023: Proportion of Participants Reporting at Least One Adverse Event Following Any Vaccination Dose, APaT**

<b>AE Type</b>	<b>PCV15 N=69 % (x participants/n)</b>	<b>PCV13 N=34 % (x participants/n)</b>
Immediate AE: 30 minutes	8.7 (6/69)	11.8 (4/34)
Solicited injection site: 14 days	69.6 (48/69)	76.5 (26/34)
Solicited systemic: 14 days	42.0 (29/69)	29.4 (10/34)
Unsolicited AE: 14 days	27.5 (19/69)	23.5 (8/34)
SAEs: Entire study period	18.8 (13/69)	23.5 (8/34)
Deaths: Entire study period	0.0 (0/69)	0.0 (0/34)

Source: Adapted from STN125741/6, Study V114-023 Clinical Study Report including Table 12-1, Table 12-3  
Abbreviations: AE=adverse event; APaT=All Participants as Treated; n=number of subjects with available data for relevant endpoint;  
SAE=serious adverse event; x participants=number of subjects who experienced the event

Reviewer Comment: Overall, the reported rates of AEs and ARs support the safety of the use of PCV15 in individuals with SCD.

#### *Maximum Body Temperatures within 7 days post-vaccination*

The rate of reported fever (i.e., body temperature  $\geq 38.0^{\circ}\text{C}$ ) reported in the 7 days following vaccination was slightly higher in the PCV15 group (PCV15: 4.4% [n=3], PCV13: 2.9% [n=1]). No participants in either group reported fevers  $\geq 40.0^{\circ}\text{C}$ . Of the reported temperature measurements, 76.5% were oral measurements and 23.5% were axillary measurements.

Reviewer Comment: Although the reported rate of fever was higher in the PCV15 group, there were no fevers  $\geq 40.0^{\circ}\text{C}$

#### *Unsolicited AEs within 14 days post-vaccination*

Unsolicited AEs were documented by the participant or the participant's legally acceptable representative in the eVRC and reviewed by the investigator at vaccine study visits and at 15 days following each vaccine dose. Rates of unsolicited AEs were generally comparable between study groups (PCV15: 41.2%, PCV13: 39.1%). The most frequently reported events in the PCV15 group, by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, were Blood and lymphatic system disorders (PCV15: 10.1%, PCV13: 17.6%; Infections and infestations (PCV15: 8.7%, PCV13: 11.8%); and Gastrointestinal disorders (PCV15: 8.7%, PCV13: 2.9%).

Reviewer Comment: The reported rates and types of unsolicited adverse events were comparable across study groups and represent medical conditions that are common in children with SCD.

#### **Deaths**

There were no deaths reported in either study group.

#### **Nonfatal Serious Adverse Events**

There were no SAEs considered to be related to the study interventions. The reported rates of SAE occurrence (PCV15 18.8% [10.4, 30.1], PCV13 23.5% [10.7, 41.2]) were comparable between study groups. SAEs were most often due to sickle cell crises (7 in the PCV15 group and

6 in the PCV13 group) followed by infections unrelated to the study intervention and common to childhood (e.g., viral respiratory tract infections, pyelonephritis).

Reviewer Comments: SAE occurrence was generally comparable between study groups and reported SAEs were consistent with diseases commonly observed in children with SCD

### Subpopulation Analyses

Subpopulation analyses were made for all groups which contained  $\geq 10$  participants in each vaccination group within that subgroup. Safety results were generally comparable with the results of the overall population for age (5 to 9 years and 10 to 14 years), Black/African American, and for participants identifying as Hispanic/Latino. Female participants in the PCV15 group were more likely to report headaches and myalgias.

### Dropouts and/or Discontinuations

There were 5 discontinuations in the PCV15 group as shown in [Table 74](#). There were no participant discontinuations due to AEs.

**Table 74. Study V114-023: Participant Dropouts and/or Discontinuations During the Study**

Reason*	PCV15 N=70	PCV13 N=34	Total N=104
All Discontinued, n (%)	5 (7.1)	0 (0.0)	5 (4.8)
Withdrawal**, n (%)	2 (2.9)	0 (0.0)	2 (1.9)
Lost to follow-up, n (%)	2 (2.9)	0 (0.0)	2 (1.9)
Physician decision, n (%)	1 (1.4)	0 (0.0)	1 (1.0)

N=all randomized participants; n=number of discontinued participants; %= % of all randomized participants

\* Reason for discontinuation

\*\* Withdrawal by parent or guardian

Reviewer Comment: Although all participant discontinuations occurred in the PCV15 group, the small number of discontinuations do not impact the interpretability of the study results.

### 6.6.13 Study Summary and Conclusions

Study V114-023 evaluated the safety and immunogenicity of a single dose of PCV15 as compared to PCV13 in participants with SCD. Safety results (ARs through 14 days post vaccination and SAEs through study completion) supported the safety of PCV15 in individuals with SCD. There were no serious safety concerns and no related SAEs. Immunogenicity endpoints (serotype-specific IgG GMCs and OPA GMTs 30 days post vaccination) evaluated descriptively supported the immunogenicity of PCV15 in individuals with SCD.

Overall, study V114-023 supported the use of PCV15 in participants with SCD.

### 6.7 Trial #7: V114-008

[NCT02987972: A Study to Evaluate the Safety, Tolerability, and Immunogenicity of Two Lots of V114 in Healthy Infants](#)

#### 6.7.1 Primary Immunogenicity Objective:

To demonstrate that PCV15 (either PCV15-Lot 1 or PCV15-Lot 2) is non-inferior to

Prenar 13™ for the 13 shared serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), based on the proportion of subjects meeting serotype-specific immunoglobulin G (IgG) threshold value of  $\geq 0.35$   $\mu\text{g}/\text{mL}$  at 1-month post-dose 3

- Endpoints: Proportion of subjects with serotype-specific  $\text{IgG} \geq 0.35 \mu\text{g}/\text{mL}$  measured by Pn ECL assay at 1-month post-dose 3 for 13 common serotypes between PCV15 (each Lot) and PCV13 in recipients of either lot of PCV15 and PCV13
- Hypotheses: The statistical criterion for non-inferiority corresponds to the lower bound of the adjusted 95% CI of the proportion difference (PCV15 minus Prenar 13™) being greater than  $-0.15$  for each of the 13 shared serotypes

#### 6.7.2 Design Overview

The purpose of this Phase 2 study was to finalize formulation selection for subsequent Phase 3 clinical development. The study evaluated the safety and immunogenicity of 2 different PCV15 drug product lot formulations that had similar composition but had different source lots of adjuvant (MAPA) and/or drug substance. There were 1051 infants randomized 1:1:1 (V114-Lot 1, V114-Lot 2, or PCV13) to receive a 4-dose series of study vaccine at 2, 4, 6, and 12-15 months of age. The primary analyses evaluated the proportion of PCV15 recipients (by lot group) who achieved serotype-specific IgG level  $\geq 0.35$   $\mu\text{g}/\text{mL}$  for the shared 13 serotypes compared to PCV13 recipients after the 3<sup>rd</sup> dose. The study design included plans for rescue dosing with a licensed PCV if the IgG level was  $< 0.35$   $\mu\text{g}/\text{mL}$  for serotype 19A or  $< 0.35$   $\mu\text{g}/\text{mL}$  for 4 or more shared serotypes. Participants were followed for safety through 1-month after the 4<sup>th</sup> dose and were enrolled at 47 sites in Finland, Spain, Israel, Denmark, Canada, and USA.

Reviewer Comment: The two different formulation PCV15 lots evaluated in Study V114-08 were non-equivalent products. As cited in the review memo for Chemistry Manufacturing and Controls, the products were considered as separate formulations because of the differences in the serotype conjugates between the 2 lots. Lot 2 was the formulation selected for commercial specification development.

#### 6.7.11 Immunogenicity Results

There were 296 V114-lot 1 recipients, 294 V114-lot 2 recipients, and 302 PCV13 recipients included in the IgG Per Protocol population post dose 3 for the primary analyses. Both Lot 1 and Lot 2 were non-inferior to PCV13 for each of the 13 serotypes as assessed by IgG response rates at 1 month post dose 3, with the lower bound of the 95% CI for the difference across groups (Lot 1 or Lot 2 minus PCV13) was greater than  $-15\%$  for all shared 13 serotypes. Notably, the proportion of responders to serotype 6A for Lot 1 was 90.6%, Lot 2 was 95.6%, and PCV13 was 96.2%; and the % difference across groups was  $-5.6\%$  (95% CI:  $-10\%$ ,  $-1.6\%$ ) for Lot 1-PCV13 and  $-0.6\%$  (95% CI:  $-4.2\%$ ,  $2.8\%$ ) for Lot 2-PCV13.

#### 6.7.12 Safety Results

The proportion of participants who reported safety events following vaccination were similar between Lot1 and Lot 2 participants, and generally followed the trends reported in Phase 3 studies described in prior sections of this memo. Across groups there were 52 reported SAEs (18 in V114-Lot 1, 19 in V114-Lot 2, and 15 in PCV13). There were two SAEs reported in the V114-Lot 2 group that were considered related to the study vaccinations by the investigators: a

9-week-old female who reported febrile convulsion following vaccination with Dose 1 of V114-Lot 2 and a 1-year-old male who reported purpura 1 day after vaccination with dose 4 of V114-Lot 2.

There was one death reported in a 10-week-old female infant that occurred 19 days after vaccination with the Dose 1 of V114-Lot 1 and concomitant routine infant vaccines. The infant was found unresponsive 90 minutes after being laid down on a bed after breast feeding. An autopsy did not determine the cause or manner of death, although environmental factors (unsafe sleep on adult bed) were cited. The investigator did not consider the event related to study vaccination.

Reviewer Comments

This clinical reviewer agrees with the investigator's assessment that the reported death was likely not related to the study intervention.

**SAE of interest: Febrile seizure**

An episode of febrile seizure was reported in a 9-week-old female infant. Following a fever of 100.7°F on the day of vaccination with V114-Lot 2 (as well as DTaP-IPV, HiB, and rotavirus vaccines), the participant developed somnolence. Seven hours later, the participant's temperature was measured at 100.9°F and she developed a generalized tonic-clonic seizure lasting 10 – 15 seconds. The patient was admitted to the hospital where the results of a diagnostic work-up, including lumbar puncture and EEG did not uncover a cause of fevers. The participant received no anticonvulsants and had no further fevers or seizure activity. Due to the timing of vaccination and the onset of the seizure the investigator considered the seizure as possibly related to the study intervention.

Reviewer Comments: This clinical reviewer agrees with the investigator's assessment that the episode of febrile seizure was possibly related to PCV15 (V114) or one of the other concomitantly administered vaccines and this event should be included in the prescribing information

**SAE of interest: Purpura**

An episode of purpura was reported in a 1-year-old male on the day following receipt of V114-Lot 2 (as well as meningococcal C conjugate vaccine and MMR vaccine). The participant developed red spots on his ankles, hands, arms and ears that were not considered to be an immediate hypersensitivity reaction. Three days later he developed hematomas and was taken to the emergency department for evaluation. Physical examination was unremarkable except for the skin findings and the participant was afebrile. Laboratory evaluation revealed a slightly prolonged activated partial thromboplastin time (aPTT) with otherwise normal values of hematologic and coagulation labs (platelets, hemoglobin/hematocrit, white blood count, fibrinogen, PT/INR) and a urinalysis that was negative for protein. The participant received diphenhydramine. The purpura lasted a total of 7 days and then resolved. Due to the timing of vaccination and the onset of the purpura the investigator considered the purpura as possibly related to the study intervention.



Reviewer Comments: This episode of purpura may have been related to PCV15 (V114) or one of the other concomitantly administered vaccines as it occurred shortly after vaccination; however, the relationship is not clear as key features of the case were not consistent with an immune mediated process (distribution of lesions and generally normal lab findings including normal platelets). Due to these features and that this case of purpura was isolated, the evidence does not support inclusion of this event in the prescribing information.

#### **SAE of interest: Serum sickness, V114 Lot 1**

An episode of serum sickness was reported in a 1-year-old male infant 16 days after dose 4 of V114 (PCV15) Lot 1 (as well as MMR and varicella vaccines). Eight days after vaccination the participant was diagnosed acute otitis media and was prescribed amoxicillin. Seven days later (16 days after vaccination) the participant developed diarrhea, tachycardia, irritability, fever of 102.7°F, a diffuse pinpoint red rash, and eyelid swelling. The patient was admitted to the hospital, diagnosed with serum sickness, and treated with diphenhydramine and dexamethasone. The patient was discharged from the hospital on the same day. The patient's fever resolved after 1 day and the rash resolved in 10 days. The investigator considered the episode of serum sickness as not related to the study vaccine and as related to the amoxicillin.

Reviewer Comments: Due to the time of onset, this clinical reviewer agrees with the investigator's determination that the serum sickness (or serum sickness-like) reaction was more likely due to antibiotic therapy than vaccination with V114 (PCV15). Although serum sickness-like reactions have been reported following pneumococcal conjugate vaccines, these typically occur within 2 weeks of vaccination. As such, and because this SAE was reported following vaccination with a formulation of V114 that was not chosen for commercial development, the evidence does not support inclusion of this event in the prescribing information

#### 6.7.13 Study Summary and Conclusion

At enrollment, the median age was 9.0 weeks of age (range 6 to 12 weeks) and included 50.2% males (49.8% females), and most participants were White (83.3%), followed by Black/African American (8.7%). Across all three study groups, 927 participants (88.2%) received all 4 study vaccine doses, and 87.6% of participants completed the study through 1 month after the 4<sup>th</sup> dose. There were 33 participants (9 in Lot 1, 12 in Lot 2, and 12 in PCV13) who were discontinued from the study due to inadequate IgG responses (determined at 1 month after 3<sup>rd</sup> dose) and were offered an additional dose of a licensed PCV outside the study.

Immunogenicity and safety data from Study V114-008 evaluating two lots of PCV15 as a 4-dose series in infants supported further clinical development of PCV15 and was used by the Applicant to finalize formulation selection (V114 Lot 2) for Phase 3 studies. The two PCV15 formulation lots evaluated in this study generated non-inferior immune responses compared PCV13 for the shared 13 vaccine serotypes.

### **7. Integrated Overview of Immunogenicity**

As described in the Integrated Statistical Analysis Plan (iSAP), immunogenicity data to support the 4-dose series in healthy infants for this licensure application was assessed from Study V114-

029, which included formal evaluations of IgG response rates and IgG GMCs after the 3<sup>rd</sup> dose, and IgG GMCs after the 4<sup>th</sup> dose. Pooling of immunogenicity data from the 3 pediatrics studies evaluating a 4-dose series (V114-029, V114-031, V114-27)) included in the application was not conducted for full-term infants but was conducted for infants born pre-term (EGA <37 weeks) from these studies. The integrated population included 236 pre-term infants who received at least 1 dose of PCV, of which the majority completed their respective study (>90%) and >70% were included in the Per Protocol Population for the pneumococcal IgG analyses for each time points for their respective study.

### **Pre-term Infants**

Integrated immunogenicity analyses included pre-term infants from studies V114-029, V114-031, V114-027 (Groups 1 and 5) who may have received non-US licensed vaccines concomitantly. The proportion of PCV15 recipients (n=142) and PCV13 recipients (n=144) after the 3<sup>rd</sup> dose with IgG GMC responses  $\geq 0.35$   $\mu\text{g/mL}$  were generally comparable for the shared serotypes excluding serotype 3; and a higher proportion of PCV15 recipients compared to PCV13 recipients were considered responders for the 2 unique serotypes (22F, 33F) and for shared serotype 3. The IgG GMCs in pre-term infants across all three studies who received PCV15 compared to PCV13 after the 3<sup>rd</sup> dose and after the 4<sup>th</sup> dose were overall numerically similar for the shared serotypes, and higher for the two unique serotypes and serotype 3.

A similar pattern of responses was seen in integrated analyses of the OPA GMTs for a subset of pre-term infants in studies V114-029 and V114-031 (PCV15 recipients: 39 to 54, PCV13 recipients: 35 to 53). Serotype-specific OPA GMTs were generally comparable across groups for the 13 shared serotypes and higher in the PCV15 group for the 2 unique serotypes.

### *Comparison: Pre-term Infants & Term Infants*

In a descriptive comparison, submitted to the sBLA as a ‘Response to FDA Request for Information’,<sup>2</sup> the immunogenicity of a 4-dose PCV15 series in pre-term infants was evaluated compared to that in term infants for Study V114-029, the main study used to support immunogenicity. As described in [Section 6.1.11](#) (V114-029, Immunogenicity Subpopulation Analyses), the proportion of pre-term infants who received PCV15 with serotype specific IgG responses  $\geq 0.35$   $\mu\text{g/mL}$  post-dose 3 was generally similar when compared to full-term infants who received PCV15. The IgG GMCs at post-dose 3 and post-dose 4 for PCV15 recipients were also comparable between pre-term and term infants.

**Reviewer Comment:** The immune responses elicited by a 4-dose PCV15 series as measured by IgG GMC immunogenicity assessments following the 3<sup>rd</sup> and 4<sup>th</sup> doses were generally similar for healthy infants born pre-term compared to those born full-term.

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<sup>2</sup> Applicant submitted these descriptive analyses to the sBLA (STN 125741/6 Am10, dated March 14, 2022) in response to CBER Information Request, sent March 9, 2022,

## 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 PCV15 in infants, children, and adolescents 6 weeks through 17 years of age were from the following sources:

Main trials:

- Phase 3: V114-029, V114-031, V114-027, V114-024, V114-030, V114-023
- Phase 2: V114-008

### 8.2 Safety Database

#### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

There were seven studies included (listed above) in this application to describe the safety profile of PCV15. The study populations (time of enrollment) and the dosing regimen evaluated were as follows:

- Infants 2 months of age (42-90 days, pneumococcal vaccine naïve): 4-dose series at 2, 4, 6, 12-15 months of age
- Children/adolescents 7 months through 17 years of age (with or without prior pneumococcal vaccination, depending on age at time of enrollment): 3-dose, 2-dose, or 1-dose catch-up vaccination schedules
- Children 6 years through 17 years of age infected with HIV (with or without prior pneumococcal vaccination): single dose, followed by Pneumovax 23 eight weeks later
- Children 5 years through 17 years of age with Sickle Cell Disease (with or without prior pneumococcal vaccination): single dose

The safety database across all seven studies included 7197 total vaccine recipients who received at least 1 study vaccine dose, which included 4778 PCV15 recipients and 2899 PCV13 recipients.

#### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The integrated summary of safety from studies (V114-029, V114-031, and V114-027 Groups 1 and 5 only) included 4,475 participants (3,004 PCV15 recipients and 1,471 PCV13 recipients). Participants may have received non-US licensed vaccines. The demographic characteristics for participants who received a 4-dose series were as follows:

- Sex: 51.8% Male, 48.2% Female
- Age: Median age 9 weeks (range 6 to 12 weeks)
- Race: White 52.4%, Asian 31.4%, Multiple races 9.2%, Black/African American 4.4%, American Indian/Alaska Native 2.3%
- Ethnicity: Hispanic 19.0%, Not Hispanic 80.4%
- Gestational Age: <37 weeks 6.4, ≥37 weeks 93.6%

Reviewer Comment: For the integrated studies, the demographic characteristics for participants in each study group (not shown) were similar to those described above for all participants. There were no imbalances observed in demographic characteristics across groups.

### 8.2.3 Categorization of Adverse Events

Safety data collected across the 3 integrated studies (V114-029, V114-031, V114-027 Groups 1 and 5 only) evaluating a 4-dose series included the following:

- Day 1 through Day 7 postvaccination (each dose): body temperature (using age-appropriate route of measurement). Temperature measure on Day 8 through Day 14 postvaccination was conducted if fever was suspected.
- Day 1 through Day 14 postvaccination (each dose)
  - Solicited injection-site ARs: redness (erythema), swelling, tenderness (pain), and hard lump (induration)
  - Solicited systemic ARs: (using age-appropriate terms for infants and children of different ages)
    - For participants <3 years of age: irritability, drowsiness (somnolence), appetite lost (decreased appetite), and hives or welts (urticaria)
    - For participants ≥3 years of age: muscle pain (myalgia), joint pain (arthralgia), headache, tiredness (fatigue), and hives or welts (urticaria)
  - Other unsolicited injection-site or systemic adverse events
  - Use/receipt of concomitant medications and vaccinations
- Intensity/Severity scale: injection-site erythema, injection-site induration, and injection-site swelling were graded by size; all other complaints were graded by intensity.
- Through 6 months after last dose for all 6 Phase 3 studies
  - Serious Adverse Events (SAEs)
  - AEs leading to study discontinuation

The investigator reviewed the data reported on the VRC with the participant or participant's legally acceptable representative and reported events meeting the protocol-specified AE definition in the clinical database.

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

As stated in the iSAP, the Applicant had integrated safety data for Studies V114-029, V114-031, and V114-027 (Groups 1 and 5 only) because of comparable study design (randomized, double-blind, active-controlled), study population (healthy infants ~42 to 90 days at enrollment), and dosing regimens (4-dose series at 2, 4, 6, 12-15 months of age). The other studies listed above were not included in the integrated analyses for safety due to differences in the cited study elements.

### 8.4 Integrated Safety Results

In the integrated analyses of safety for the 4-dose series in all infants (term and pre-term) (N=4,475), the reported rates of adverse events were generally similar across groups, with slightly higher rates of reactogenicity in the PCV15 group compared to PCV13 groups. The trends in observed AE rates across groups were generally similar to those reported in Study V114-031

(N=2400) and in Study V114-029 (N=1,713) that included concomitant vaccination with ACIP recommended routine infant vaccines.

*Comparison: Pre-term Infants (PCV15 vs PCV13) & Term Infants (PCV15 vs PCV13)*

In a descriptive comparison of the safety of a 4-dose PCV15 series in the pre-term infants with EGA <37 was evaluated compared to that in term infants with EGA  $\geq$ 37 weeks for participants in Studies V114-029, V114-031, V114-027 (Groups 1 and 5 only). The participants included in these analyses (Total N) by study groups were as follows:

- Pre-term infants: 142 PCV15 recipients and 144 PCV13 recipients
- Term infants: 2860 PCV15 recipients and 1323 PCV13 recipients

The proportion of participants who reported AEs (%) or solicited ARs in Pre-term infants vs. Term infants were as follows by group:

- With  $\geq$ 1 adverse event (following any dose)
  - Pre-term infants: 95.1 % PCV15 vs 95.1% PCV13
  - Term infants: 93.5% PCV15 vs 92.6% PCV13
- Solicited Local ARs
  - Erythema:
    - Pre-term infants: 45.8% PCV15 vs 41.0% PCV13
    - Term infants: 43.2% PCV15 vs. 42.7% PCV13
  - Induration
    - Pre-term infants: 23.9% PCV15 vs 29.2% PCV13
    - Term infants: 27.3% PCV15 vs 30.5% PCV13
  - Pain
    - Pre-term infants: 54.2% PCV15 vs 51.4% PCV13
    - Term infants: 46.4% PCV15 vs 48.0% PCV13
  - Swelling
    - Pre-term infants: 26.8% PCV15 vs 27.1% PCV13
    - Term infants: 28.3% PCV15 vs 24.8% PCV13
- Solicited Systemic ARs
  - Fever (Temperature  $\geq$ 38.0C)
    - Pre-term infants: 74.0% PCV15 vs. 78.5% PCV13
    - Term infants: 74.7% PCV15 vs. 74.5% PCV13
  - Decreased appetite
    - Pre-term infants: 38.7% PCV15 vs 41.0 % PCV13
    - Term infants: 39.1% PCV15 vs 35.4% PCV13
  - Irritability
    - Pre-term infants: 80.0% PCV15 vs 78.5% PCV13
    - Term infants: 74.9% PCV15 vs 72.1% PCV13
  - Somnolence
    - Pre-term infants: 66.2% PCV15 vs 63.9% PCV13
    - Term infants: 56.2% PCV15 vs 58.8% PCV13
  - Urticaria
    - Pre-term infants: 5.6% PCV15 vs 4.2% PCV13

- Term infants: 6.1% PCV15 vs 7.0% PCV13
- SAE (following any dose)
  - Pre-term infants: 14.8% PCV15 vs 10.4% PCV13
    - None considered related
  - Term infants: 9.8% PCV15 vs 10.0% PCV13
    - 2 events in the PCV15 group considered related, both were pyrexia events reported in Study V114-31 (described in [Section 6.2.12](#))

Reviewer Comment: There were 142 pre-term infants and 2860 term infants who received a 4-dose PCV15 series at 2,4,6, and 12-15 months of age that were included in this descriptive comparison of safety endpoints. Due to difference in overall size of each safety database (pre-term vs term infants) it is not possible to make definitive conclusions on potential differences in rates of safety events when PCV15 is administered as a 4-dose series in pre-term infants versus term infants. However, the overall findings are reassuring and generally suggest similar safety profiles of PCV15 in pre-term versus term infants, with similar between group differences (PCV15 vs PCV13) observed as well.

## 8.5 Safety Conclusions

In a total of 7 randomized clinical studies conducted in 24 countries, 3354 infants received 4 doses of the intended final formulation of PCV15. 575 children ages 7 months through 17 years of age received 1 to 3 doses of PCV15. Reported rates of local and systemic adverse reactions were generally comparable between PCV15 and PCV13 recipients although fevers were slightly more common in PCV15 recipients. The reactogenicity profiles of PCV15 were similar to those observed with other licensed childhood vaccines. No serious safety concerns were identified for any of the evaluated age groups.

## 9. Additional Clinical Issues

### 9.1 Special Populations

Section 8 of the US prescribing information (USPI) was edited to include the information in [Section 9.1.1](#) and [Section 9.1.2](#) below.

#### 9.1.1 Pediatric Use and PREA Considerations

Studies V114-029, -024, -027, and -030, included in this sBLA submission, fulfill the 4 post-marketing requirements (PMRs) identified under PREA in the initial BLA approval (July 16, 2021) for the deferred evaluation of Vaxneuvance in children 6 weeks through 17 years of age. These 4 studies were presented to the FDA's Pediatric Review Committee on February 22, 2022. The committee agreed that the Applicant's PMRs for children 6 weeks through 17 years of age were fulfilled by the included studies.

#### 9.1.2 Immunocompromised Patients

##### *Children with HIV infection*

In Study V114-030, the safety and immunogenicity of PCV15 were descriptively evaluated in HIV-infected children 6 through 17 years of age who were either pneumococcal vaccine naïve or who had received PCV 13 at least 3 years prior to study day 1 or PPSV23 at least 5 years before

study day 1. Participants had a CD4+ T-cell count  $\geq 200$  cells/ $\mu$ L and plasma HIV RNA value  $< 50,000$  copies/mL. Participants were randomized to receive PCV15 (n=203) or PCV13 (n=204), followed by PPSV23 two months later. Thirty days after PCV, IgG GMCs/GMFRs and OPA GMTs for the 13 shared serotypes were generally comparable between study groups and higher in the PCV15 group for the 2 serotypes unique to PCV15. Thirty days after sequential administration of PPSV23, IgG GMCs/GMFRs and OPA GMTs were generally comparable between study groups for all 15 serotypes contained in PCV15. The reported occurrences of SAEs through study completion and solicited ARs/unsolicited AEs through 14 days post-vaccination with PCV and PPSV23 were generally comparable between the two vaccination groups. The effectiveness of PCV15 for the prevention of IPD in HIV-infected individuals has not been evaluated.

#### *Children with SCD*

In Study V114-023, the safety and immunogenicity of PCV15 were descriptively evaluated in children 5 through 17 years of age who were either pneumococcal vaccine naïve or who had received a pneumococcal vaccine (PCV13 or PPSV23) at least 3 years prior to study day 1. Participants were randomized to receive a single dose of PCV15 (n=69) or PCV13 (n=34). Thirty days after PCV, IgG GMCs/GMFRs and OPA GMTs for the 13 shared serotypes were generally comparable between study groups and higher in the PCV15 group for the 2 serotypes unique to PCV15. The reported occurrences of SAEs through study completion and solicited ARs/unsolicited AEs through 14 days post-vaccination were generally comparable between the two vaccination groups. The effectiveness of PCV15 for the prevention of IPD in individuals with SCD has not been evaluated.

## **10. Conclusions**

In healthy immunocompetent children 6 weeks through 3 months of age without a prior history of pneumococcal vaccination, immunogenicity (inferred effectiveness), study V114-029 demonstrated non-inferiority of the serotype-specific IgG antibody responses to the 13 shared serotypes and statistically significantly greater serotype-specific IgG antibody responses for serotypes 3, 22F, and 33F following a 4-dose series of PCV15 (doses administered at 2 months, 4 months, 6 months, and 12-15 months). In study V114-027, descriptive evaluation of the immune responses supported the completion of a 4-dose PCV series with PCV15 when the series was initiated with PCV13.

In studies V114-029, V114-031, and V114-027, the safety profiles of 4-dose series of PCV15 were comparable to those of 4-dose series of PCV13 in healthy immunocompetent children 6 weeks through 3 months of age who were pneumococcal vaccine naïve. These safety data support usage of PCV15 in this population.

In study V114-024, descriptive evaluations supported the comparability of PCV15 and PCV13 for the immune responses elicited to the 13 shared serotypes and greater responses in the PCV15 group to the 2 serotypes unique to PCV15 when administered as 1 to 3 doses for catch-up vaccination of healthy children 7 months of age through 17 years of age who were pneumococcal vaccine naïve and those 2 years through 17 years of age who had received a partial vaccine series of any currently available PCV or a complete series of either PCV7 or PCV10. The safety

profiles between groups were similar for each age cohort and support usage of PCV15 in this population.

Study V114-030 supported the general comparability of the immune responses to the 13 shared serotypes in otherwise healthy children 6 years through 17 years of age who received 1 dose of either PCV15 or PCV13 and greater immune responses in PCV15 recipients to the 2 unique serotypes. Following administration of PPSV23 ~2 months later, the immune responses to all 15 serotypes were generally comparable between groups. Participants in the study may have received PCV at least 3 years prior or PPSV at least 5 years prior to study initiation. The safety profiles following PCV and PPSV23 were comparable between groups and support usage of PCV15 in this population.

Study V114-023 supported the general comparability of the immune responses to the 13 shared serotypes in otherwise healthy children with SCD 5 years through 17 years of age who received 1 dose of either PCV15 or PCV13 and of greater immune responses in PCV15 recipients to the 2 unique serotypes. Participants were either pneumococcal vaccine naïve or had received a pneumococcal vaccine at least 3 years before the study.

PCV15 was slightly more reactogenic; however, the overall safety profiles were comparable across groups in all studies. 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 75. PCV15: Risk-Benefit Considerations**

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p>As of 2020, there are 100 identified serotypes of <i>S. pneumoniae</i> and most serotypes can cause invasive pneumococcal disease (IPD), including meningitis and bacteremia, and children may have multiple episodes of IPD due to different serotypes. IPD can result in significant morbidity, permanent sequelae, and death.</p> <p>Children with decreased immune function due to HIV infection and functional/anatomic asplenia from sickle cell disease (SCD) are at increased risk of IPD.</p>	<p>IPD is a serious and life-threatening condition that can result in significant morbidity and mortality in children &lt;18 years of age.</p> <p>The risk of serious pneumococcal disease is greatest in immunocompromised children.</p>
Unmet Medical Need	<p>Pneumovax 23 and Prevnar 13 are two pneumococcal vaccines approved for use in persons &lt;18 years of age in the US. PCV15 includes 13 serotypes in common with PCV13 and 15 serotypes in common with PPV23. PPSV23 is not considered effective in young children, especially those less than 2 years of age, due to poor elicited antibody responses.</p> <p>The two serotypes unique to PCV15, 22F and 33F, are responsible for approximately 17% of cases of IPD in children less than 5 years of age (<a href="#">Gierke, 2021</a>). Also, the incidence of IPD due to serotype 3 has not decreased as anticipated following the implementation of PCV13</p> <p>Effective antibiotic therapy is available for the treatment of IPD; however, antibiotic resistance can complicate treatment, and may not prevent sequelae of serious IPD.</p>	<p>In children &lt;18 years of age, there is an unmet medical need for effective prevention of IPD caused by serotypes 22F and 33F, which are included in PCV15, but not in PCV13.</p> <p>PCV15 elicited IgG GMCs and OPA GMTs to serotype 3 that were significantly greater compared to those elicited by PCV13</p>
Clinical Benefit	<p>PCV15 effectiveness against IPD was primarily inferred from serotype specific IgG responses as compared to PCV13.</p> <ul style="list-style-type: none"> <li>• For the 13 common serotypes: the IgG responses elicited by PCV15 were non-inferior to those elicited by PCV13</li> <li>• For serotypes 22F, 33F, and 3: IgG responses elicited by PCV15 were statistically significantly greater than those elicited by PCV13</li> </ul> <p>Immunological interference was not observed when PCV15 was administered concomitantly with ACIP-recommended routine US vaccines (i.e., Pentacel, Rotateq, Hiberix, Recombivax HiB, Varivax, M-M-R II, VAQTA).</p>	<p>The immunogenicity data support the effectiveness of PCV15 to prevent vaccine-serotype IPD and lack of immune interference when administered concomitantly with routine ACIP-recommended infant vaccines.</p>

<b>Decision Factor</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
Risk	<p>For the 4-dose series of PCV15 in infants, the rates of solicited injection site and systemic adverse reactions (ARs) after PCV15 were as follows: local pain (42.9 – 57.5), local erythema (40.6 – 48.4), local swelling (25.0 – 29.8), local induration (25.3 – 33.1), decreased appetite (35.5 – 41.6), irritability (74.9-81.1), somnolence (55.4 – 68.5), urticaria (4.0 – 6.0)</p> <p>For a single dose of PCV15 given to participants <math>\geq 2</math> years of age who were either pneumococcal vaccine-naïve or partially vaccinated with a lower-valency pneumococcal vaccine or fully vaccinated with a lower valency vaccine other than PCV13, the rates of solicited injection site and systemic adverse reactions (ARs) after PCV15 were as follows: local pain (54.8), local swelling (20.9), local erythema (19.2), local induration (6.8), myalgia (23.7), fatigue (15.8), headache (11.9), irritability (2.8), somnolence (2.8), decreased appetite (2.3), urticaria (1.1), and arthralgia (0.0)</p>	<p>The data from PCV15 clinical studies adequately characterize the safety of PCV15. The safety profile of PCV15 is acceptable for its intended use.</p>
Risk Management	<p>See “Clinical Benefit” and “Risk” sections above.</p>	<p>The reactogenicity of PCV15 described in the prescribing information and routine pharmacovigilance adequately mitigate the risks.</p>

### **11.2 Risk-Benefit Summary and Assessment**

The overall clinical benefit of PCV15 in individuals 6 weeks to <18 years of age in preventing invasive pneumococcal disease is favorable compared to the risks associated with vaccination. Data submitted to this supplemental BLA establish the safety and effectiveness of a 4-dose series of PCV15 in infants, and 1 to 3 dose series in children 7 months to < 18 years of age. The safety of PCV15 is adequately described in the prescribing information, and the Applicant's routine pharmacovigilance is adequate for monitoring AEs post-marketing. There was no evidence of immune interference when routine infant vaccines when administered concomitantly with PCV15 as compared to PCV13.

### **11.3 Recommendations on Regulatory Actions**

This clinical reviewer recommends approval of this efficacy supplement application as the clinical data provided support the safety and effectiveness of PCV15 in individuals 6 weeks to <18 years of age in preventing invasive pneumococcal disease.

### **11.4 Labeling Review and Recommendations**

The proprietary name VAXNEUVANCE was previously reviewed by the Advertising and Promotional Labeling Branch at CBER as a part of the initial BLA and found to be acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant. All issues were satisfactorily resolved.