Application Type	BLA
STN	125741/6
CBER Received Date	September 30, 2021
Goal Date	Initial Action Due Date: April 1, 2022 Revised Date Due to Major Amendment: July 1, 2022
Division / Office	DVRPA/OVRR
Committee Chair	Kamal Velmurugan, Ph.D.
Clinical Reviewer(s)	Mark Connelly, MD
Project Manager	Juan Lacayo, PhD Tatiana Claro Da Silva, PhD
Priority Review	Yes
Reviewer Name(s)	Zhong Gao, Ph.D. Mathematical Statistician Therapeutics Evaluation Branch 2, DB, OBPV
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lihan Yan, Ph.D. Acting Branch Chief Therapeutics Evaluation Branch 2, DB, OBPV
	Tsai-Lien Lin, Ph.D. Chief, Vaccine Evaluation Branch, DB, OBPV
Applicant	Merck Sharp and Dohme Corp.
Established Name	Pneumococcal 15-Valent Conjugate Vaccine
(Proposed) Trade Name	Vaxneuvance
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Contains 15 Streptococcus pneumoniae serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F)
Dosage Form(s) and Route(s) of Administration	Suspension for intramuscular injection
Dosing Regimen	0.5 mL dose
Indication(s) and Intended Population(s)	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 from 6 weeks through 17 years of age.

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List of Abbreviations and Definitions of Terms

AE	Adverse event
Anti-PnPs	Anti-pneumococcal polysaccharide
APaT	All participants as treated
sBLA	Supplement to Biologic license application
CI	Confidence interval
CRF	Case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eVRC	Electronic Vaccine Report Card
(b) (4)	(b) (4)
FAS	Full analysis set
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
H	Hypothesis
Hib	Haemophilus influenzae type B
Hib-PRP	Haemophilus influenzae type b polyribosylribitol phosphate
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IM	Intramuscular
ISS	Integrated Summary of Safety
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
OPA	Opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
PD	Postdose
PnECL	Pneumococcal electrochemiluminescence
PnP	Pneumococcal polysaccharides
PP	Per protocol
PPV23	PNEUMOVAX™23 (Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCD	Sickle cell disease
V114	Pneumococcal 15-valent Conjugate Vaccine [CRM197 protein], (b) (4) (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F)
VZV	Varicella-zoster virus

1. EXECUTIVE SUMMARY

Merck submitted a supplement to Biologics License Application (sBLA)125741 for V114, Pneumococcal 15-valent Conjugate Vaccine. V114 was approved for prevention of invasive pneumococcal disease caused by Streptococcus pneumoniae serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in adults 18 years of age and older on July 16, 2021. This sBLA is to extend the age range for the use of the vaccine to include children from 6 weeks through 17 years of age. The main immunogenicity and safety results are summarized below:

Immunogenicity:
This submission includes two studies (Studies V114-029 and V114-027) in healthy infants receiving 4 doses of pneumococcal conjugate vaccine (PCV). Two different pentavalent combination vaccines were used in these studies as concomitant pediatric vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus influenzae* type b: Pentacel was used at study sites located in the US and Puerto Rico, and Pentavac was used at study sites located in Turkey and Thailand. Since Pentavac is not licensed in the U.S., the immunogenicity analyses are focused on the subjects who received US-licensed Pentacel in this review.

- The pivotal study V114-029 was a Phase 3, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety and immunogenicity of V114 in healthy infants 6 to 12 weeks of age at enrollment who received 4 doses of PCV (single dose administered at ~2, 4, 6, and 12 to 15 months). The primary immunogenicity analyses from V114-029 showed:
  o V114 was noninferior to Prevnar 13 for all 15 serotypes, as assessed by the proportion of participants meeting the serotype-specific IgG threshold value of $\geq 0.35\mu g/mL$ (response rate) at 30 days post Dose 3 (PD3).
  o V114 was noninferior to Prevnar 13 for 14 of 15 serotypes, as assessed by serotype specific IgG geometric mean concentrations (GMCs) at 30 days PD3. The IgG response to serotype 6A missed the prespecified noninferiority criterion (the lower bound of the 2-sided 95% CI for the GMC ratio being 0.48 versus >0.5).
  o V114 was noninferior to Prevnar 13 for all 15 serotypes, as assessed by serotype-specific IgG GMCs at 30 days post Dose 4 (PD4).
- Study V114-027 was a multicenter, randomized, active-controlled, parallel-group, double-blind interchangeability study to evaluate the safety and immunogenicity of mixed pneumococcal conjugate vaccine (PCV) regimens in infants approximately 2 months of age. Serotype-specific IgG GMCs at 30 days PD4 for the 13 shared serotypes were generally comparable for participants administered mixed regimens and for participants administered a complete dosing regimen of Prevnar 13 as assessed by IgG GMC ratios. Serotype-specific immune responses at 30 days PD3 were generally comparable across intervention groups for the 13 shared serotypes as assessed by IgG response rates and IgG GMCs. Serotype-specific immune responses varied for the 2 unique serotypes (22F and 33F) across the mixed regimens at 30 days PD3.

- Studies V114-029 and V114-027 evaluated the administration of V114 concomitantly with licensed pediatric vaccines Pentacel, VAQTA, M-M-RII, VARIVAX, HIBERIX, RECOMBIVAX HB, and RotaTeq as part of recommended pediatric vaccination schedules. Responses to the assessed antigens in the concomitant vaccines met noninferiority criteria for V114 and Prevnar 13 recipients for all antigens except that the responses to mumps antigen slightly missed the prespecified noninferiority margin of -5% (the lower bound of the 2-sided 95% CI for the difference in response rates was -5.4%).

Study V114-024 evaluated healthy infants and children 7 months through 17 years of age administered catch-up vaccination regimens. Catch-up vaccination with V114 elicited serotype-specific immune responses, as assessed by IgG GMCs at 30 days after the last dose of study intervention for all 15 serotypes contained in the vaccine. Serotype-specific IgG GMCs and response rates at 30 days after the last dose of study intervention were generally comparable between the V114 and Prevnar 13 intervention groups for the 13 shared serotypes and higher in the V114 group than in the Prevnar 13 group for the 2 unique V114 serotypes.

The applicant evaluated the vaccine in specific populations with increased risk of pneumococcal disease.
- Preterm Infants: the analysis of the preterm infants from study V114-031 and integrated immunogenicity analysis showed that V114 elicited immune responses in preterm infants (<37 weeks gestational age at birth) administered with a 4-dose series that were generally comparable to Prevnar 13 for the shared serotypes and higher than Prevnar 13 for 2 serotypes unique to V114 (22F and 33F).
- Children with Sickle Cell Disease (SCD): study V114-023 showed that a single dose of V114, administered to children 5 through 17 years of age with SCD, elicited immune responses that were generally comparable to Prevnar 13 for the 13 shared serotypes and higher than Prevnar 13 for 2 serotypes unique to V114 (22F and 33F) at 30 days postvaccination.
- Children with HIV: study V114-030 showed that a single dose of V114, administered to children 6 through 17 years of age with HIV, elicited immune responses that were generally comparable to Prevnar 13 for the 13 shared serotypes and higher than Prevnar 13 for 2 serotypes unique to V114 (22F and 33F) at 30 days postvaccination.

Safety:
- In healthy infants receiving a 4-dose regimen of PCV starting at 6 to 12 weeks of age, the safety profile was generally comparable between V114 and Prevnar 13.
- Among participants 7 to 11 months of age, 12 to 23 months of age, and 2 through 17 years of age who received catch-up vaccination, the safety profiles of 1, 2, or 3-dose catch-up regimens of V114 were generally comparable to those of Prevnar 13.
- V114 was generally tolerated when changing from Prevnar 13 to V114 at Doses 2, 3 or 4 during a 4-dose PCV dosing regimen. The proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, and SAEs were generally comparable across mixed PCV regimens and complete V114 or Prevnar 13 regimens.

- The proportions of preterm infants with AEs after any dose, including injection-site AEs, systemic AEs, vaccine-related AEs, and SAEs were generally comparable in both intervention groups.
- In children 5 through 17 years of age with Sickle Cell Disease (SCD), the overall proportions of participants with AEs and SAEs were generally comparable across intervention groups. However, there was a higher proportion of vaccine-related systemic AEs reported in the V114 group compared to the Prevnar 13 group.
- In children 6 through 17 years of age with HIV, the proportions of participants with 1 or more AEs were generally comparable in both intervention groups. However, vaccine-related injection-site and systemic AEs were reported for a higher proportion of participants in the V114 group compared with the Prevnar 13 group.

Overall, the studies showed that V114 met the pre-specified immunogenicity criteria for all serotypes in V114 except for serotype 6A and for all antigens in the concomitant vaccines except for the mumps antigen. In both cases, the misses appear to be numerically small. Hence, the immunogenicity results appear to be adequate to support the proposed indication. Regarding safety evaluation, the studies showed that the safety profiles were generally comparable between the V114 and Prevnar 13 groups among healthy infants and children. However, in Studies V114-023 and V114-030, a higher proportion of participants with vaccine-related AEs was reported for the V114 group than the Prevnar 13 group among children with SCD and children with HIV. I defer to the clinical reviewers on whether the safety results are adequate to support the proposed indication based on the totality of the evidence.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

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

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

PNEUMOVAX23 (PPV23) was first licensed in the US in 1983. Prevnar was introduced in 2000 and has been widely adopted in national childhood vaccination schedules worldwide. Synflorix and Prevnar 13 were licensed in 2009 and 2010, respectively, and replaced Prevnar for pediatric immunization worldwide. V114 (Vaxneuvance) was approved for prevention of invasive pneumococcal disease caused by 15 Streptococcus pneumoniae serotypes in adults 18 years of age and older on July 16, 2021.

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

N.A.

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

This application is a supplement to Biologics License Application 125741 for V114, Pneumococcal 15-valent Conjugate Vaccine, which was approved for adults 18 years of age and older on July 16, 2021. This application for licensure is based on the inference of V114 effectiveness for the prevention of vaccine serotype-specific pneumococcal disease by demonstration of noninferior immune responses to the 13 shared serotypes in Prevnar 13.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance with Good Clinical Practices and Data Integrity

The submission presented no data integrity issues.

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

N/A

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

5.1 Review Strategy

This review focuses on six Phase 3 studies V114-023, V114-024, V114-027, V114-029, V114-030 and V114-031.

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

- STN 125741/6.0 Module 2.5. Clinical Overview
- STN 125741/6.0 Module 2.7.3. Summary of Clinical Efficacy
- STN 125741/6.0 Module 2.7.4. Summary of Clinical Safety
- STN 125741/6.0 Module 5.3.5.1. Study V114-023 Clinical Study Report
- STN 125741/6.0 Module 5.3.5.1. Study V114-024 Clinical Study Report
- STN 125741/6.0 Module 5.3.5.1. Study V114-027 Clinical Study Report
- STN 125741/6.0 Module 5.3.5.1. Study V114-029 Clinical Study Report
- STN 125741/6.0 Module 5.3.5.1. Study V114-030 Clinical Study Report
- STN 125741/6.0 Module 5.3.5.1. Study V114-031 Clinical Study Report
- STN 125741/6.0 Module 5.3.5.3. Integrated Summary of Immunogenicity

- STN 125741/6.0 Module 5.3.5.3. Integrated Summary of Safety
- STN 125741/6.13 Module 1.11.3. Clinical Information Amendment
- STN 125741/6.15 Module 1.11.3. Clinical Information Amendment
- STN 125741/6.16 Module 1.11.3. Clinical Information Amendment
- STN 125741/6.17 Module 1.11.3. Clinical Information Amendment
- STN 125741/6.18 Module 1.11.3. Clinical Information Amendment

5.3 Table of Studies/Clinical Trials

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

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

Trial ID and Title	Trial Design	Dosing regimen	Trial population	Subject exposure
V114-023 A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children with Sickle Cell Disease (PNEU–SICKLE)	Randomized, active comparator-controlled, parallel-group, multisite, double-blind	0.5 mL intramuscular dose of V114 or Prevnar 13 on Day 1	Male/Female participants between the ages of 5 and 17 years (inclusive) with SCD who were either PCV naïve or had received a lower valent PCV or PnPs vaccine 3 years or more prior to Day 1	V114: 69 Prevnar 13: 34
V114-024 A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of Catch-up Vaccination Regimens of V114 in Healthy Infants, Children, and Adolescents (PNEU-PLAN)	Multicenter, immunogenicity, safety, tolerability, parallel assignment, double-blind, active comparator	Schedule A: 7 to 11 months of age (PCV-naïve): 3 doses of V114 or Prevnar 13 Schedule B: 12 to 23 months of age (PCV-naïve): 2 doses of V114 or Prevnar 13 Schedule C: 2 to 17 years of age (PCV-naïve or PCV-experienced): Single dose of V114 or Prevnar 13	Healthy children 7 months to 17 years of age (inclusive) who were either pneumococcal vaccine-naïve or who previously received a partial regimen of licensed PCV (PCV7, PCV10, or PCV13) or a full regimen of PCV7 or PCV10	V114 group: 63 participants 7 to 11 months of age received 3 doses of V114. 1 participant 7 to 11 months of age received 1 dose of V114. 62 participants 12 to 23 months of age received 2 doses of V114. 177 participants received 1 dose of V114 Prevnar 13 group: 64 participants 7 to 11 months of age received 3 doses of Prevnar 13. 64 participants 12 to 23 months of age received 2 doses of Prevnar 13. 175 participants received 1 dose of Prevnar 13.
V114-027 A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13 with Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants (PNEU-DIRECTION)	Randomized, double-blind, parallel group, Active comparator controlled, multi-site	Single 0.5 mL intramuscular dose of V114 or Prevnar 13 at Visits 1, 2, 3, and 5 (~2, 4, 6, and 12 to 15 months of age) Licensed pediatric vaccines administered concomitantly. Group 1: Prevnar 13 → Prevnar 13 → Prevnar 13 → Prevnar 13 Group 2: Prevnar 13 → Prevnar 13 → Prevnar 13 → V114 Group 3: Prevnar 13 → Prevnar 13 → V114 → V114	Healthy male/female infants ~ 2 months of age (42 to 90 days, inclusive) without history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine	896 vaccinated V114: 677* Prevnar 13: 717* (*participants administered at least 1 dose)

Trial ID and Title	Trial Design	Dosing regimen	Trial population	Subject exposure
		Group 4: Prevnar 13 → V114→ V114 → V114 *Group 5: V114 → V114 → V114 → V114		
V114-029 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)	Randomized, active-comparator-controlled, parallel-group, multi-site, double blind	0.5 mL intramuscular doses of V114 or Prevnar 13 at ~2, 4, 6 and 12 to 15 months of age	Healthy male/female infants approximately 2 months of age, from 42 to 90 days without a history of invasive Pneumococcal disease or prior administration of any pneumococcal vaccine.	V114: 858 Prevnar 13: 855
V114-030 A Phase 3, Multicenter, Randomized, Double blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX23 Eight Weeks Later in Children Infected with Human Immunodeficiency Virus (HIV) (PNEU–WAY PED)	Randomized, active Comparator-controlled, parallel-group, multisite, double-blind study	Single dose of V114/Prevnar 13 at Day 1 Single dose of PNEUMOVAX23 at Week 8	Males or females between the ages of 6 to 17 years (inclusive) living with HIV without a prior history of invasive pneumococcal disease and were (1) pneumococcal conjugate vaccine (PCV) naïve, previously vaccinated with a <13-valent PCV, partially vaccinated with Prevnar 13, or had a history of previous Prevnar 13 vaccination ≥3 years before Day 1; and (2) pneumococcal polysaccharide (PnPs) vaccine naïve or had a history of 1 previous PnPs vaccination ≥5 years before Day 1.	V114: 203 participants received V114. 203 Participants Received PNEUMOVAX23. Prevnar 13: 204 participants received Prevnar 13. 202 participants received PNEUMOVAX23.
V114-031 A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety and Tolerability of V114 in Healthy Infants (PNEULINK)	Multicenter, safety, tolerability, immunogenicity (premature infants only), parallel-group, double blind, active comparator	Following randomization, participants received a single 0.5 mL intramuscular injection of double-blind V114 or Prevnar 13 at ~ 2, 4, 6, and 12-15 months of age (Study Day 1, Month 2, Month 4, and Month 10-13). Non-study pediatric vaccines were permitted and administered according to the local recommended schedule.	Males/females Full-term infants (≥37 weeks gestational age) and premature infants (<37 weeks gestational age).	In each randomized arm: V114 group Dose 1: 1967 Dose 2: 1932 Dose 3: 1913 Dose 4: 1856 Prevnar 13 group Dose 1: 436 Dose 2: 422 Dose 3: 417 Dose 4: 401

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

5.4 Consultations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Pivotal Study V114-029: A Phase 3, Multicenter, Randomized, Double-blind, Active-Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of a 4-doseRegimen of V114 in Healthy Infants (PNEU-PED)

6.1.1 Objectives

6.1.1.1 Primary Objectives

Table 2. Primary Study Objectives and Endpoints for Study V114-029

Objectives	Endpoints
Objective 1: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	Following any vaccination with V114: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination • Solicited systemic AEs from Day 1 through Day 14 postvaccination • Vaccine-related serious adverse events (SAEs) through completion of study participation
Objective 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 ≥0.35μg/mL) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13. **Hypothesis (H1):** V114 is non-inferior to Prevnar 13 for the 13 shared serotypes between V114 and Prevnar 13 based on response rates at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in the response rates [V114 minus Prevnar 13] to be greater than -0.1.) **Hypothesis (H2):** V114 is non-inferior to Prevnar 13 for the 2 unique V114 serotypes based on the response rate of the 2 unique V114 serotypes compared with the lowest response rate of any of the shared serotypes in Prevnar 13, excluding serotype 3, at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for the difference in the response rates [V114 minus Prevnar 13] to be greater than -0.1.)	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 3 (PD3)
Objective 3: To compare anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13. **Hypothesis (H3):** V114 is non-inferior to Prevnar 13 for the 13 shared serotypes between V114 and Prevnar 13 based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (V114/ Prevnar 13) to be greater than 0.5.) **Hypothesis (H4):** V114 is non-inferior to Prevnar 13 for the 2 unique V114 serotypes based on the anti-PnPs serotype specific IgG GMCs of the 2 unique V114 serotypes compared with the lowest IgG GMC of any of the shared serotypes in Prevnar 13, excluding serotype 3, at 30 days following Dose 3. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (V114/ Prevnar 13) to be greater than 0.5.)	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3
Objective 4: To compare anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13.	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days Postdose 4 (PD4)

Objectives	Endpoints
Hypothesis (H5): V114 is non-inferior to Prevnar 13 for the 13 shared serotypes between V114 and Prevnar 13 based on anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (V114/ Prevnar 13) to be greater than 0.5.) **Hypothesis (H6):** V114 is non-inferior to Prevnar 13 for the 2 unique V114 serotypes based on anti-PnPs serotype specific IgG GMCs of the 2 unique V114 serotypes compared with the lowest IgG GMC of any of the shared serotypes in Prevnar 13, excluding serotype 3, at 30 days following Dose 4. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI for anti-PnPs serotype-specific IgG GMC ratio (V114/ Prevnar 13) to be greater than 0.5.)	

Source: Section 8 in Study V114-029 CSR.

6.1.1.2 Secondary Objectives

Table 3. Secondary Study Objectives and Endpoints for Study V114-029

Objectives	Endpoints
Objective 1: To compare the antigen specific response rate to each antigen and the antigen-specific GMCs for the pertussis antigens included in Pentacel at 30 days following Dose 3 for participants administered V114 concomitantly with Pentacel versus participants administered Prevnar 13 concomitantly with Pentacel. **Hypothesis (H7):** Pentacel administered concomitantly with V114 is non-inferior to Pentacel administered concomitantly with Prevnar 13 at 30 days following Dose 3 for each antigen included in Pentacel.	Antibody responses to: • diphtheria toxoid • tetanus toxoid • pertussis toxin (PT) • pertussis filamentous hemagglutinin (FHA) • pertussis fimbrae types 2/3 (FIM 2/3) • pertussis pertactin (PRN) • poliovirus serotypes 1, 2 and 3 • Haemophilus influenzae type b • polyribosylribitol phosphate (Hib-PRP) at 30 days PD3 of V114 or Prevnar 13.
Objective 2: To compare the response rate to anti-hepatitis A antigen at 30 days following Dose 4 for participants administered V114 concomitantly with VAQTA versus participants administered Prevnar 13 concomitantly with VAQTA. **Hypothesis (H8):** VAQTA administered concomitantly with V114 is non-inferior to VAQTA administered concomitantly with Prevnar 13 at 30 days following Dose 4.	Antibody responses to hepatitis A antigen at 30 days PD4 of V114 or Prevnar 13
Objective 3: To compare the response rate to each antigen included in M-M-RII at 30 days following Dose 4 for participants administered V114 concomitantly with MM-RII versus participants administered Prevnar 13 concomitantly with M-MRII. **Hypothesis (H9):** M-M-RII administered concomitantly with V114 is non-inferior to M-M-RII administered concomitantly with Prevnar 13 at 30 days following Dose 4 for each antigen included in M-MRII.	Antibody responses to measles, mumps, and rubella virus at 30 days PD4 of V114 or Prevnar 13
Objective 4: To compare the response rate to anti-varicella antigen at 30 days following Dose 4 for participants administered V114 concomitantly with VARIVAX versus participants administered Prevnar 13 concomitantly with VARIVAX. **Hypothesis (H10):** VARIVAX administered concomitantly with V114 is non-inferior to VARIVAX administered concomitantly with Prevnar 13 at 30 days following Dose 4.	Antibody responses to varicella-zoster virus (VZV) at 30 days PD4 of V114 or Prevnar 13
Objective 5: To compare the response rate to anti-PRP antigen at 30 days following Dose 4 for participants administered V114 concomitantly with HIBERIX versus participants administered Prevnar 13 concomitantly with HIBERIX. **Hypothesis (H11):** HIBERIX administered concomitantly with V114 is non-inferior to HIBERIX administered concomitantly with Prevnar 13 at 30 days following Dose 4.	Antibody responses to PRP at 30 days PD4 of V114 or Prevnar 13

Objectives	Endpoints
Objective 6: To compare the anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13. **Hypothesis (H12):** V114 is superior to Prevnar 13 for the 2 unique V114 serotypes based on the response rates at 30 days following Dose 3. **Hypothesis (H13):** V114 is superior to Prevnar 13 for the 2 unique V114 serotypes based on anti-PnPs serotype specific IgG GMCs at 30 days following Dose 3.	Anti-PnPs serotype-specific IgG responses for the 2 unique serotypes contained in V114 at 30 days PD3
Objective 7: To compare the anti-PnPs serotype-specific IgG responses for the 2 unique V114 serotypes at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13. **Hypothesis (H14):** V114 is superior to Prevnar 13 for the 2 unique V114 serotypes based on anti-PnPs serotype specific IgG GMCs at 30 days following Dose 4.	Anti-PnPs serotype-specific IgG responses for the 2 unique serotypes contained in V114 at 30 days PD4
Objective 8: To compare the anti-PnPs serotype 3 IgG responses at 30 days following Dose 3 for participants administered V114 versus participants administered Prevnar 13. **Hypothesis (H15):** V114 is superior to Prevnar 13 for serotype 3 based on the response rates at 30 days following Dose 3. **Hypothesis (H16):** V114 is superior to Prevnar 13 for serotype 3 based on anti-PnPs IgG GMCs at 30 days following Dose 3.	Anti-PnPs serotype 3 IgG responses at 30 days PD3
Objective 9: To compare the anti-PnPs serotype 3 IgG GMCs at 30 days following Dose 4 for participants administered V114 versus participants administered Prevnar 13. **Hypothesis (H17):** V114 is superior to Prevnar 13 for serotype 3 based on anti-PnPs IgG GMCs at 30 days following Dose 4.	Anti-PnPs serotype 3 IgG responses at 30 days PD4

Source: Section 8 in Study V114-029 CSR.

6.1.2 Design Overview

This was a randomized, active comparator-controlled, parallel-group, multi-site, double-blind study of V114 in healthy infants enrolled at approximately 2 months of age. Participants were randomly assigned in a 1:1 ratio to receive either V114 or Prevnar 13 at approximately 2, 4, 6, and 12 to 15 months of age. Participants were to also receive the following pediatric vaccines administered concomitantly according to the schedule recommended by the US ACIP: RotaTeq, Pentacel, RECOMBIVAX HB, VAQTA, M-M-RII, VARIVAX, and HIBERIX.

6.1.3 Population

Healthy infants enrolled at approximately 2 months of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Experimental treatment: V114
- Active Comparator: Prevnar 13

6.1.6 Sites and Centers

This study was conducted at 82 centers in 3 countries. A total of 75 centers randomized participants.

6.1.7 Surveillance/Monitoring

N/A

6.1.8 Endpoints

Please see sections 6.1.1.1 and 6.1.1.2.

6.1.9 Statistical Considerations & Statistical Analysis Plan

- Blinding
This study was a double-blind study. The participants and the investigators who were involved in the clinical evaluation of the participants remained blinded to the group assignments. Because V114 and Prevnar 13 are different in appearance, V114 and Prevnar 13 were prepared and/or dispensed by an unblinded pharmacist or unblinded qualified study site personnel. To avoid bias, the unblinded study personnel had no further contact with study participants for any study-related procedures/assessments after administration of study vaccines.
- Randomization
Participants were assigned randomly in a 1:1 ratio to receive V114 or Prevnar 13. No stratification based on age, sex, or other characteristics was used in this study.

- Definitions of analysis populations
  - Immunogenicity Analysis Populations
    - Per-Protocol (PP) population: all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. The PP population served as the primary population for the analysis of immunogenicity data in this study.
    - Full Analysis Set (FAS): all randomized participants who received all study vaccinations required at the timepoint for the analysis and have serology result. FAS was used for supportive analyses.
  - Safety Analysis Population: safety analysis was conducted in the All Participants as Treated (APaT) population, which consisted of all randomized participants who received at least one dose of study vaccination.

- Sample size planning
The planned overall sample size was approximately 1720 with 860 participants in each vaccination group. It was expected that the overall power for all the primary hypotheses would be >95% to demonstrate non-inferiority of V114 to Prevnar 13 for the 13 shared serotypes and the 2 unique serotypes for V114.

- Statistical Analysis for Primary Immunogenicity Endpoints
  - Primary Endpoints/Hypotheses (H1 and H2)
The first primary objective was to compare the response rates of anti-PnPs serotype-specific IgG between V114 and Prevnar 13 at 30 days PD3. The response rate was defined as the proportion of participants with anti-PnPs serotype-specific IgG responses achieving the threshold value of 0.35μg/mL. The objective was assessed via the following noninferiority hypotheses:

H0: $p_1 - p_2 \leq -0.1$ versus

H1: $p_1 - p_2 > -0.1$.

For the 13 shared serotypes contained in V114 and Prevnar 13, p_1 is the response rate for the V114 group and p_2 is the response rate for the Prevnar 13 group. For the 2 serotypes unique to V114, p_1 is the response rate of the 2 unique serotypes for the V114 group and p_2 is the lowest response rate among all 13 shared serotypes, excluding serotype 3, for the Prevnar 13 group. V114 is non-inferior to Prevnar 13 if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13) is greater than -0.1. The M&N method was used for this analysis [Miettinen, O. and Nurminen, M. 1985].

  o   Primary Endpoints/Hypotheses (H3 to H6)

The second and third primary objectives were to compare the anti-PnPs serotype-specific IgG GMCs between V114 and Prevnar 13 at 30 days PD3 and 30 days PD4, respectively. The objectives were assessed via the following non-inferiority hypotheses:

H0: $GMC_1/GMC_2 \leq 0.5$ versus

H1: $GMC_1/GMC_2 > 0.5$.

For the 13 shared serotypes contained in V114 and Prevnar 13, GMC_1 is the anti-PnPs serotype-specific IgG GMCs for the V114 group and GMC_2 is the anti-PnPs serotype specific IgG GMCs for the Prevnar 13 group. For the 2 serotypes unique to V114, GMC_1 is the anti-PnPs serotype-specific IgG GMCs of the 2 unique serotypes for the V114 group and GMC_2 is the lowest anti-PnPs IgG GMCs among all 13 shared serotypes, excluding serotype 3, for the Prevnar 13 group. V114 is non-inferior to Prevnar 13 if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13) is greater than 0.5. Estimation of the IgG GMC ratios and corresponding 95% CIs were performed using a t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody concentrations as the response and a single term for vaccination group.

- Statistical Analysis for Secondary Immunogenicity Endpoints
    o   Secondary Endpoints/Hypotheses (H7 to H11)

To address the secondary objectives for evaluating the concomitant vaccines, between-group comparison was made based on the response rate of the antigens contained in Pentacel at 30 days PD3 and the antigens contained in VAQTA, M-M-RII, VARIVAX, and HIBERIX at 30 days PD4. The response rate was defined as the proportion of participants achieving the antigen-specific threshold value. Each objective was assessed via the following non-inferiority hypotheses:

H0: $p_1 - p_2 \leq \delta$ versus

H1: $p_1 - p_2 > \delta$,

where p_1 is the response rate for the V114 group, p_2 is the response rate for the Prevnar 13 group, and δ is the pre-specified non-inferiority margin. The concomitant vaccine administered concomitantly with V114 is non-inferior to the concomitant vaccine administered concomitantly with Prevnar 13 if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13) is greater than δ. The M&N method was used for this analysis.

In addition, the between-group comparison was made based on the antigen-specific GMCs of pertussis contained in Pentacel at 30 days PD3. The objective was assessed via the following non-inferiority hypotheses:

H0: $GMC_1/GMC_2 \leq 0.67$ versus

H1: $GMC_1/GMC_2 > 0.67$,

where GMC_1 is the antigen-specific pertussis GMCs for the V114 group and GMC_2 is the antigen-specific pertussis GMCs for the Prevnar 13 group. V114 is non-inferior to Prevnar 13 if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13) is greater than 0.67. Estimation of the GMC ratios and corresponding 95% CIs were performed using a t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody concentrations as the response and a single term for vaccination group.

o   Secondary Endpoints/Hypotheses (H12, H13, and H14)

To address the secondary objectives for evaluating the 2 unique V114 serotypes, between-group comparisons were made based on the anti-PnPs serotype-specific IgG response rates and GMCs at 30 days PD3, and the anti-PnPs serotype-specific IgG GMCs at 30 days PD4, for the 2 V114 unique serotypes. The comparison of the response rates was assessed via the following superiority hypotheses:

H0: $p_1-p_2 \leq 0.1$ versus

H1: $p_1-p_2 > 0.1$,

where p_1 is the response rate for the V114 group and p_2 is the response rate for the Prevnar 13 group. V114 is superior to Prevnar 13 if the lower bound of the 2-sided 95% CI for the between-treatment differences (V114 minus Prevnar 13) is greater than 0.1. The M&N method was used for this analysis.

The comparison of the GMCs was assessed via the following superiority hypotheses:

H0: $GMC_1/GMC_2 \leq 2.0$ versus

H1: $GMC_1/GMC_2 > 2.0$,

where GMC_1 is the anti-PnPs serotype-specific IgG GMCs for the V114 group and GMC_2 is the anti-PnPs serotype-specific IgG GMCs for the Prevnar 13 group. V114 is superior to Prevnar 13 if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13) is greater than 2.0. Estimation of the IgG GMC ratios and corresponding 95% CIs were performed using a t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody concentrations as the response and a single term for vaccination group.

o   Secondary Endpoints/Hypotheses (H15, H16, and H17)

To address the secondary objectives for evaluating the superiority of serotype 3, between-group comparisons were made based on the anti-PnPs serotype 3 IgG response rates and GMCs at 30 days PD3, and the anti-PnPs serotype 3 IgG GMCs at 30 days PD4. The comparison of the response rates was assessed via the following superiority hypothesis:

H0: $p_1-p_2 \leq 0$ versus

H1: $p_1-p_2 > 0$,

where p_1 is the response rate for the V114 group and p_2 is the response rate for the Prevnar 13 group. V114 is superior to Prevnar 13 if the lower bound of the 2-sided 95%

CI for the between-treatment differences (V114 minus Prevnar 13) is greater than 0. The M&N method was used for this analysis.

The comparison of the GMCs was assessed via the following superiority hypotheses:

H_0: $GMC_1/GMC_2 \leq 1.2$ versus

H_1: $GMC_1/GMC_2 > 1.2$,

where GMC_1 is the anti-PnPs serotype 3 IgG GMCs for the V114 group and GMC_2 is the anti-PnPs serotype 3 IgG GMCs for the Prevnar 13 group. V114 is superior to Prevnar 13 if the lower bound of the 2-sided 95% CI for the GMC ratios (V114/Prevnar 13) is greater than 1.2. Estimation of the IgG GMC ratios and corresponding 95% CIs were performed using the t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody concentrations as the response and a single term for vaccination group.

- Statistical Methods for Safety Analyses

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

- Multiplicity adjustment

The study is considered to have met its primary objectives if non-inferiority is demonstrated for the 13 shared serotypes and for the 2 unique serotypes for IgG GMCs and IgG response rates at 30 days PD3 and for IgG GMCs at 30 days PD4. All hypotheses were tested individually for each serotype at a 1-sided 0.025 alpha level. This approach controls the 1-sided type-I error rate at 0.025, thus no multiplicity adjustment is required.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed
6.1.10.1.1 Demographics
Demographic and baseline characteristics were generally comparable between intervention groups. The median age of participants at the time of consent was 8.0 weeks (range: 6 to 12 weeks). Approximately 52% of the participants were male; 55% were white, and 26% were Asian. The majority (>74%) of participants were of non-Hispanic or Latino ethnicity. Approximately 9% of participants were preterm infants (gestational age <37 weeks).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.1.10.1.3 Subject Disposition

The disposition of participants was generally comparable in both intervention groups (Table 3):

- A total of 1720 participants were randomized (1714 were vaccinated).
- There were 2 different pentavalent combination vaccines used in this study: Pentacel was used at study sites located in the US and Puerto Rico, and Pentavac was used at study sites located in Turkey and Thailand. A total of 1204 participants received Pentacel at study sites in the US and Puerto Rico. Since Pentavac is not licensed in the U.S., the immunogenicity analyses are focused on the subjects who received US-licensed Pentacel in this review memo. As a result, the sample size is reduced by 30% from all enrolled population in these analyses. Because randomization in the study was stratified by site, randomization maintained when excluding all subjects enrolled in Turkey and Thailand, where Pentavac was given. The proportion of participants who received Pentacel was generally comparable between intervention groups.
- Of the participants who received Pentacel, most (>99%) participants received the first dose of all protocol-specified study interventions; a majority (>80%) received all subsequent doses.
- Of the participants who received Pentacel, the majority (>80%) of participants in each intervention group completed the study. The most common reasons for discontinuing study intervention in both intervention groups were withdrawal by parent/guardian (10.0%) and lost to follow-up (5.0%). The disposition of participants was generally comparable in both intervention groups (Table 3).

Table 3. Disposition of Participants (All Randomized Participants)
(Excluding Participants Who Received Pentavac)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Total n	Total (%)
Participants in population	600		604		1,204	
Vaccinated at ~2 months of age with						
PCV	598	(99.7)	601	(99.5)	1,199	(99.6)
Pentacel™	598	(99.7)	601	(99.5)	1,199	(99.6)
RECOMBIVAX HB™	598	(99.7)	601	(99.5)	1,199	(99.6)
RotaTeq™	598	(99.7)	601	(99.5)	1,199	(99.6)
Vaccinated at ~4 months of age with						
PCV	584	(97.3)	571	(94.5)	1,155	(95.9)
Pentacel™	584	(97.3)	571	(94.5)	1,155	(95.9)
RECOMBIVAX HB™	14	(2.3)	14	(2.3)	28	(2.3)
RotaTeq™	584	(97.3)	571	(94.5)	1,155	(95.9)
Vaccinated at ~6 months of age with						
PCV	559	(93.2)	541	(89.6)	1,100	(91.4)
Pentacel™	559	(93.2)	541	(89.6)	1,100	(91.4)
RECOMBIVAX HB™	559	(93.2)	541	(89.6)	1,100	(91.4)
RotaTeq™	559	(93.2)	540	(89.4)	1,099	(91.3)
Vaccinated at ~12 to 15 months of age with						
PCV	532	(88.7)	508	(84.1)	1,040	(86.4)
VAQTA™	532	(88.7)	507	(83.9)	1,039	(86.3)

M-M-R™ II	531	(88.5)	506	(83.8)	1,037	(86.1)
VARIVAX™	531	(88.5)	506	(83.8)	1,037	(86.1)
HIBERIX™	532	(88.7)	508	(84.1)	1,040	(86.4)
Trial Disposition						
Completed	509	(84.8)	493	(81.6)	1,002	(83.2)
Discontinued	91	(15.2)	111	(18.4)	202	(16.8)
Death	1	(0.2)	0	(0.0)	1	(0.1)
Lost To Follow-Up	34	(5.7)	26	(4.3)	60	(5.0)
Physician Decision	7	(1.2)	14	(2.3)	21	(1.7)
Withdrawal By Parent/Guardian	49	(8.2)	71	(11.8)	120	(10.0)

Source: Table 10 in the Clinical Information Amendment submitted in STN 125741/6.13.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

- Serotype-specific IgG Response Rates at 30 Days Postdose 3
  - o V114 met noninferiority criteria for the 13 shared serotypes as assessed by the proportions of participants meeting the IgG threshold value of ≥0.35μg/mL (response rates) for each serotype at 30 days PD3 (Table 4). The lower bound of the 2-sided 95% CI for the difference in the response rates [V114 minus Prevnar 13] was greater than -10% for each shared serotype.
  - o V114 met noninferiority criteria for the 2 unique serotypes as assessed by the response rate for serotypes 22F and 33F compared with the response rate for serotype 23F (lowest response rate of the shared serotypes in Prevnar 13, excluding serotype 3) at 30 days PD3. The lower bound of the 2-sided 95% CI for the difference in the response rates [V114 minus Prevnar 13] was greater than -10% for each serotype (Table 5).

Table 4. Analysis of the Proportions of Participants with IgG ≥0.35μg/mL for the 13 Shared Serotypes at 30 Days Postdose 3 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
13 Shared Serotypes (Non-inferiority)			
1	93.8 (427/455)	98.6 (424/430)	-4.8 (-7.5, -2.4)
3	93.1 (421/452)	74.0 (316/427)	19.1 (14.4, 24.0)
4	94.7 (428/452)	98.1 (420/428)	-3.4 (-6.1, -1.0)
5	93.4 (425/455)	96.0 (412/429)	-2.6 (-5.7, 0.3)
6A	92.7 (422/455)	99.3 (425/428)	-6.6 (-9.4, -4.2)
6B	86.7 (392/452)	89.9 (384/427)	-3.2 (-7.5, 1.1)
7F	98.7 (448/454)	100.0 (430/430)	-1.3 (-2.9, -0.4)
9V	96.7 (438/453)	97.2 (414/426)	-0.5 (-2.9, 1.9)
14	97.8 (443/453)	98.1 (418/426)	-0.3 (-2.4, 1.7)

Pneumococcal Serotype	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
18C	96.2 (436/453)	98.1 (419/427)	-1.9 (-4.3, 0.3)
19A	97.4 (443/455)	99.8 (429/430)	-2.4 (-4.3, -1.0)
19F	98.5 (446/453)	100.0 (428/428)	-1.5 (-3.2, -0.6)
23F	89.8 (406/452)	91.4 (391/428)	-1.5 (-5.4, 2.4)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response.
Source: Table 13 in the Clinical Information Amendment submitted in STN 125741/6.13.

Table 5. Analysis of the Proportions of Participants with IgG ≥0.35μg/mL for the 2 Serotypes Unique to V114 at 30 Days Postdose 3 (Comparison to the Lowest Observed Response Rate in Prevnar 13, Excluding Serotype 3) (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype in V114	V114 (N=598) Observed Response Percentage (m/n)	Pneumococcal Serotype in Prevnar 13	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
22F	98.0 (445/454)	6B	89.9 (384/427)	8.1 (5.1, 11.5)
33F	84.8 (386/455)	6B	89.9 (384/427)	-5.1 (-9.5, -0.7)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response.
Source: Table 14 in the Clinical Information Amendment submitted in STN 125741/6.13.

- Serotype-specific IgG GMCs at 30 Days Postdose 3
    - V114 met noninferiority criteria for 12 of the 13 shared serotypes as assessed by serotype-specific IgG GMCs at 30 days PD3. The lower bound of the 2-sided 95% CI for serotype-specific IgG GMC ratio (V114 / Prevnar 13) was greater than 0.5 for 12 of the 13 shared serotypes (Table 6). The antibody response to serotype 6A missed the pre-specified statistically noninferiority criterion by a small margin (the lower bound of the 2-sided 95% CI for the GMC ratio being 0.48 versus >0.5).
    - V114 met noninferiority criteria for the 2 unique V114 serotypes as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F compared with the IgG GMC for serotype 4 (lowest IgG GMC of the shared serotypes in Prevnar 13, excluding serotype 3) at 30 days PD3. The lower bound of the 2-sided 95% CI for serotype-specific IgG GMC ratio (V114 / Prevnar 13) was greater than 0.5 for each serotype (Table 7).

Table 6. Analysis of IgG GMCs for the 13 Shared Serotypes at 30 Days Postdose 3 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype	V114 (N=598) n	V114 (N=598) GMC	Prevnar13 (N=601) n	Prevnar13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
13 Shared Serotypes (Non-inferiority)					
1	455	1.02	430	1.54	0.66 (0.61, 0.73)
3	452	0.96	427	0.56	1.70 (1.54, 1.86)
4	452	1.07	428	1.11	0.97 (0.89, 1.06)
5	455	1.29	429	1.69	0.76 (0.68, 0.85)
6A	455	1.33	428	2.48	0.53 (0.48, 0.60)
6B	452	1.42	427	1.58	0.90 (0.76, 1.06)
7F	454	2.17	430	2.83	0.77 (0.70, 0.84)
9V	453	1.47	426	1.48	1.00 (0.90, 1.10)
14	453	4.17	426	5.57	0.75 (0.66, 0.85)
18C	453	1.29	427	1.55	0.83 (0.76, 0.91)
19A	455	1.39	430	1.88	0.74 (0.67, 0.82)
19F	453	1.82	428	2.33	0.78 (0.72, 0.85)
23F	452	1.09	428	1.23	0.89 (0.79, 1.01)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis.
Source: Table 15 in the Clinical Information Amendment submitted in STN 125741/6.13.

Table 7. Analysis of IgG GMCs for the 2 Serotypes Unique to V114 at 30 Days Postdose 3 (Comparison to the Lowest Observed GMC in Prevnar 13, Excluding Serotype 3) (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype in V114	V114 (N=598) n	V114 (N=598) GMC	Pneumococcal Serotype in Prevnar 13	Prevnar 13 (N=601) n	Prevnar 13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
22F	454	4.01	4	428	1.11	3.63 (3.26, 4.04)
33F	455	1.38	4	428	1.11	1.25 (1.09, 1.44)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis.
Source: Table 16 in the Clinical Information Amendment submitted in STN 125741/6.13.

- Serotype-specific IgG GMCs at 30 days Postdose 4
  - V114 met noninferiority criteria for the 13 shared serotypes as assessed by serotype-specific IgG GMCs at 30 days PD4. The lower bound of the 2-sided 95% CI for serotype-specific IgG GMC ratio (V114 / Prevnar 13) was greater than 0.5 for each shared serotype (Table 8).
  - V114 met noninferiority criteria for the 2 unique V114 serotypes as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F compared with IgG GMC for serotype 4 (lowest IgG GMC of the shared serotypes in Prevnar 13, excluding serotype 3) at 30 days PD4. The lower bound of the 2-sided 95% CI for serotype-

specific IgG GMC ratio (V114 / Prevnar 13) was greater than 0.5 for each serotype (Table 9).

Table 8. Analysis of IgG GMCs for the 13 Shared Serotypes at 30 Days Postdose 4 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype 13 Shared Serotypes (Non-inferiority)	V114 (N=598) n	V114 (N=598) GMC	Prevnar 13 (N=601) N	Prevnar 13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
1	469	1.21	446	1.82	0.66 (0.60, 0.73)
3	466	0.91	447	0.63	1.43 (1.30, 1.57)
4	467	1.07	443	1.42	0.76 (0.68, 0.84)
5	467	2.21	443	3.47	0.64 (0.57, 0.71)
6A	467	3.56	443	5.93	0.60 (0.54, 0.67)
6B	466	4.70	443	6.07	0.77 (0.69, 0.87)
7F	468	3.22	447	4.65	0.69 (0.62, 0.77)
9V	470	2.18	447	2.86	0.76 (0.69, 0.84)
14	470	5.09	446	6.21	0.82 (0.72, 0.93)
18C	467	2.37	445	2.59	0.92 (0.82, 1.02)
19A	469	3.86	446	4.93	0.78 (0.71, 0.86)
19F	469	3.32	446	4.02	0.83 (0.75, 0.91)
23F	467	1.85	444	2.88	0.64 (0.57, 0.72)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis.
Source: Table 17 in the Clinical Information Amendment submitted in STN 125741/6.13.

Table 9 Analysis of IgG GMCs for the 2 Serotypes Unique to V114 at 30 Days Postdose 4 (Comparison to the Lowest Observed GMC in Prevnar 13, Excluding Serotype 3) (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype in V114	V114 (N=598) n	V114 (N=598) GMC	Pneumococcal Serotype in Prevnar 13	Prevnar 13 (N=601) n	Prevnar 13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
22F	468	6.76	4	443	1.42	4.77 (4.28, 5.32)
33F	468	3.80	4	443	1.42	2.68 (2.40, 3.00)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis.
Source: Table 18 in the Clinical Information Amendment submitted in STN 125741/6.13.

6.1.11.2 Analyses of Secondary Endpoints

- Responses to Antigens in Pentacel at 30 Days Postdose 3
  - o Immune responses to Pentacel administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants meeting specified antibody responses to antigens included in Pentacel (response rates) at 30 days PD3. The lower bound of the 2-sided 95% CI for the difference in response rates (V114 group minus Prevnar 13 group) was greater than the specified noninferiority margin for each antigen (Table 10).

o Immune responses to Pentacel administered concomitantly with V114 met noninferiority criteria as assessed by the antigen-specific GMCs of pertussis antigens contained in Pentacel at 30 days PD3. The lower bound of the 2-sided 95% CI for the GMC ratio (V114 group / Prevnar 13 group) was greater than 0.67 for each antigen (Table 11).

Table 10. Analysis of the Proportions of Participants Meeting Specified Pentacel Antigen Responses at 30 Days Postdose 3 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
Diphtheria toxoid	% ≥0.1 IU/mL	-10%	95.4 (435/456)	96.3 (415/431)	-0.9 (-3.6, 1.8)
Tetanus toxoid	% ≥0.1 IU/mL	-5%	100.0 (456/456)	99.8 (430/431)	0.2 (-0.6, 1.3)
Pertussis - PT	% ≥5 EU/mL	-10%	98.5 (449/456)	97.7 (421/431)	0.8 (-1.1, 2.9)
Pertussis - FHA	% ≥5 EU/mL	-10%	98.7 (450/456)	99.1 (427/431)	-0.4 (-2.0, 1.2)
Pertussis - FIM 2/3	% ≥20 EU/mL	-10%	92.8 (423/456)	91.0 (392/431)	1.8 (-1.8, 5.5)
Pertussis - PRN	% ≥5 EU/mL	-10%	95.0 (433/456)	93.0 (401/431)	1.9 (-1.2, 5.2)
Poliovirus 1	% with NAb≥1:8 dilution	-5%	99.8 (417/418)	99.7 (388/389)	0.0 (-1.1, 1.2)
Poliovirus 2	% with NAb≥1:8 dilution	-5%	100.0 (410/410)	100.0 (386/386)	0.0 (-0.9, 1.0)
Poliovirus 3	% with NAb≥1:8 dilution	-5%	100.0 (410/410)	100.0 (384/384)	0.0 (-0.9, 1.0)
Hib-PRP	% ≥0.15 µg/mL	-10%	89.3 (358/401)	90.8 (345/380)	-1.5 (-5.8, 2.8)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response.
Source: Table 19 in the Clinical Information Amendment submitted in STN 125741/6.13.

Table 11. Analysis of Antigen-specific GMCs of Pertussis Contained in Pentacel at 30 Days Postdose 3 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Antigen	V114 (N=598) n	V114 (N=598) GMC	Prevnar 13 (N=601) n	Prevnar 13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
Pertussis - PT	456	33.40	431	33.12	1.01 (0.89, 1.14)
Pertussis - FHA	456	41.95	431	45.16	0.93 (0.82, 1.05)
Pertussis - FIM 2/3	456	100.70	431	91.85	1.10 (0.94, 1.27)
Pertussis - PRN	456	32.27	431	33.59	0.96 (0.83, 1.12)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis,
Source: Table 20 in the Clinical Information Amendment submitted in STN 125741/6.13.

- Response Rates to Anti-Hepatitis A Antigens at 30 Days Postdose 4

Immune responses to VAQTA administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with antibody concentration ≥10 mIU/mL to anti-hepatitis A antigen (response rates) at 30 days PD4. The lower bound of the 2-sided 95% CI for the difference in response rates (V114 group minus Prevnar 13 group) was greater than -10% (the specified noninferiority margin) (Table 12).

Table 12. Analysis of the Proportions of Participants Meeting Specified VAQTA Antigen Responses at 30 Days Postdose 4 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
Hepatitis A	% ≥10 mIU/mL	-10%	97.3 (394/405)	97.4 (381/391)	-0.2 (-2.6, 2.2)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response.
Source: Table 1 in the Clinical Information Amendment submitted in STN 125741/6.17.

- Response Rates to Antigens in M-M-RII at 30 days Postdose 4

Immune responses to M-M-RII administered concomitantly with V114 met noninferiority criteria, as assessed by the proportions of participants, specified for antibody responses to measles and rubella antigens (response rates) at 30 days PD4. The responses to mumps antigen missed the prespecified noninferiority margin of -5% (Table 13).

Table 13. Analysis of the Proportions of Participants Meeting Specified M-M-RII Antigen Responses at 30 Days Postdose 4 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
Measles	% ≥255 mIU/mL	-5%	97.9 (457/467)	98.4 (438/445)	-0.6 (-2.5, 1.3)
Mumps	% ≥10 mumps Ab units/mL	-5%	94.4 (441/467)	97.1 (432/445)	-2.6 (-5.4, -0.0)
Rubella	% ≥10 IU/mL	-5%	97.2 (454/467)	98.9 (440/445)	-1.7 (-3.7, 0.2)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response.
Source: Table 2 in the Clinical Information Amendment submitted in STN 125741/6.17.

- Response Rates to Anti-Varicella Antigens at 30 Days Postdose 4

Immune responses to VARIVAX administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with antibody concentration ≥5 (b) (4) units/ml to anti-varicella antigen (response rates) at 30 days PD4. The lower bound of the 2-sided 95% CI for the difference in response rates (V114

group minus Prevnar 13 group) was greater than -10% (the specified noninferiority margin) (Table 14).

Table 14. Analysis of the Proportions of Participants Meeting Specified VARIVAX Antigen Responses at 30 Days Postdose 4 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
VZV	% ≥5 (b) (4) units/ml	-10%	97.2 (456/469)	97.3 (434/446)	-0.1 (-2.3, 2.2)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response
Source: Table 3 in the Clinical Information Amendment submitted in STN 125741/6.17.

- Response Rates to Anti-PRP Antigens at 30 days Postdose 4
Immune responses to HIBERIX administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with antibody concentration ≥0.15μg/mL to anti-PRP antigen (response rates) at 30 days PD4. The lower bound of the 2-sided 95% CI for the difference in response rates (V114 group minus Prevnar 13 group) was greater than -10% (the specified noninferiority margin) (Table 15).

Table 15 Analysis of the Proportions of Participants Meeting Specified HIBERIX Antigen Responses at 30 Days Postdose 4 (Per-Protocol Population)
(Excluding Participants Who Received Pentavac)

Antigen	Endpoint	Non-inferiority Margin	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
Hib-PRP	% ≥0.15 μg/mL	-10%	98.5 (401/407)	100.0 (392/392)	-1.5 (-3.2, -0.5)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response
Source: Table 4 in the Clinical Information Amendment submitted in STN 125741/6.17. .

- Serotypes 22F and 33F IgG Responses at 30 Days Postdose 3
  - V114 was statistically significantly higher in the proportions of participants with IgG ≥0.35μg/mL (response rates) than Prevnar 13 for serotypes 22F and 33F at 30 days PD3. The lower bound of the 2-sided 95% CI for the difference in response rates (V114 minus Prevnar 13) was greater than 10% for each serotype (Table 16).
  - V114 was statistically significantly higher in the serotype specific IgG GMC than Prevnar 13 for serotypes 22F and 33F at 30 days PD3. The lower bound of the 2-

sided 95% CI for serotype specific IgG GMC ratio (V114/Prevnar 13) was greater than 2.0 for each serotype (Table 17).

Table 16. Analysis of the Proportions of Participants with IgG ≥0.35μg/mL for the 2 Serotypes Unique to V114 at 30 Days Postdose 3 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
22F	98.0 (445/454)	3.3 (14/425)	94.7 (92.1, 96.5)
33F	84.8 (386/455)	1.9 (8/429)	83.0 (79.1, 86.2)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response
Source: Table 1 in the Clinical Information Amendment submitted in STN 125741/6.15.

Table 17. Analysis of IgG GMCs for the 2 Serotypes Unique to V114 at 30 Days Postdose 3 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype in V114	V114 (N=598) n	V114 (N=598) GMC	Prevnar 13 (N=601) n	Prevnar 13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
22F	454	4.01	425	0.05	83.58 (73.75, 94.73)
33F	455	1.38	429	0.05	28.15 (24.24, 32.70)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis.
Source: Table 2 in the Clinical Information Amendment submitted in STN 125741/6.15.

- Serotypes 22F and 33F IgG GMCs at 30 Days Postdose 4

V114 was statistically significantly higher in the serotype specific IgG GMCs than Prevnar 13 for serotypes 22F and 33F at 30 days PD4. The lower bound of the 2-sided 95% CI for serotype specific IgG GMC ratio (V114/Prevnar 13) was greater than 2.0 for each serotype (Table 18).

Table 18 Analysis of IgG GMCs for the 2 Serotypes Unique to V114 at 30 Days Postdose 4 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype in V114	V114 (N=598) n	V114 (N=598) GMC	Prevnar 13 (N=601) n	Prevnar 13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
22F	468	6.76	443	0.09	72.52 (65.07, 80.82)
33F	468	3.80	441	0.08	45.25 (40.37, 50.73)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response
Source: Table 3 in the Clinical Information Amendment submitted in STN 125741/6.15. Table 11-15 in Study V114-029 CSR.

- Serotype 3 IgG Responses at 30 Days Postdose 3
  - o V114 was statistically significantly higher in the proportion of participants with IgG ≥0.35μg/mL than Prevnar 13 for serotype 3 at 30 days PD3. The lower bound

of the 2-sided 95% CI for the difference in response rates (V114 minus Prevnar 13) was greater than 0% (Table 19).
  o V114 was statistically significantly higher in the serotype-specific IgG GMCs than Prevnar 13 for serotype 3 at 30 days PD3. The lower bound of the 2-sided 95% CI for the serotype-specific IgG GMC ratio (V114/Prevnar 13) was greater than 1.2 (Table 20).

Table 19. Analysis of the Proportions of Participants with IgG ≥0.35μg/mL For Serotype 3 at 30 Days Postdose 3 (Per-Protocol Population)
(Excluding Participants Who Received Pentavac)

Pneumococcal Serotype	V114 (N=598) Observed Response Percentage (m/n)	Prevnar 13 (N=601) Observed Response Percentage (m/n)	Percentage Point Difference (V114 - Prevnar 13) Estimate (95% CI)
3	93.1 (421/452)	74.0 (316/427)	19.1 (14.4, 24.0)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis, m=Number of participants with the indicated response
Source: Table 4 in the Clinical Information Amendment submitted in STN 125741/6.15.

Table 20. Analysis of IgG GMCs For Serotype 3 at 30 Days Postdose 3 (Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype	V114 (N=598) n	V114 (N=598) GMC	Prevnar 13 (N=601) n	Prevnar 13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
3	452	0.96	427	0.56	1.70 (1.54, 1.86)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis,
Source: Table 5 in the Clinical Information Amendment submitted in STN 125741/6.15.

- Serotype 3 IgG GMCs at 30 Days Postdose 4
V114 was statistically significantly higher in the serotype-specific IgG GMCs than Prevnar 13 for serotype 3 at 30 days PD4. The lower bound of the 2-sided 95% CI for the serotype-specific IgG GMC ratio (V114/Prevnar 13) was greater than 1.2 (Table 21).

Table 21. Analysis of IgG GMCs For Serotype 3 at 30 Days Postdose 4
(Per-Protocol Population) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype	V114 (N=598) n	V114 (N=598) GMC	Prevnar 13 (N=601) n	Prevnar 13 (N=601) GMC	GMC Ratio (V114 / Prevnar 13) Estimate (95% CI)
3	466	0.91	447	0.63	1.43 (1.30, 1.57)

Note: N=Number of participants randomized and vaccinated, n=Number of participants contributing to the analysis,
Source: Table 6 in the Clinical Information Amendment submitted in STN 125741/6.15.

Reviewer Comments:
- *My analysis showed similar results for the primary and secondary immunogenicity endpoint analyses.*
- *V114 met noninferiority criteria for 12 of the 13 shared serotypes as assessed by serotype-specific IgG GMCs at 30 days PD3. The antibody response to serotype 6A*

missed the pre-specified statistical criteria for noninferiority (the lower bound of the 2-sided 95% CI for the GMC ratio being 0.48 versus the criterion >0.5). This difference appears to be numerically small and may not be clinically meaningful. Therefore, the immunogenicity results appear to be generally adequate to support the proposed indication based on the totality of evidence.

- *Among the subjects who received Pentacel, immune responses to M-M-RII administered concomitantly with V114 missed the noninferiority criteria specified for antibody responses to mumps antigen at 30 days PD4. This difference appears to be numerically small. I defer to the clinical reviewers on whether this difference is clinically meaningful.*

6.1.11.3 Subpopulation Analyses
Serotype-specific IgG GMCs and response rates at 30 days PD3 and serotype-specific IgG GMCs at 30 days PD4 for all 15 serotypes within sex, race, and ethnicity groups were generally consistent with the results observed in the overall population.

6.1.11.4 Dropouts and/or Discontinuations
Please refer to section 6.1.10.1.3.

6.1.11.5 Exploratory and Post Hoc Analyses
N/A

6.1.12 Safety Analyses

The proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, and SAEs were generally comparable between intervention groups (Table 22 and 23). AEs were reported for the majority (>92%) of participants in both intervention groups. SAEs were reported for approximately 10% of participants; none were considered by the investigator to be related to study intervention. No participant discontinued study intervention due to an AE. Two participants died during the study (1 participant in the V114 group and 1 participant in the Prevnar 13 group); both deaths were assessed by the investigator to be not related to the study vaccine.

The proportions of participants with AEs and SAEs following each dose of study intervention were generally comparable between intervention groups.

Table 22. Analysis of Adverse Event Summary (All Participants as Treated Population) (Following Any Dose)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Difference in % vs. Prevnar 13 Estimate (95% CI)
Participants in population	858		855		
with one or more adverse events	805	(93.8)	790	(92.4)	1.4 (-1.0, 3.9)
injection-site	598	(69.7)	595	(69.6)	
systemic	785	(91 5)	766	(89.6)	
with no adverse event	53	(6 2)	65	(7.6)	
with vaccine-related adverse events	758	(88.3)	740	(86.5)	1.8 (-1.4, 5.0)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Difference in % vs. Prevnar 13 Estimate (95% CI)
injection-site	595	(69 3)	593	(69.4)	
systemic	651	(75 9)	646	(75.6)	
with serious adverse events	88	(10 3)	81	(9.5)	0.8 (-2.1, 3.6)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0.0 (-0.4, 0.4)
who died	1	(0 1)	1	(0.1)	-0.0 (-0.6, 0.5)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0.0 (-0.4, 0.4)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	

Source: Table 12-1 in Study V114-029 CSR.

Table 23. Analysis of Participants with Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated Population) (Following Any Dose)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Difference in % vs. Prevnar 13 Estimate (95% CI)
Participants in population	858		855		
with one or more solicited adverse events	768	(89.5)	766	(89.6)	
with no solicited adverse events	90	(10.5)	89	(10.4)	
Solicited injection site adverse events	592	(69.0)	592	(69.2)	
Injection site erythema	289	(33.7)	329	(38.5)	-4.8 (-9.3, -0.2)
Injection site induration	226	(26.3)	229	(26.8)	-0.4 (-4.6, 3.7)
Injection site pain	427	(49.8)	401	(46.9)	2.9 (-1.9, 7.6)
Injection site swelling	226	(26.3)	205	(24.0)	2.4 (-1.7, 6.5)
Solicited systemic adverse events	724	(84.4)	725	(84.8)	
Decreased appetite	294	(34.3)	308	(36.0)	-1.8 (-6.3, 2.8)
Irritability	656	(76.5)	645	(75.4)	1.0 (-3.0, 5.1)
Somnolence	506	(59.0)	530	(62.0)	-3.0 (-7.6, 1.6)
Urticaria	56	(6.5)	56	(6.5)	-0.0 (-2.4, 2.3)

Source: Table 12-3 in Study V114-029 CSR.

Reviewer Comments: The applicant used the clinical event data reported by investigators in the Case Report Forms (eCRF) as the primary data source for the safety analyses. The applicant also submitted the safety data analysis based on clinical event data reported by participants on the Vaccination report card (VRC, not shown here). The results were generally similar between the two data sources except that there appeared to be some numerical differences in the rates of Urticaria. I defer to the clinical reviewers on whether the differences are clinically substantial.

In participants who received Pentacel, the proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, and SAEs were generally comparable

between intervention groups (Tables 24 and 25). AEs were reported for the majority (>94%) of participants in both intervention groups. No SAEs were considered by the investigator to be related to study intervention. No participant discontinued study intervention due to an AE. One participant died during the study (V114 group); this death was assessed by the investigator to be not related to the study vaccine.

Table 24. Analysis of Adverse Event Summary (All Participants as Treated Population) (Following Any Dose) (Excluding Participants Who Received Pentavac)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Difference in % vs. Prevnar 13 Estimate (95% CI)
Participants in population	598		600		
with one or more adverse events	575	(96.2)	566	(94.3)	1.8 (-0.6, 4.3)
injection-site	475	(79.4)	467	(77.8)	
systemic	562	(94.0)	548	(91.3)	
with no adverse event	23	(3.8)	34	(5.7)	
with vaccine-related adverse events	547	(91.5)	533	(88.8)	2.6 (-0.7, 6.1)
injection-site	473	(79 1)	465	(77.5)	
systemic	471	(78.8)	460	(76.7)	
with serious adverse events	38	(6.4)	40	(6.7)	-0.3 (-3.2, 2.5)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
who died	1	(0 2)	0	(0.0)	0.2 (-0.5, 0.9)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0.0 (-0.6, 0.6)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	

Source: Table 21 in the Clinical Information Amendment submitted in STN 125741/6.13.

Table 25. Analysis of Participants with Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) (All Participants as Treated Population) (Following Any Dose) (Excluding Participants Who Received Pentavac)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Difference in % vs. Prevnar 13 Estimate (95% CI)
Participants in population	598		600		
with one or more solicited adverse events	559	(93.5)	556	(92.7)	
with no solicited adverse events	39	(6.5)	44	(7.3)	
Solicited injection site adverse events	469	(78.4)	465	(77.5)	
Injection site erythema	243	(40.6)	269	(44.8)	-4.2 (-9.8, 1.4)
Injection site induration	197	(32.9)	190	(31.7)	1.3 (-4.0, 6.6)
Injection site pain	344	(57.5)	338	(56.3)	1.2 (-4.4, 6.8)
Injection site swelling	178	(29.8)	152	(25.3)	4.4 (-0.6, 9.5)
Solicited systemic adverse events	529	(88.5)	528	(88.0)	
Decreased appetite	231	(38.6)	238	(39.7)	-1.0 (-6.6, 4.5)

	V114 n	V114 (%)	Prevnar 13 n	Prevnar 13 (%)	Difference in % vs. Prevnar 13 Estimate (95% CI)
Irritability	485	(81.1)	484	(80.7)	0.4 (-4.0, 4.9)
Somnolence	376	(62.9)	399	(66.5)	-3.6 (-9.0, 1.8)
Urticaria	36	(6.0)	34	(5.7)	0.4 (-2.4, 3.1)

Source: Table 22 in the Clinical Information Amendment submitted in STN 125741/6.13.

6.1.12.1 Methods

Please see Statistical Methods for Safety Analyses in section 6.1.9.

6.1.12.3 Deaths

Two participants died during the study (1 participant in the V114 group and 1 participant in the Prevnar 13 group); both deaths were assessed by the investigator to be not related to the study vaccine.

6.1.12.4 Nonfatal Serious Adverse Events

The proportions of participants with SAEs were comparable between intervention groups (V114 6.4% vs. Prevnar 13 6.7%). None of the SAEs were assessed by the investigator to be related to the study intervention.

6.1.12.5 Adverse Events of Special Interest (AESI)

No AEs of special interest were identified for this study.

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

There were no discontinuations due to an AE reported in either intervention group.

6.2 Study V114-027: A Phase 3, Multicenter, Randomized, Double-blind Study to Evaluate the Interchangeability of V114 and Prevnar 13 with Respect to Safety, Tolerability, and Immunogenicity in Healthy Infants (PNEU-DIRECTION)

6.2.1 Objectives

6.2.1.1. Primary Objectives

Table 26. Primary Study Objectives and Endpoints for Study V114-027

Objectives	Endpoints
Objective: To evaluate the safety and tolerability of complete V114 (Group 5) and mixed Prevnar 13/V114 dosing schedules (Groups 2, 3, and 4) compared with a complete dosing schedule of Prevnar 13 (Group 1) with respect to the proportion of participants with adverse events (AEs).	Following any vaccination with V114 or Prevnar 13: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination. • Solicited systemic AEs from Day 1 through Day 14 postvaccination. • Vaccine-related serious adverse events (SAEs) through completion of study participation
Objective: To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days following Dose 4 for	Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in V114 and Prevnar 13 at 30 days postdose 4 (PD4)

participants administered mixed dosing schedules of Prevnar 13 /V114 (Groups 2, 3, and 4) compared with participants administered a complete dosing schedule of Prevnar 13 (Group 1).	

Source: section 8 in Study V114-027 CSR.

6.2.1.2 Secondary Objectives

Table 27. Secondary Study Objectives and Endpoints for Study V114-027

Objectives	Endpoints
Objective: To compare the proportion of participants with anti-hepatitis B surface antigen (HBsAg) concentration ≥10 mIU/mL at 30 days following Dose 3 for participants administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RECOMBIVAX HB versus participants administered a complete primary infant series dosing schedule of Prevnar 13 (Groups 1 and 2) concomitantly with RECOMBIVAX HB. **Hypothesis (H1):** RECOMBIVAX HB administered concomitantly with V114 is noninferior to RECOMBIVAX HB administered concomitantly with Prevnar 13 as measured by the proportion of participants with anti-HBsAg concentration ≥10 mIU/mL at 30 days following Dose 3. (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the difference in proportions of participants with anti-HBsAg concentration≥10 mIU/mL [V114 minus Prevnar 13] to be greater than -0.10)	Anti-HBsAg response at 30 days postdose 3 (PD3) of V114 or Prevnar 13
Objective: To compare the anti-rotavirus Immunoglobulin A (IgA) Geometric Mean Titer (GMT) at 30 days following Dose 3 for participants administered a complete primary infant series dosing schedule of V114 (Group 5) concomitantly with RotaTeq versus participants administered a complete primary infant series dosing schedule of Prevnar 13 (Groups 1 and 2) concomitantly with RotaTeq. **Hypothesis (H2)**: RotaTeq administered concomitantly with V114 is noninferior to RotaTeq administered concomitantly with Prevnar 13 as measured by anti-rotavirus IgA GMT at 30 days following Dose 3. (The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the anti-rotavirus IgA GMT ratio [V114/Prevnar 13] to be greater than 0.50)	Anti-rotavirus IgA response at 30 days PD3 of V114 or Prevnar 13™
Objectives: 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 ≥0.35µg/mL) at 30 days following Dose 3 separately for each vaccination group (Groups 1, 2, 3, 4, and 5).	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3
Objective: To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days following Dose 4 for participants administered a complete dosing schedule of V114 (Group 5) compared with participants administered a complete dosing schedule of Prevnar 13 (Group 1).	Anti-PnPs serotype-specific IgG responses for the 13 shared serotypes contained in V114 and Prevnar 13™ at 30 days PD4

Source: section 8 in Study V114-027 CSR.

6.2.2 Design Overview

This was a multicenter, randomized, active-controlled, parallel-group, double-blind interchangeability study to evaluate the safety, tolerability, and immunogenicity of mixed pneumococcal conjugate vaccine (PCV) regimens in infants approximately 2 months of age (Table 28). In 2 intervention groups, infants received a 4-dose series of either Prevnar

13 (Group 1) or V114 (Group 5). In 3 other intervention groups, the immunization series was initiated with Prevnar 13 and changed to V114 at Dose 2, 3 or 4 (Groups 4, 3, and 2, respectively). Infants also received other licensed pediatric vaccines administered concomitantly with the PCV, including RECOMBIVAX HB and RotaTeq. Eligible participants were randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 intervention groups.

6.2.3 Population

Healthy male or female infant approximately 2 months of age, from 42 days to 90 days inclusive, at the time of obtaining the informed consent.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Table 28. V114/Prevnar 13 Dosing Schedule

Intervention Group	Dose 1 (Visit 1, ~2 months of age)	Dose 2 (Visit 2, ~4 months of age)	Dose 3 (Visit 3, ~6 months of age)	Dose 4 (Visit 5, ~12 to 15 months of age)
Group 1	Prevnar 13	Prevnar 13	Prevnar 13	Prevnar 13
Group 2	Prevnar 13	Prevnar 13	Prevnar 13	V114
Group 3	Prevnar 13	Prevnar 13	V114	V114
Group 4	Prevnar 13	V114	V114	V114
Group 5	V114	V114	V114	V114

Source: Table for V114/Prevnar 13 Dosing Schedule in the synopsis of Study V114-027 CSR.

6.2.6 Sites and Centers

This study was conducted at 34 centers in 3 countries.

6.2.7 Surveillance/Monitoring

N/A

6.2.8 Endpoints

Please see sections 6.2.1.1 and 6.2.1.2.

6.2.9 Statistical Considerations & Statistical Analysis Plan

- Sample size determination
  Approximately 900 healthy infants were planned to be randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 intervention groups (180 per group).

- Definitions of analysis populations
  Same as the analysis population definitions in Study V114-029. Please see section 6.1.9.

- Statistical Methods for Primary Immunogenicity Endpoint
The primary immunogenicity analysis was descriptive analysis without formal hypothesis testing. The serotype-specific IgG GMCs for 13 shared serotypes contained in V114 and

Prevnar 13 at 30 days PD4 were compared between groups through the estimation of serotype specific IgG GMC ratios for each serotype. The IgG GMC ratios and corresponding 95% CIs were calculated using an 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.

- Statistical Methods for Secondary Immunogenicity Endpoints

For the secondary objective of the noninferiority evaluation of immunogenicity of RECOMBIVAX HB when given concomitantly with V114 or Prevnar 13, the proportions of participants with anti-HBsAg concentration ≥10 mIU/mL at 30 days PD3 of V114 or Prevnar 13 were compared between groups. The between-treatment difference based on the proportions of participants with anti-HBsAg concentration ≥10 mIU/mL [V114 (Group 5) minus Prevnar 13 (Group 1 + Group 2)] and its 95% CI were calculated using stratified Miettinen and Nurminen method.

For the secondary objective of the noninferiority evaluation of immunogenicity of RotaTeq when given concomitantly with V114 or Prevnar 13, the anti-rotavirus IgA GMT at 30 days PD3 of V114 or Prevnar 13 was compared between groups through the estimation of anti-rotavirus IgA GMT ratios. Estimation of the anti-rotavirus IgA GMT ratio [V114 (Group 5)/Prevnar 13 (Group 1 + Group 2)] and the corresponding 95% CIs were calculated using ANCOVA with vaccination group and stratification factor (hepatitis B vaccination status before enrollment = Yes, No) as covariates.

- Multiplicity adjustment

There was no multiplicity adjustment for the primary immunogenicity objective as there was no formal hypothesis testing. No multiplicity adjustments were made for both secondary objectives/hypotheses for the non-inferiority of immunogenicity of V114 and Prevnar 13 when given concomitant use with RECOMBIVAX HB and RotaTeq.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed
6.2.10.1.1 Demographics
Demographic and baseline characteristics were generally comparable across intervention groups. The median age of participants at the time of consent was 9.0 weeks (range: 6 to 12 weeks). Overall, 52.8% were male, 61.4% were white, and 76.2% were of non-Hispanic or Latino ethnicity. Approximately 10% of participants were preterm infants (gestational age < 37 weeks). Most participants (97.8%) received a hepatitis B vaccination before study enrollment.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.2.10.1.3 Subject Disposition
A total of 900 participants were randomized (896 were vaccinated). A total of 640 participants received Pentacel at study sites in the US and Puerto Rico. The proportion of

participants who received Pentacel was generally comparable across intervention groups. Of the participants who received Pentacel, most (>99%) participants received the first dose of all protocol-specified study interventions; a majority (>90%) received all subsequent doses. The disposition of participants was generally comparable across intervention groups.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoints
Overall, serotype-specific IgG GMCs at 30 days PD4 for the 13 shared serotypes were generally comparable for participants administered mixed regimens and for participants administered a complete dosing regimen of Prevnar 13 as assessed by IgG GMC ratios (Table 29).

Table 29. Analysis of IgG GMCs for the 13 Shared Serotypes at 30 Days Postdose 4 (Per-Protocol Population) (Groups 4, 3, and 2 versus Group 1) (Excluding Participants Who Received Pentavac)

Pneumococcal Serotype	Vaccination Group	N	n	GMC	GMC Ratio (Group 4, 3, 2 / Group 1) Estimate (95% CI)
1	Group 4	127	101	1 51	0.82 (0.67, 1.01)
	Group 3	123	87	1.73	0.94 (0.76, 1.16)
	Group 2	137	109	1 57	0.86 (0.70, 1.05)
	Group 1	129	105	1 84	
3	Group 4	127	101	0.70	1.02 (0.84, 1.23)
	Group 3	123	87	0.61	0.89 (0.73, 1.09)
	Group 2	137	109	0.68	0.99 (0.82, 1.20)
	Group 1	129	106	0 68	
4	Group 4	127	101	1 32	0.75 (0.60, 0.95)
	Group 3	123	87	1 28	0.73 (0.57, 0.93)
	Group 2	137	109	1.47	0.84 (0.66, 1.06)
	Group 1	129	104	1.75	
5	Group 4	127	101	2 98	0.78 (0.62, 0.99)
	Group 3	123	87	3.73	0.98 (0.76, 1.25)
	Group 2	137	109	3.80	1.00 (0.79, 1.26)
	Group 1	129	105	3.81	
6A	Group 4	127	101	4.71	0.88 (0.70, 1.11)
	Group 3	123	87	6 39	1.19 (0.94, 1.52)
	Group 2	137	109	7 19	1.34 (1.07, 1.69)
	Group 1	129	104	5 36	
6B	Group 4	127	101	6 36	1.08 (0.86, 1.36)
	Group 3	123	87	6 30	1.07 (0.84, 1.35)
	Group 2	137	109	8 14	1.38 (1.11, 1.73)
	Group 1	129	104	5.89	
7F	Group 4	127	101	3.75	0.76 (0.60, 0.96)
	Group 3	123	87	5.08	1.03 (0.81, 1.31)
	Group 2	137	109	5 26	1.07 (0.85, 1.34)
	Group 1	129	104	4 93	

Pneumococcal Serotype	Vaccination Group	N	n	GMC	GMC Ratio (Group 4, 3, 2 / Group 1) Estimate (95% CI)
9V	Group 4	127	101	2.61	0.88 (0.72, 1.09)
	Group 3	123	87	2 50	0.84 (0.68, 1.05)
	Group 2	137	109	2.85	0.96 (0.78, 1.18)
	Group 1	129	105	2 96	
14	Group 4	127	101	6.79	1.00 (0.78, 1.28)
	Group 3	123	87	10.07	1.48 (1.15, 1.92)
	Group 2	137	109	9 92	1.46 (1.14, 1.86)
	Group 1	129	104	6.79	
18C	Group 4	127	101	2.67	1.10 (0.88, 1.37)
	Group 3	123	87	3.58	1.48 (1.17, 1.86)
	Group 2	137	109	4.01	1.65 (1.33, 2.06)
	Group 1	129	105	2.43	
19A	Group 4	127	101	4.64	0.84 (0.66, 1.05)
	Group 3	123	87	4.66	0.84 (0.66, 1.07)
	Group 2	137	109	5.55	1.00 (0.80, 1.25)
	Group 1	129	106	5.55	
19F	Group 4	127	101	4.44	0.90 (0.73, 1.10)
	Group 3	123	87	5.18	1.04 (0.84, 1.30)
	Group 2	137	109	5.19	1.05 (0.85, 1.28)
	Group 1	129	106	4.96	
23F	Group 4	127	101	2.26	0.75 (0.58, 0.97)
	Group 3	124	86	2.34	0.78 (0.60, 1.02)
	Group 2	137	108	2.75	0.92 (0.71, 1.18)
	Group 1	129	104	3.00	

Note: N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Source: Table 5 in the Clinical Information Amendment submitted in STN125741/6.13.

6.2.11.2 Analyses of Secondary Endpoints

- Anti-HBsAg Response at 30 Days Postdose 3

Following 3 doses of either V114 (Group 5) or Prevnar 13 (Groups 1 and 2) in the infant primary series, RECOMBIVAX HB administered concomitantly with V114 elicited an immune response that was comparable to that elicited by RECOMBIVAX HB administered concomitantly with Prevnar 13. Responses to RECOMBIVAX HB administered concomitantly with V114 met noninferiority criteria as assessed by the proportions of participants with anti-HBsAg concentration ≥10 mIU/mL at 30 days PD3. The lower bound of the 2-sided 95% CI for the difference in proportions of participants with anti-HBsAg concentration ≥10 mIU/mL [Group 5 minus (Group 1 + Group 2)] was greater than -10% (Table 30).

Table 30. Analysis of the Proportions of Participants with Anti-HBsAg Concentration ≥10 mIU/mL at 30 Days Postdose 3 (Per-Protocol Population) (Group 5 versus Group 1+Group 2) (Excluding Participants Who Received Pentavac)

Antigen	Group 5 (N=124) Observed Response Percentage (m/n)	Group 1+Group 2 (N=266) Observed Response Percentage (m/n)	Percentage Point Difference (Group 5 - Group 1+Group 2) Estimate (95% CI)
Anti-HBsAg	98.0 (100/102)	99.0 (199/201)	-0.9 (-6.0, 2.0)

Note: N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
Source: Table 4 in the Clinical Information Amendment submitted in STN 125741/6.16.

- Anti-rotavirus IgA Response at 30 Days Postdose 3

Following 3 doses of either V114 (Group 5) or Prevnar 13 (Groups 1 and 2) in the infant primary series, RotaTeq administered concomitantly with V114 elicited an immune response that was generally comparable to that elicited by RotaTeq administered concomitantly with Prevnar 13. Responses to RotaTeq administered concomitantly with V114 met noninferiority criteria as assessed by anti-rotavirus IgA GMTs at 30 days PD3. The lower bound of the 2-sided 95% CI of the anti-rotavirus IgA GMT ratio [Group 5/(Group 1 + Group 2)] was greater than 0.50 (Table 31).

Table 31. Analysis of Anti-rotavirus IgA GMTs at 30 Days Postdose 3 (Per-Protocol Population) (Group 5 versus Group 1+Group 2) (Excluding Participants Who Received Pentavac)

Antigen	Group 5 (N=124) n	Group 5 (N=124) GMT	Group1 +Group 2 (N=266) n	Group1+Group 2 (N=266) GMT	GMT Ratio (Group 5/Group 1+Group 2) Estimate (95% CI)
Rotavirus	102	309.1	209	298.1	1.04 (0.72, 1.49)

Note: N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.
Source: Table 5 in the Clinical Information Amendment submitted in STN 125741/6.16.

Reviewer Comment:
My analyses showed similar results for the primary and secondary immunogenicity endpoint analyses.

6.2.11.3 Subpopulation Analyses
Serotype-specific IgG GMCs at 30 days PD4 for the 13 shared serotypes in V114 and Prevnar 13 were generally consistent across sex, race and ethnicity subgroups.

6.2.11.4 Dropouts and/or Discontinuations
Please refer to section 6.2.10.1.3.

6.2.11.5 Exploratory and Post Hoc Analyses
N/A

6.2.12 Safety Analyses

The proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, and SAEs were generally comparable across the intervention groups with complete or mixed V114 dosing regimens compared with a complete dosing regimen of Prevnar 13. The proportions of participants with AEs and SAEs following each dose of study intervention were also generally comparable between intervention groups with complete V114 or mixed dosing regimens compared with a complete dosing regimen of Prevnar 13. The subjects who received Pentacel showed a similar trend.

6.2.12.1 Methods

Safety analysis was performed with descriptive statistics.

6.2.12.3 Deaths

There were no deaths due to AEs reported for this study.

6.2.12.4 Nonfatal Serious Adverse Events

The proportions of participants with SAEs were comparable across intervention groups. Similar results were observed following each dose of study intervention.

6.2.12.5 Adverse Events of Special Interest (AESI)

N/A

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

One participant (Group 3) had an SAE (epilepsy) considered to be related to study intervention (following Dose 2, Prevnar 13 and concomitant vaccinations) and discontinued from the study.

6.3 Study V114-024: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of Catch-up Vaccination Regimens of V114 in Healthy Infants, Children, and Adolescents (PNEU-PLAN)

6.3.1 Objectives

6.3.1.1 Primary Objectives

Table 32. Primary Study Objectives and Endpoints for Study V114-024

Objectives	Endpoints
Objective: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	Following any vaccination with V114: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination • Solicited systemic AEs from Day 1 through Day 14 postvaccination • Vaccine-related serious adverse events (SAEs) through completion of study participation

Objectives	Endpoints
Objective: To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days following the last dose for each vaccination group.	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days after the last dose of study vaccine.

Source: section 8 in Study V114-024 CSR.

6.3.1.2 Secondary Objectives

Table 33. Secondary Study Objectives and Endpoints for Study V114-024

Objective	Endpoints
Objective: To evaluate the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35μg/mL) at 30 days following the last dose for each vaccination group.	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days after the last dose of study vaccine.

Source: section 8 in Study V114-024 CSR.

6.3.2 Design Overview

This was a randomized, active comparator-controlled, parallel-group, multi-site, double-blind study of V114 in healthy children who were either pneumococcal vaccine-naïve or who previously received a partial regimen of licensed PCV (PCV7, PCV10, or PCV13) or a full regimen of PCV7 or PCV10 (Table 34). Approximately 600 individuals were to be randomly assigned, in a 1:1 ratio, to receive either V114 or Prevnar 13. Randomization was stratified by age (7 to 11 months, 12 to 23 months, ≥2 to <6 years, and ≥6 to 17 years [inclusive]). A maximum of 300 participants were to be ≥6 years of age. Participants ≥2 years of age were to be further stratified based on history of prior PCV vaccination status (Yes and No). Participants <2 years of age were to be PCV-naïve.

Table 34. Catch-Up Vaccination Schedules in V114-024

Age at Randomization	PCV Status	Number of Doses of V114 or Prevnar 13	Dose Schedule
7 to 11 months	Naïve	3 doses	**Dose 1:** At randomization **Dose 2:** 4 to 8 weeks after Dose 1 **Dose 3:** 8 to 12 weeks after Dose 2 AND ≥12 months of age
12 to 23 months	Naïve	2 doses	**Dose 1:** At randomization **Dose 2:** 8 to 12 weeks after Dose 1
2 to 17 years	Naïve	1 dose	**Dose 1:** At randomization
	Partial regimen of Prevnar, Synflorix, or Prevnar 13	1 dose	**Dose 1:** At randomization (at least 8 weeks after previous dose of PCV)
	Complete regimen of Prevnar or Synflorix	1 dose	**Dose 1:** At randomization (at least 8 weeks after previous dose of PCV)

Source: Table 1 in Study V114-024 protocol.

6.3.3 Population

Healthy children who were either pneumococcal vaccine-naïve or who previously received a partial regimen of licensed PCV (PCV7, PCV10, or PCV13) or a full regimen of PCV7 or PCV10.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Please see section 6.3.2.

6.3.6 Sites and Centers

This study was conducted at 25 centers in 5 countries.

6.3.7 Surveillance/Monitoring

N/A

6.3.8 Endpoints

Please see sections 6.3.1.1 and 6.3.1.2.

6.3.9 Statistical Considerations & Statistical Analysis Plan

- Definitions of analysis populations

The definitions for the analysis populations are same as those in Study V114-029. Please see section 6.1.9.

- Statistical Methods for Immunogenicity Analyses

To address the primary immunogenicity objective, anti-PnPs serotype-specific IgG GMCs at 30 days after receipt of the last dose of study intervention were evaluated for each of the 15 pneumococcal serotypes contained in V114. Point estimates for the IgG GMCs were calculated by exponentiating the estimates of the mean of the natural log values. 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 1-sample t-distribution. For the secondary endpoint, the within-group CIs were calculated based on the exact method proposed by Clopper and Pearson.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed
6.3.10.1.1 Demographics

Demographic characteristics were generally comparable for vaccinated participants in each age range between the intervention groups. All participants 7 to 11 and 12 to 23 months of age were PCV-naïve, and the majority were Asian (82.8% and 83.3%, respectively). Approximately 57% of participants 2 to 17 years of age were PCV-naïve. Approximately 65% of participants 2 to 17 years of age were 2 to <6 years of age. Most participants 2 to 17 years of age were white (66.8%) and of non-Hispanic or Latino ethnicity (99.4%).

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.3.10.1.3 Subject Disposition

The disposition of participants was generally comparable between the intervention groups. Among a total of 606 randomized participants, all received V114 or Prevnar 13, and all but one completed the study. One participant discontinued from the study due to withdrawal by parent/guardian.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Catch-up vaccination with V114 elicited serotype-specific immune responses in pneumococcal vaccine-naïve infants 7 to 11 months of age, pneumococcal vaccine-naïve toddlers 12 to 23 months of age, and pneumococcal vaccine-naïve and PCV-experienced children 2 to 17 years of age, as assessed by IgG GMCs at 30 days PD3 for all 15 serotypes contained in the vaccine (Tables 35, 36, and 37). Overall, serotype-specific IgG GMCs at 30 days PD3 appeared to be numerically higher in the Prevnar 13 group than the V114 group for the 13 shared serotypes except for Serotype 3 among PCV-naïve infants 7 to 11 months of age. GMCs at 30 days PD3 were numerically higher for some serotypes and lower for other serotypes in the V114 group when compared to those in the Prevnar 13 group for the 12 to 23 months and 2 to 17 years age groups. IgG GMCs for the 2 serotypes (22F and 33F) unique to V114 at 30 days PD3 were higher in the V114 group than in the Prevnar 13 group.

- Participants 7 to 11 Months of Age

Table 35. Summary of IgG GMCs at 30 Days Postdose 3 of PCV (Per-Protocol Population) (Participants 7 to 11 Months of Age)

Pneumococcal Serotype	V114 (N = 64) n	V114 (N = 64) Observed GMC	V114 (N = 64) 95% CI	Prevnar 13 (N = 64) n	Prevnar 13 (N = 64) Observed GMC	Prevnar 13 (N = 64) 95% CI
13 Shared Serotypes						
1	60	2.47	(2.09, 2.92)	59	3.66	(2.98, 4.50)
3	60	2.65	(2.30, 3.05)	59	1.71	(1.40, 2.08)
4	60	2.21	(1.82, 2.68)	59	3.85	(3.12, 4.76)
5	60	3.82	(3.14, 4.63)	59	4.56	(3.58, 5.80)
6A	60	2.23	(1.71, 2.91)	59	4.30	(3.28, 5.65)
6B	60	3.03	(2.41, 3.82)	59	4.17	(3.25, 5.36)
7F	60	5.16	(4.27, 6.23)	59	6.42	(5.25, 7.85)
9V	60	2.61	(2.09, 3.26)	59	3.59	(2.86, 4.51)
14	60	9.62	(7.94, 11.67)	59	13.07	(10.40, 16.42)
18C	60	3.45	(2.80, 4.24)	59	3.50	(2.75, 4.45)
19A	60	4.59	(3.95, 5.33)	59	5.81	(4.92, 6.85)

Pneumococcal Serotype	V114 (N = 64) n	V114 (N = 64) Observed GMC	V114 (N = 64) 95% CI	Prevnar 13 (N = 64) n	Prevnar 13 (N = 64) Observed GMC	Prevnar 13 (N = 64) 95% CI
19F	60	3.49	(2.94, 4.15)	59	4.83	(4.03, 5.79)
23F	60	2.62	(2.02, 3.39)	59	2.79	(2.10, 3.69)
2 Serotypes Unique to						
22F	60	9.04	(7.48, 10.93)	58	0.14	(0.10, 0.19)
33F	60	3.37	(2.78, 4.10)	59	0.13	(0.10, 0.16)

Source: Table 11-1 in Study V114-024 CSR.

- Participants 12 to 23 Months of Age

Table 36. Summary of IgG GMCs at 30 Days Postdose 2 of PCV (Per-Protocol Population) (Participants 12 to 23 Months of Age)

Pneumococcal Serotype	V114 (N = 62) n	V114 (N = 62) Observed GMC	V114 (N = 62) 95% CI	Prevnar 13 (N = 64) n	Prevnar 13 (N = 64) Observed GMC	Prevnar 13 (N = 64) 95% CI
13 Shared Serotypes						
1	56	3.83	(3.07, 4.77)	60	4.20	(3.30, 5.34)
3	56	2.96	(2.44, 3.58)	60	1.68	(1.29, 2.20)
4	56	3.46	(2.67, 4.50)	60	4.89	(3.76, 6.36)
5	56	3.39	(2.65, 4.34)	60	3.12	(2.52, 3.88)
6A	56	2.05	(1.30, 3.23)	60	3.73	(2.64, 5.29)
6B	56	2.69	(1.70, 4.25)	60	2.87	(1.92, 4.30)
7F	56	4.80	(3.63, 6.34)	60	5.42	(4.30, 6.82)
9V	56	2.48	(1.97, 3.11)	60	2.89	(2.21, 3.78)
14	56	8.23	(6.19, 10.94)	60	8.30	(6.56, 10.51)
18C	56	5.09	(3.98, 6.52)	60	3.68	(2.85, 4.75)
19A	56	6.74	(5.29, 8.60)	60	5.87	(4.85, 7.11)
19F	56	5.90	(4.69, 7.43)	60	5.92	(4.93, 7.11)
23F	56	2.85	(1.99, 4.07)	60	2.18	(1.54, 3.07)
2 Serotypes Unique to V114						
22F	56	15.90	(12.16, 20.78)	60	0.12	(0.09, 0.16)
33F	56	5.17	(3.96, 6.74)	60	0.15	(0.12, 0.19)

Source: Table 11-2 in Study V114-024 CSR.

- Participants 2 to 17 Years of Age

Table 37. Summary of IgG GMCs at Day 30 (Per-Protocol Population) (Participants 2 to 17 Years of Age)

Pneumococcal Serotype	V114 (N = 177) n	V114 (N = 177) Observed GMC	V114 (N = 177) 95% CI	Prevnar 13 (N = 175) n	Prevnar 13 (N = 175) Observed GMC	Prevnar 13 (N = 175) 95% CI
13 Shared Serotypes						
1	162	3.00	(2.60, 3.46)	162	3.99	(3.48, 4.58)
3	162	1.37	(1.19, 1.58)	162	1.03	(0.88, 1.21)
4	162	2.53	(2.17, 2.96)	162	5.22	(4.52, 6.03)
5	162	3.43	(2.89, 4.07)	162	4.24	(3.46, 5.20)
6A	162	9.03	(7.07, 11.53)	162	8.81	(6.96, 11.14)
6B	162	13.55	(10.52, 17.46)	161	10.51	(8.01, 13.78)
7F	162	4.03	(3.46, 4.70)	162	4.63	(3.92, 5.46)
9V	162	3.60	(3.06, 4.24)	162	4.35	(3.65, 5.20)
14	162	9.21	(7.11, 11.92)	162	8.04	(6.24, 10.36)
18C	162	7.16	(6.03, 8.52)	162	4.46	(3.76, 5.30)
19A	162	10.99	(9.12, 13.26)	162	14.90	(12.23, 18.16)
19F	162	8.95	(7.45, 10.76)	162	12.28	(10.07, 14.97)
23F	162	5.36	(4.41, 6.50)	162	5.12	(4.12, 6.37)
2 Serotypes Unique to V114						
22F	162	14.99	(12.73, 17.66)	159	0.31	(0.24, 0.38)
33F	162	4.89	(4.12, 5.80)	160	0.27	(0.22, 0.32)

Source: Table 11-3 in Study V114-024 CSR.

Reviewer Comment:
My analysis of the primary immunogenicity endpoints showed similar results.

6.3.11.2   Analyses of Secondary Endpoints

For participants 7 to 11 months of age, ≥95.0% participants in the V114 group achieved the IgG threshold value of ≥0.35μg/mL at 30 days PD3 for each of the 15 serotypes contained in the vaccine. Serotype-specific IgG response rates at 30 days PD3 were generally comparable between the intervention groups for the 13 shared serotypes in V114 and Prevnar 13. IgG response rates for the 2 serotypes (22F and 33F) unique to V114 at 30 days PD3 were higher in the V114 group than in the Prevnar 13 group.

For participants 12 to 23 months of age, >83.0% of participants in the V114 group achieved the IgG threshold value of ≥0.35μg/mL at 30 days PD2 for each of the 15 serotypes contained in the vaccine. Serotype-specific IgG response rates at 30 days PD2 were generally comparable between the intervention groups for the 13 shared serotypes in V114 and Prevnar 13. IgG response rates for the 2 serotypes unique to V114 (serotypes 22F and 33F) at 30 days PD2 were higher in the V114 group than in the Prevnar 13 group.

For participants 2 to 17 years of age, >95.0% participants in the V114 group achieved the IgG threshold value of ≥0.35μg/mL at Day 30 for each of the 15 serotypes contained in the vaccine. Serotype-specific IgG response rates at Day 30 were generally comparable between the intervention groups for the 13 shared serotypes in V114 and Prevnar 13. IgG response rates for the 2 serotypes unique to V114 (serotypes 22F and 33F) at Day 30 were higher in the V114 group than in the Prevnar 13 group.

6.3.11.3 Subpopulation Analyses
Serotype-specific IgG GMCs at 30 days following the last dose of study intervention in sex, race, and ethnicity subgroups were generally consistent with the results in the overall population of each age group.

6.3.11.4 Dropouts and/or Discontinuations
Please refer to 6.3.10.1.3.

6.3.11.5 Exploratory and Post Hoc Analyses
N/A

6.3.12 Safety Analyses

For participants 7 to 11 months of age, the proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, and SAEs were generally comparable between the intervention groups in participants 7 to 11 months of age following any dose of PCV (3-dose series).

For participants 12 to 23 months of age, the proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, were higher in the V114 group compared with the Prevnar 13 group in participants 12 to 23 months of age following any dose of PCV (2-dose series). The proportions of participants with SAEs were generally comparable between the intervention groups.

For participants 2 to 17 years of age, the proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, and SAEs were generally comparable between the intervention groups in participants 2 to 17 years of age following 1 dose of PCV.
6.3.12.1 Methods
Safety analysis was conducted with descriptive statistics.

6.3.12.3 Deaths
There were no deaths due to AEs reported for this study.

6.3.12.4   Nonfatal Serious Adverse Events
The proportions of participants with SAEs were generally comparable between the intervention groups across vaccination regimens.

6.3.12.5 Adverse Events of Special Interest (AESI)
NA

6.3.12.6 Clinical Test Results
N/A

6.3.12.7 Dropouts and/or Discontinuations
No participants discontinued study vaccine due to an AE within the protocol-defined reporting period.

6.4 Study V114-031: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety and Tolerability of V114 in Healthy Infants (PNEU-LINK)

6.4.1 Objectives

6.4.1.1 Primary Objectives:
Table 38. Primary Study Objective and Endpoints for Study V114-031

Objective	Endpoints
Objective: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	Following any vaccination with V114: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination. • Solicited systemic AEs from Day 1 through Day 14 postvaccination. • Vaccine-related serious adverse events (SAEs) through completion of study participation.

Source: section 8 in Study V114-031 CSR.

6.4.1.2 Secondary Objectives:
Table 39. Secondary Study Objectives and Endpoints for Study V114-031

Objectives	Endpoints
Objective (Premature Infant Immunogenicity Sub-study only): To evaluate the anti-PnPs serotype-specific IgG GMCs at 30 days PD3, Predose 4, and at 30 days PD4 for each vaccination group.	Anti-PnP serotype-specific IgG responses for the 15 serotypes contained in V114 at 30 days PD3, Predose 4, and at 30 days PD4
Objective (Premature Infant Immunogenicity Sub-study only): To evaluate the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35μg/mL) at 30 days following Dose 3 for each vaccination group.	Anti-PnP serotype-specific IgG response rates for the 15 serotypes contained in V114 at 30 days PD3

Source: section 8 in Study V114-031 CSR.

6.4.2 Design Overview

This was a randomized, active comparator-controlled, parallel-group, multisite, double-blind study evaluating safety and tolerability of V114 in healthy infants (42 to 90 days of age); preterm infants (gestational age <37 weeks) enrolled in this study also participated in the Premature Infant Sub-study.

Approximately 2400 healthy infants were planned for random assignment and vaccination with either V114 (approximately 2000 participants) or Prevnar 13 (approximately 400 participants) at Visits 1, 2, 3, and 5 (at approximately 2, 4, 6, and 12 to 15 months of age, respectively) in the following ratios based on gestational age:
• Full-term infants (gestational age ≥37 weeks) 5:1 to V114 or Prevnar 13.
• Preterm infants (gestational age <37 weeks) 1:1 to V114 or Prevnar 13.

6.4.3 Population

Healthy infants (42 to 90 days of age).

6.4.4 Study Treatments or Agents Mandated by the Protocol

- V114 (Experimental)
- Prevnar 13 (Control)

6.4.6 Sites and Centers

This study was conducted at 72 centers in 10 countries.

6.4.7 Surveillance/Monitoring

N/A

6.4.8 Endpoints

Please see sections 6.4.1.1 and 6.4.1.2.

6.4.9 Statistical Considerations & Statistical Analysis Plan

- Definitions of analysis populations
  - Per-Protocol (PP) Population: all randomized participants in the Premature Infant Immunogenicity Substudy without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s). The PP population served as the primary population for the analysis of immunogenicity data in this study.
  - Full Analysis Set (FAS) Population: all randomized participants who received all study vaccinations required at the time point for the analysis and have serology result. The FAS population was used for supportive analysis.
  - Safety Analysis Population (All Participants as Treated (APaT) population): all randomized participants who received at least 1 dose of study vaccination.

- Statistical Analysis Methods
  - Safety data analysis: Descriptive statistics were provided by intervention group.
  - Immunogenicity data analysis: Immunogenicity analysis was conducted separately for each of the 15 pneumococcal serotypes in V114 (Premature Infant Immunogenicity Substudy only). Anti-PnPs serotype-specific IgG GMCs and OPA GMTs at 30 days PD3, prior to dose 4, and at 30 days PD4 were calculated within each intervention group separately. Point estimates were calculated by exponentiating the estimates of the mean of the natural log values. Confidence intervals were derived by exponentiating the CIs of the mean of the natural log values based on the one-sample t-distribution. For the secondary endpoints regarding anti-PnPs serotype specific IgG response rates at 30 days PD3 for the 15 serotypes contained in the V114 group, the within-group CIs were calculated based on the exact method proposed by Clopper and Pearson.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed
6.4.10.1.1 Demographics
Demographic characteristics were generally comparable between the two groups. The median age of participants was 9 weeks (range: 6 to 12 weeks). About half of the participants were male and half were White; the majority of participants were of non-Hispanic or Latino ethnicity (84.6%).

Approximately 4% of participants were preterm infants (gestational age <37 weeks). The median gestational age of preterm infants (<37 weeks) enrolled in the study was 36 weeks (range: 32 to 37 weeks). The majority of preterm infants were male, White, and of non-Hispanic or Latino ethnicity.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.4.10.1.3 Subject Disposition
The disposition of participants was generally comparable in both study intervention groups. Among a total of 2409 randomized participants, the majority (>90%) of randomized participants received 4 doses of either V114 or Prevnar 13 and completed the study. The most common reasons for discontinuing study intervention in both intervention groups were withdrawal by parent/guardian (4.0%) and lost to follow-up (1.4%).

6.4.11 Efficacy Analyses

6.4.11.1 Analyses of Primary Endpoint(s)
The primary endpoints for this study were to evaluate the safety and tolerability of V114. There were no primary immunogenicity endpoints. Please see section 6.4.12 for the safety analysis.

6.4.11.2 Analyses of Secondary Endpoints
The secondary immunogenicity endpoint analysis was conducted for the premature infant immunogenicity sub-study.
• Serotype-specific IgG GMCs at 30 Days PD3, Predose 4, and at 30 Days PD4
V114 elicited serotype-specific immune responses in preterm infants (gestational age <37 weeks) to each of the 15 serotypes contained in the vaccine at each timepoint (Table 40). Serotype specific IgG GMCs were slightly higher in the Prevnar 13 group than those in the V114 group for the 13 shared serotypes in V114 and Prevnar 13 at all timepoints except for Serotype 3. IgG GMCs for the 2 serotypes unique to V114 (22F and 33F) were higher in the V114 group compared with the Prevnar 13 group at all timepoints.

Table 40. Summary of IgG Antibody Responses GMC (Per-Protocol Population) (Premature Infants)

	Timepoint	V114 (N=51) n	V114 (N=51) Observed response	V114 (N=51) 95% CI	Prevnar 13 (N=48) n	Prevnar 13 (N=48) Observed response	Prevnar 13 (N=48) 95% CI
13 Shared Serotypes							
1	30 Days Postdose 3	38	1.15	(0.88, 1.52)	35	1.61	(1.25, 2.09)
	Prior to Dose 4	38	0.30	(0.24, 0.38)	40	0.47	(0.38, 0.59)
	30 Days Postdose 4	34	1.56	(1.19, 2.06)	39	1.96	(1.54, 2.50)
3	30 Days Postdose 3	38	0.86	(0.65, 1.13)	35	0.58	(0.45, 0.76)
	Prior to Dose 4	38	0.22	(0.16, 0.29)	40	0.13	(0.10, 0.17)
	30 Days Postdose 4	34	1.04	(0.80, 1.36)	39	0.79	(0.60, 1.06)
4	30 Days Postdose 3	38	1.41	(1.01, 1.99)	35	1.27	(0.96, 1.68)
	Prior to Dose 4	38	0.24	(0.19, 0.31)	40	0.31	(0.24, 0.38)
	30 Days Postdose 4	34	1.55	(1.11, 2.16)	39	1.61	(1.21, 2.15)
5	30 Days Postdose 3	38	1.48	(1.04, 2.10)	35	1.66	(1.09, 2.53)
	Prior to Dose 4	38	0.77	(0.60, 1.01)	40	0.89	(0.65, 1.22)
	30 Days Postdose 4	34	3.30	(2.34, 4.65)	39	3.60	(2.53, 5.13)
6A	30 Days Postdose 3	38	1.37	(0.95, 1.96)	35	3.19	(2.31, 4.43)
	Prior to Dose 4	38	0.32	(0.24, 0.43)	40	0.72	(0.52, 0.99)
	30 Days Postdose 4	34	4.18	(3.17, 5.49)	39	6.38	(4.69, 8.68)
6B	30 Days Postdose 3	38	1.69	(1.15, 2.48)	35	2.53	(1.64, 3.89)
	Prior to Dose 4	38	0.59	(0.47, 0.75)	40	0.61	(0.43, 0.87)
	30 Days Postdose 4	34	6.62	(5.24, 8.37)	39	6.75	(4.43, 10.28)
7F	30 Days Postdose 3	38	1.95	(1.46, 2.62)	35	2.92	(2.21, 3.87)
	Prior to Dose 4	38	0.57	(0.44, 0.73)	40	0.95	(0.74, 1.21)
	30 Days Postdose 4	34	4.01	(2.98, 5.40)	39	5.10	(3.76, 6.90)
9V	30 Days Postdose 3	38	1.47	(1.08, 2.00)	35	1.50	(1.07, 2.12)
	Prior to Dose 4	38	0.40	(0.32, 0.51)	40	0.46	(0.35, 0.62)
	30 Days Postdose 4	34	3.10	(2.36, 4.08)	39	3.09	(2.31, 4.12)
14	30 Days Postdose 3	38	4.38	(3.18, 6.03)	35	6.52	(4.35, 9.77)
	Prior to Dose 4	38	1.14	(0.84, 1.54)	40	2.22	(1.73, 2.84)
	30 Days Postdose 4	34	5.40	(3.89, 7.49)	39	7.15	(5.33, 9.61)
18C	30 Days Postdose 3	38	1.46	(1.08, 1.96)	35	1.54	(1.16, 2.04)
	Prior to Dose 4	38	0.35	(0.28, 0.45)	40	0.36	(0.27, 0.49)
	30 Days Postdose 4	34	3.21	(2.32, 4.45)	39	2.77	(1.99, 3.85)
19A	30 Days Postdose 3	38	1.63	(1.25, 2.13)	35	3.00	(2.18, 4.11)
	Prior to Dose 4	38	0.38	(0.29, 0.51)	40	0.81	(0.52, 1.24)
	30 Days Postdose 4	34	4.96	(3.85, 6.39)	39	6.47	(4.46, 9.40)
19F	30 Days Postdose 3	38	2.03	(1.53, 2.68)	35	2.78	(2.17, 3.58)
	Prior to Dose 4	38	0.41	(0.31, 0.53)	40	0.69	(0.52, 0.90)
	30 Days Postdose 4	34	4.48	(3.51, 5.73)	39	4.83	(3.66, 6.38)
23F	30 Days Postdose 3	38	1.17	(0.81, 1.70)	35	1.18	(0.82, 1.68)
	Prior to Dose 4	38	0.33	(0.24, 0.45)	40	0.37	(0.26, 0.52)
	30 Days Postdose 4	34	2.38	(1.76, 3.20)	39	3.04	(2.16, 4.27)

	Timepoint	V114 (N=51) n	V114 (N=51) Observed response	V114 (N=51) 95% CI	Prevnar 13 (N=48) n	Prevnar 13 (N=48) Observed response	Prevnar 13 (N=48) 95% CI
2 Serotypes Unique to V114							
22F	30 Days Postdose 3	38	4.33	(3.18, 5.90)	35	0.05	(0.03, 0.07)
	Prior to Dose 4	38	1.24	(0.98, 1.58)	40	0.05	(0.04, 0.07)
	30 Days Postdose 4	34	9.83	(7.47,	38	0.08	(0.07, 0.11)
33F	30 Days Postdose 3	38	1.58	(0.93, 2.69)	35	0.05	(0.04, 0.08)
	Prior to Dose 4	38	1.09	(0.82, 1.45)	40	0.05	(0.04, 0.07)
	30 Days Postdose 4	34	5.46	(4.29, 6.96)	37	0.10	(0.07, 0.13)

Source: Table 11-1 in in Study V114-031 CSR.

- Serotype-specific IgG Response Rate at 30 Days PD3

For each of the 15 serotypes contained in the vaccine, the majority (>86%) of participants in the V114 group achieved the IgG threshold value of ≥0.35μg/mL (response rate) at 30 days PD3. Serotype-specific IgG response rates at 30 days PD3 were generally comparable between intervention groups for the 13 shared serotypes in V114 and Prevnar 13. IgG response rates for the 2 serotypes unique to V114 (22F and 33F) at 30 days PD3 were higher in the V114 group compared with the Prevnar 13 group (Table 41).

Table 41. Summary of the Proportions of Participants with IgG ≥0.35μg/mL at 30 Days Postdose 3 (Per-Protocol Population) (Premature Infants)

Pneumococcal Serotype	V114 (N = 51) Observed Response Percentage (m/n)	V114 (N = 51) 95% CI	Prevnar 13 (N = 48) Observed Response Percentage (m/n)	Prevnar 13 (N = 48) 95% CI
13 Shared Serotypes				
1	97.4% (37/38)	(86.2, 99.9)	97.1% (34/35)	(85.1, 99.9)
3	89.5% (34/38)	(75.2, 97.1)	74.3% (26/35)	(56.7, 87.5)
4	94.7% (36/38)	(82.3, 99.4)	97.1% (34/35)	(85.1, 99.9)
5	97.4% (37/38)	(86.2, 99.9)	88.6% (31/35)	(73.3, 96.8)
6A	97.4% (37/38)	(86.2, 99.9)	97.1% (34/35)	(85.1, 99.9)
6B	92.1% (35/38)	(78.6, 98.3)	94.3% (33/35)	(80.8, 99.3)
7F	97.4% (37/38)	(86.2, 99.9)	100% (35/35)	(90.0, 100.0)
9V	97.4% (37/38)	(86.2, 99.9)	94.3% (33/35)	(80.8, 99.3)
14	100% (38/38)	(90.7, 100.0)	97.1% (34/35)	(85.1, 99.9)
18C	97.4% (37/38)	(86.2, 99.9)	94.3% (33/35)	(80.8, 99.3)
19A	94.7% (36/38)	(82.3, 99.4)	97.1% (34/35)	(85.1, 99.9)
19F	97.4% (37/38)	(86.2, 99.9)	100% (35/35)	(90.0, 100.0)
23F	89.5% (34/38)	(75.2, 97.1)	94.3% (33/35)	(80.8, 99.3)
2 Serotypes Unique to V114				

Pneumococcal Serotype	V114 (N = 51) Observed Response Percentage (m/n)	V114 (N = 51) 95% CI	Prevnar 13 (N = 48) Observed Response Percentage (m/n)	Prevnar 13 (N = 48) 95% CI
22F	97.4% (37/38)	(86.2, 99.9)	2.9% (1/35)	(0.1, 14.9)
33F	86.8% (33/38)	(71.9, 95.6)	2.9% (1/35)	(0.1, 14.9)

Source: Table 11-2 in in Study V114-031 CSR.

Reviewer Comment:
My analysis showed similar results for the secondary immunogenicity endpoint analysis.

6.4.11.3 Subpopulation Analyses
NA

6.4.11.4 Dropouts and/or Discontinuations
Please refer to section 6.4.10.1.3.

6.4.11.5 Exploratory and Post Hoc Analyses
N/A

6.4.12 Safety Analyses

The proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, and SAEs were generally comparable between the intervention groups following any dose of PCV. AEs were reported for the majority (>93%) of participants in both intervention groups. Solicited events (injection-site, systemic) accounted for the majority of all AEs and vaccine related AEs; Higher rates of solicited AEs were observed for injection site erythema, injection site pain, decreased appetite and irritability in the V114 group when compared to the Prevnar 13 group.

The applicant also evaluated the safety profiles between the gestational age groups (<37 weeks vs. ≥37 weeks). (Table 42). Infants < 37 weeks of age tended to have higher vaccine-related events than infants ≥ 37 weeks of age. I defer to the clinical reviewer to determine whether the differences observed were clinically significant.

Table 42. Adverse Event Summary by Gestational Age (All Participants as Treated Population) (Following Any Dose)

	<37 Weeks V114 n	<37 Weeks V114 (%)	<37 Weeks Prevnar 13 n	<37 Weeks Prevnar 13 (%)	≥37 Weeks V114 n	≥37 Weeks V114 (%)	≥37 Weeks Prevnar 13 n	≥37 Weeks Prevnar 13 (%)
Participants in population	51		48		1914		385	
with one or more adverse events	49	(96.1)	47	(97.9)	1791	(93.6)	357	(92.7)
injection-site	39	(76.5)	30	(62.5)	1310	(68.4)	236	(61.3)
systemic	48	(94.1)	47	(97.9)	1741	(91.0)	346	(89.9)
with no adverse event	2	(3.9)	1	(2.1)	123	(6.4)	28	(7.3)
with vaccine-related adverse events	48	(94.1)	44	(91.7)	1715	(89.6)	334	(86.8)
injection-site	39	(76.5)	30	(62.5)	1310	68.4	236	61.3
systemic	46	(90.2)	42	(87.5)	1601	(83.6)	308	(80.0)
with serious adverse events	5	(9.8)	5	(10.4)	187	(9.8)	40	(10.4)

with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
who died	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.3)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious vaccine related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Source: Table 14.3-78 in Study V114-031 CSR.

6.4.12.1 Methods
The safety analyses were performed using descriptive statistics.

6.4.12.3 Deaths
Two participant deaths occurred during the study (1 in each intervention group). Neither of the deaths were considered by the investigator to be related to study intervention.

6.4.12.4 Nonfatal Serious Adverse Events
The proportions of participants with SAEs were generally comparable between intervention groups. Approximately 10% of the participants reported an SAE.

6.4.12.5 Adverse Events of Special Interest (AESI)
There were no AEs of special interest for this study.

6.4.12.6 Clinical Test Results
N/A

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

6.5 Study V114-023: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children with Sickle Cell Disease (PNEU-SICKLE)

6.5.1 Objectives

6.5.1.1 Primary Objectives

Table 43. Primary Study Objectives and Endpoints for Study V114-023

Objectives	Endpoints
Objective: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs from Day 1 through Day 14 postvaccination • Solicited systemic AEs from Day 1 through Day 14 postvaccination • Vaccine-related serious adverse events (SAEs) through completion of study participation
Objective: 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.	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at Day 30

Source: section 8 in Study V114-023 CSR.

6.5.1.2 Secondary Objectives

Table 44. Secondary Study Objectives and Endpoints for Study V114-023

Objectives	Endpoints
Objective: To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination (Day 30) for each vaccination group.	Anti-PnPs serotype specific OPA responses for the 15 serotypes contained in V114 at Day 30
Objective: To evaluate the anti-PnPs serotype-specific Geometric Mean Fold Rises (GMFRs) from pre-vaccination (Day 1) to 30 days postvaccination (Day 30) for both OPA and IgG responses for each vaccination group.	Anti-PnPs serotype specific OPA and IgG responses for the 15 serotypes contained in V114 at Day 1 and Day 30

Source: section 8 in Study V114-023 CSR.

6.5.2 Design Overview

This was a randomized, active comparator-controlled, parallel-group, multisite, double-blind study of V114 in participants 5 to 17 years of age (inclusive) with Sickle Cell Disease (SCD). Approximately 100 participants were to be randomly assigned in a 2:1 ratio to receive either V114 (67 participants) or Prevnar 13 (33 participants).

6.5.3 Population

Males and females 5 to 17 years of age (inclusive) with Sickle Cell Disease.

6.5.4 Study Treatments or Agents Mandated by the Protocol

- Experimental: V114.
- Active Comparator: Prevnar 13.

6.5.6 Sites and Centers

This study was conducted at 19 centers in 7 countries.

6.5.7 Surveillance/Monitoring

N/A

6.5.8 Endpoints

Please see sections 6.5.1.1 and 6.5.1.2.

6.5.9 Statistical Considerations & Statistical Analysis Plan

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

- Statistical Analysis Methods

To address the primary immunogenicity objective, evaluation of the IgG GMCs at 30 days postvaccination with V114 or Prevnar 13 were provided as descriptive summaries. 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 t-distribution. A similar statistical approach was used to evaluate the serotype specific OPA GMTs at 30 days postvaccination with V114 or Prevnar 13.

- Multiplicity adjustment

No adjustment was made for multiplicity.

6.5.10 Study Population and Disposition

6.6.10.1 Populations Enrolled/Analyzed
6.5.10.1.1 Demographics
Demographic characteristics were generally comparable in both groups. The median age of participants was 11 years (range: 5 to 17 years). The majority of participants were male (54.4%), Black or African American (60.2%), and of Hispanic or Latino ethnicity (66.0%).

6.5.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.5.10.1.3 Subject Disposition
A total of 104 participants were randomized (103 vaccinated). All but 5 participants completed the study.

6.5.11 Efficacy Analyses

6.5.11.1 Analyses of Primary Endpoint(s)
V114 was immunogenic as assessed by IgG GMCs at 30 days postvaccination for all 15 serotypes contained in the vaccine. Serotype-specific IgG GMCs were generally comparable for the 13 shared serotypes in V114 and Prevnar 13 for participants in both intervention groups at 30 days postvaccination (Table 45). Serotype-specific IgG GMCs were higher for the 2 unique serotypes (22F and 33F) to V114 for participants in the V114 group compared with the Prevnar 13 group at 30 days postvaccination.

Table 45. Summary of IgG GMCs at Day 30 (Per-Protocol Population)

Pneumococcal Serotype	V114 (N = 69) n	V114 (N = 69) Observed Response	V114 (N = 69) 95% CI	Prevnar 13 (N = 34) n	Prevnar 13 (N = 34) Observed Response	Prevnar 13 (N = 34) 95% CI
13 Shared Serotypes						
1	66	2.12	(1.63, 2.75)	32	2.76	(1.95, 3.91)
3	66	1.09	(0.87, 1.38)	31	1.07	(0.70, 1.65)
4	66	1.58	(1.18, 2.10)	31	2.90	(2.00, 4.20)

5	66	4.44	(3.19, 6.17)	31	6.56	(4.09, 10.52)
6A	66	23.29	(17.22, 31.52)	31	15.97	(8.82, 28.91)
6B	66	38.38	(28.53, 51.64)	31	22.94	(13.60, 38.71)
7F	66	5.81	(4.42, 7.64)	32	4.65	(3.06, 7.06)
9V	66	4.46	(3.44, 5.78)	32	5.36	(3.45, 8.33)
14	66	16.03	(11.23, 22.90)	31	20.53	(12.39, 34.03)
18C	66	6.11	(4.47, 8.35)	32	4.20	(2.66, 6.62)
19A	66	19.86	(14.77, 26.70)	32	21.65	(14.45, 32.44)
19F	66	13.88	(9.96, 19.35)	32	12.80	(9.10, 18.01)
23F	63	5.38	(3.88, 7.46)	31	6.88	(4.01, 11.83)
2 Serotypes Unique to V114						
22F	66	7.30	(5.68, 9.36)	30	0.49	(0.33, 0.73)
33F	66	4.46	(3.38, 5.87)	32	0.97	(0.62, 1.51)

Source: Table 11-1 in Study V114-023 CSR.

6.5.11.2   Analyses of Secondary Endpoints

- Serotype-specific OPA GMTs at 30 Days Postvaccination

As observed with IgG GMCs, V114 was immunogenic as assessed by OPA GMTs at 30 days postvaccination for all 15 serotypes contained in the vaccine. Serotype-specific OPA GMTs were generally comparable for the 13 shared serotypes in V114 and Prevnar 13 for participants in both intervention groups at 30 days postvaccination. Serotype-specific OPA GMTs were higher for the 2 unique serotypes (22F and 33F) to V114 for participants in the V114 group compared with the Prevnar 13 group at 30 days postvaccination.

- Additional Serotype-specific IgG and OPA Endpoints at 30 Days

Postvaccination V114 was immunogenic as assessed by serotype specific GMFRs from Day 1 to Day 30 for all 15 serotypes contained in the vaccine.

6.5.11.3 Subpopulation Analyses

Serotype-specific IgG GMCs at 30 days postvaccination within the age, sex, race and ethnicity subgroups were generally consistent with the results in the overall population.

6.5.11.4 Dropouts and/or Discontinuations

Please refer to section 6.5.10.1.3.

6.5.11.5 Exploratory and Post Hoc Analyses

N/A

6.5.12 Safety Analyses

The overall proportions of participants with AEs and SAEs were generally comparable across intervention groups (Table 46).

- The majority of participants (V114 81.2%, Prevnar 13 79.4%) experienced 1 or more AE during the study.
- There was a higher proportion of vaccine-related systemic AEs reported in the V114 group compared to the Prevnar 13 group.

Table 46. Summary of Adverse Events (All Participants as Treated Population) (Following PCV)

	V114 n	V114 (%)	V114 95% CI	Prevnar 13 n	Prevnar 13 (%)	Prevnar 13 95% CI
Participants in population	69			34		
with one or more adverse events	56	(81.2)	(69.9, 89.6)	27	(79.4)	(62.1, 91.3)
injection-site	48	(69.6)		26	(76.5)	
systemic	42	(60.9)	(61.9, 83.7)	19	(55.9)	(58.8, 89.3)
with no adverse event	13	(18.8)		7	(20.6)	
with vaccine-related adverse events	51	(73.9)	(10.4, 30.1)	26	(76.5)	(10.7, 41.2)
injection-site	48	(69.6)	(0.0, 5.2)	26	(76.5)	(0.0, 10.3)
systemic	28	(40.6)	(0.0, 5.2)	7	(20.6)	(0.0, 10.3)
with serious adverse events	13	(18.8)		8	(23.5)	
with serious vaccine-related adverse events	0	(0.0)		0	(0.0)	
who died	0	(0.0)		0	(0.0)	

Source: Table 12-1 in Study V114-023 CSR.

6.5.12.1 Methods
The safety analyses were performed using descriptive statistics.

6.5.12.3 Deaths
No deaths.

6.5.12.4   Nonfatal Serious Adverse Events
The proportions of participants with SAEs were comparable across intervention groups. None of the SAEs were considered by the investigator to be related to study vaccine.

6.5.12.5 Adverse Events of Special Interest (AESI)
There were no AEs of special interest for this study.

6.5.12.6 Clinical Test Results
N/A

6.5.12.7 Dropouts and/or Discontinuations
No participants discontinued due to an AE.

6.6 Study V114-030: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 Followed by Administration of PNEUMOVAX23 Eight Weeks Later in Children Infected with Human Immunodeficiency Virus (HIV) (PNEU-WAY PED))

6.6.1 Objectives

6.6.1.1 Primary Objectives

Table 47. Primary Study Objectives and Endpoints for Study V114-030

Objectives	Endpoints
Objective: To evaluate the safety and tolerability of V114 with respect to the proportion of participants with adverse events (AEs).	Following vaccination with V114: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination • Solicited systemic AEs from Day 1 through Day 14 postvaccination • Vaccine-related serious adverse events (SAEs) through completion of study participation
Objective: To evaluate the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) at 30 days postvaccination (Day 30) with V114 or Prevnar 13 by each vaccination group.	Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at Day 30

Source: section 8 in Study V114-030 CSR.

6.6.1.2 Secondary Objectives

Table 48. Secondary Study Objectives and Endpoints for Study V114-030

Objectives	Endpoints
Objective: To evaluate the safety and tolerability of PNEUMOVAX23 administered 8 weeks following V114 with respect to the proportion of participants with AEs.	Following vaccination with PNEUMOVAX23: • Solicited injection-site AEs from Day 1 through Day 14 postvaccination • Solicited systemic AEs from Day 1 through Day 14 postvaccination
Objective: To evaluate the anti-PnPs serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs) at 30 days postvaccination (Day 30) with V114 or Prevnar 13 by each vaccination group.	Anti-PnPs serotype specific OPA responses for the 15 serotypes contained in V114 at Day 30
Objective: To evaluate the anti-PnPs serotype specific OPA GMTs and IgG GMCs at 30 days postvaccination with PNEUMOVAX23 (Week 12) by each vaccination group.	Anti-PnPs serotype specific OPA and IgG responses for the 15 serotypes contained in V114 at Week 12

Source: section 8 in Study V114-030 CSR.

6.6.2 Design Overview

This was a randomized, active comparator-controlled, parallel-group, multisite, double-blind study of V114 in participants 6 to 17 years of age (inclusive) living with HIV. Approximately 400 participants were to be randomly assigned in a 1:1 ratio to receive either V114 (200 participants) or Prevnar 13 (200 participants) at Visit 2 (Day 1). Randomization was stratified by CD4+ T-cell count as follows:
- Stratum 1: CD4+ T-cell count ≥200 to <500 cells/μL.
- Stratum 2: CD4+ T-cell count ≥500 cells/μL.

6.6.3 Population

Subjects 6 to 17 years of age (inclusive) with HIV (CD4+ T-cell count was ≥200 cells/µL and plasma HIV RNA was <50,000 copies/mL at screening).

6.6.4 Study Treatments or Agents Mandated by the Protocol

- Experimental: V114 followed by PNEUMOVAX23 (PPV23)
- Active Comparator: Prevnar 13 followed by PNEUMOVAX23 (PPV23)

6.6.6 Sites and Centers

This study was conducted at 12 centers in 3 countries.

6.6.7 Surveillance/Monitoring

N/A

6.6.8 Endpoints

Please see sections 6.6.1.1 and 6.6.1.2.

6.6.9 Statistical Considerations & Statistical Analysis Plan

- Definitions of analysis populations
  The analysis population definitions are same as those in Study V114-023. Please see section 6.5.9.
- Statistical Methods for Immunogenicity Analyses
  To address the primary immunogenicity objective, evaluation of the IgG GMCs at 30 days postvaccination with V114 or Prevnar 13 included descriptive summaries and within group 95% CIs. The 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 CIs of the mean of the natural log values based on the t-distribution.). A similar statistical approach was used to evaluate the serotype specific OPA GMTs at 30 days postvaccination with V114 or Prevnar 13 and for IgG GMCs and OPA GMTs at 30 days postvaccination with PPV23 (Week 12).

6.6.10 Study Population and Disposition

6.6.10.1 Populations Enrolled/Analyzed
6.6.10.1.1 Demographics
Demographic characteristics were generally comparable in both intervention groups. The median age of participants was 13 years (range: 6 to 17 years). The majority of participants (91.6%) had CD4+ T-cell count ≥500 cells/µL at screening. The proportions of participants in both CD4+ T-cell count categories were generally comparable in both intervention groups. The majority of participants (92.6%) in both groups were PCV naïve, and all but 1 participant were PPV23 naïve.

6.6.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.6.10.1.3 Subject Disposition

The disposition of participants was generally comparable in both intervention groups. A total of 407 participants were randomized. All randomized participants received PCV at Day 1 and nearly all (99.5%) received PPV23 at Week 8. All participants in the V114 group and all but 3 participants in the Prevnar 13 group completed the study. One participant was lost to follow-up, and 2 participants were discontinued from the study due to parent/guardian withdrawal in the Prevnar 13 group.

6.6.11 Efficacy Analyses

6.6.11.1 Analyses of Primary Endpoint

V114 was immunogenic for all 15 serotypes contained in the vaccine, as assessed by IgG GMCs at 30 days postvaccination. Overall, serotype-specific IgG GMCs at 30 days postvaccination with PCV were generally comparable in both intervention groups for the 13 shared serotypes, and higher for the 2 serotypes unique to V114 (22F and 33F) in the V114 group compared with the Prevnar 13 group (Table 49).

Table 49 Summary of IgG GMCs at Day 30 (Per-Protocol Population)

Pneumococcal Serotype	V114 (N=203) n	V114 (N=203) Observed Response	V114 (N=203) 95% CI	Prevnar 13 (N=204) n	Prevnar 13 (N=204) Observed Response	Prevnar 13 (N=204) 95% CI
13 Shared Serotypes						
1	194	2.17	(1.89, 2.48)	196	3.26	(2.82, 3.77)
3	194	1.05	(0.93, 1.19)	196	0.84	(0.73, 0.97)
4	194	2.59	(2.23, 3.00)	196	4.27	(3.57, 5.11)
5	194	2.94	(2.44, 3.54)	196	2.78	(2.30, 3.37)
6A	194	7.98	(6.30, 10.11)	196	7.56	(6.06, 9.45)
6B	194	11.44	(9.07, 14.43)	196	6.92	(5.45, 8.79)
7F	194	4.84	(4.10, 5.71)	196	5.00	(4.29, 5.83)
9V	194	4.15	(3.56, 4.85)	196	4.78	(4.03, 5.66)
14	194	20.38	(16.39, 25.35)	196	18.29	(14.43, 23.17)
18C	194	5.18	(4.32, 6.20)	196	5.15	(4.29, 6.18)
19A	194	14.20	(11.81, 17.07)	196	14.78	(12.45, 17.54)
19F	194	9.76	(8.03, 11.85)	196	8.61	(7.28, 10.18)
23F	194	6.71	(5.42, 8.31)	196	6.35	(5.14, 7.85)
2 Serotypes Unique to V114						
22F	194	9.28	(7.76, 11.09)	193	0.24	(0.20, 0.29)
33F	194	4.53	(3.80, 5.39)	196	0.29	(0.25, 0.33)

Source: Table 11-1 in Study V114-030.

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

6.6.11.2 Analyses of Secondary Endpoints

• Serotype-specific OPA GMTs at 30 Days Postvaccination with PCV

V114 was immunogenic for all 15 serotypes contained in the vaccine, as assessed by OPA GMTs at 30 days postvaccination. Overall, serotype specific OPA GMTs at 30 days postvaccination with PCV were generally comparable in both intervention groups for the 13 shared serotypes, and higher for the 2 serotypes unique to V114 (22F and 33F) in the V114 group compared with the Prevnar 13 group.

• Serotype-specific IgG GMCs and OPA GMTs at 30 Days Postvaccination with PPV23

In the V114 group, PPV23 was immunogenic for all 15 serotypes contained in V114, as assessed by IgG GMCs and OPA GMTs at 30 days postvaccination with PPV23 (Week 12). Serotype-specific IgG GMCs and OPA GMTs at 30 days postvaccination with PPV23 (Week 12) were generally comparable in both intervention groups for the 15 serotypes in V114. PPV23 elicited an immune response as assessed by IgG GMCs and OPA GMTs at 30 days postvaccination with PPV23 (Week 12) for serotypes 22F and 33F in the Prevnar 13 group.

6.6.11.3 Subpopulation Analyses

Serotype-specific IgG GMCs at 30 days postvaccination with PCV within each age, sex, race and ethnicity subgroup were generally consistent with the results observed in the overall population. Serotype-specific IgG GMCs at 30 days postvaccination with PCV were, however, generally lower in participants with a CD4+ T-cell count ≥200 to <500 cells/μL than those observed in the overall population in both intervention groups.

6.6.11.4 Dropouts and/or Discontinuations

Please refer to section 6.6.10.1.3.

6.6.11.5 Exploratory and Post Hoc Analyses

N/A

6.6.12 Safety Analyses

• Following Vaccination with PCV

The proportions of participants with 1 or more AEs were 78.8% and 69.6%, respectively in the V114 and Prevnar 13 group. Vaccine-related injection-site and systemic AEs were reported for a higher proportion of participants in the V114 group following vaccination with PCV (injection site 71.4% V114 vs. 59.8% Prevnar 13; systemic 47.8% V114 vs. 37.7% Prevnar 13). One participant in the V114 group and one participant in the Prevnar 13 group experienced 1 or more SAEs; no SAEs were considered to be vaccine-related. No deaths were reported during the study.

• Following Vaccination with PPV23

The proportions of participants with 1 or more AEs were generally comparable in both intervention groups following vaccination with PPV23. AEs were reported for the majority (>75%) of participants in both intervention groups. Two participants in the V114 group and 2 participants in the Prevnar 13 group experienced 1 or more SAEs; none of the SAEs were considered to be vaccine related.

6.6.12.1 Methods

The safety analyses were performed using descriptive statistics.

6.6.12.3 Deaths

No deaths were reported during the trial.

6.6.12.4 Nonfatal Serious Adverse Events

• Following Vaccination with PCV

One participant in the V114 group and one participant in the Prevnar 13 group experienced 1 or more SAEs.

• Following Vaccination with PPV23

Two participants in the V114 group and 2 participants in the Prevnar 13 group experienced 1 or more SAEs.

6.6.12.5 Adverse Events of Special Interest (AESI)

NA

6.6.12.6 Clinical Test Results

N/A

6.6.12.7 Dropouts and/or Discontinuations

One participant in the Prevnar 13 group discontinued study intervention (i.e., did not receive PPV23 at Week 8) due to vaccine-related AEs of injection-site erythema, injection-site induration, and injection-site swelling following Prevnar 13.

7. INTEGRATED OVERVIEW OF EFFICACY

There were no efficacy studies conducted as part of the V114 Phase 3 development program. The applicant compared the immunogenicity data across studies V114-029, V114-027 and V114-008 and concluded that a consistent pattern of immune responses was observed across studies in healthy infants receiving 4 doses of PCV, at 30 days PD3, Predose 4, and at 30 days PD4. The applicant performed an integrated immunogenicity analysis on preterm infants (V114-027, V114-029, V114-031). This section is focused on the integrated analysis on preterm infants.

7.1 Indication #1

Prevention of Pneumococcal Disease (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F).

7.1.1 Methods of Integration

The applicant performed an integrated immunogenicity analysis on preterm infants (V114-027, V114-029, V114-031). Per CBER recommendation, the subjects that received Pentavac were not included in the analysis. The integrated population included 236 preterm infants who received at least 1 dose of PCV (115 subjects received V114 and 121 subjects received Prevnar 13). Overall, ≥60% of participants were included in the PP

population for pneumococcal IgG analyses for each time point. The reasons for exclusion from the PP population were generally comparable between intervention groups.

7.1.2 Demographics and Baseline Characteristics

NA

7.1.4 Analysis of Primary Endpoints

- Serotype-specific IgG Response Rates at 30 Days PD3

The majority (>89%) of preterm infants in the V114 group achieved the IgG threshold value of ≥0.35μg/mL at 30 days PD3 for each of the 15 serotypes contained in the vaccine. Serotype-specific IgG response rates at 30 days PD3 were generally comparable between the V114 and Prevnar 13 intervention groups for the 13 shared serotypes and higher in the V114 group for the 2 serotypes unique to V114 (22F and 33F).

- Serotype-specific IgG GMCs at 30 Days PD3, Predose 4, and at 30 Days PD4
  - Serotype-specific IgG GMCs for each time point were generally comparable between the V114 and Prevnar 13 intervention groups for the 13 shared serotypes and higher for serotypes 22F and 33F in V114 recipients.
  - The immune responses observed to all 15 serotypes in the subset of preterm infants were similar to those observed in the overall healthy infant population (including preterm and term infants) receiving 4 doses of V114.

7.1.5 Analysis of Secondary Endpoints

NA

7.1.6 Other Endpoints

NA

7.1.7 Subpopulations

NA

7.1.10 Additional Efficacy Issues/Analyses

NA

7.1.11 Efficacy Conclusions

In preterm infants, V114 elicited serotype-specific immune responses to all 15 serotypes included in the vaccine when administered as a 4-dose series.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data from the three Phase 3 studies conducted in healthy infants receiving a 4-dose regimen of V114 or Prevnar 13 (V114-027 [Groups 1 and 5 only], V114-029, and V114-031) were integrated based on similarities in study design, population, and dosing

schedule. Safety analyses were performed in the APaT population, defined as all randomized participants who received at least 1 dose of study intervention. Results are shown for all infants (regardless of gestational age) and separately for the subset of preterm infants (<37 weeks gestational age at birth) who were enrolled in these studies.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

V114-027 [Groups 1 and 5 only], V114-029, and V114-031.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Nearly all randomized participants in the integrated population received at least 1 dose of V114 (>99%) or Prevnar 13 (>99%) and the majority completed the 4-dose vaccine regimen (93.1% in V114 and 89.2% in Prevnar 13). All randomized participants in the integrated preterm infant population received at least 1 dose of V114 or Prevnar 13 and the majority (>90%) completed the 4-dose vaccine regimen.

Demographic characteristics in the integrated overall population and preterm population were comparable across intervention groups.

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

N/A

8.4 Safety Results

8.4.1 Deaths

Integrated population: Four deaths were reported (2 in V114 vs. 2 in Prevnar 13). None of the deaths were considered by the investigator to be related to study intervention.

Preterm infants: There were no deaths reported in the integrated Preterm Infant population

8.4.2 Nonfatal Serious Adverse Events

Integrated Population: SAEs were reported for 10.0% of participants in both intervention groups. Nearly all SAEs were considered by the investigator to be unrelated to study intervention. Vaccine-related SAEs were reported for 2 (0.1%) participants in the V114 group.

Preterm Infants: SAEs were reported for 14.8% of preterm infants in the V114 group and 10.4% of preterm infants in the Prevnar 13 group; no SAEs were considered by the investigator to be related to study intervention.

8.4.3 Study Dropouts/Discontinuations

Integrated Population: No participants in the integrated population discontinued study intervention due to AEs.

Preterm Infants: No preterm infants discontinued study intervention due to AEs.

8.4.4 Common Adverse Events

The proportions of participants with AEs after any dose, including injection-site AEs, systemic AEs, vaccine-related AEs, and SAEs, were generally comparable in both intervention groups in the integrated overall population and the Preterm Infant population.

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Immunogenicity:
This submission includes two studies in healthy infants receiving 4 doses of PCV.
- The pivotal study V114-029 was a Phase 3, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety and immunogenicity of V114 in healthy infants 6 to 12 weeks of age at enrollment who received 4 doses of PCV (single dose administered at ~2, 4, 6, and 12 to 15 months). The primary immunogenicity analyses from V114-029 showed:
  o V114 was noninferior to Prevnar 13 for all 15 serotypes, as assessed by the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35µg/mL (response rate) at 30 days PD3.
  o V114 was noninferior to Prevnar 13 for 14 of 15 serotypes, as assessed by serotype specific IgG GMCs at 30 days PD3. The IgG response to serotype 6A missed the prespecified noninferiority criterion (the lower bound of the 2-sided 95% CI for the GMC ratio being 0.48 versus >0.5).
  o V114 was noninferior to Prevnar 13 for all 15 serotypes, as assessed by serotype-specific IgG GMCs at 30 days PD4.
- Study V114-027 was an interchangeability study to evaluate the safety and immunogenicity of mixed pneumococcal conjugate vaccine (PCV) regimens in infants approximately 2 months of age. Serotype-specific IgG GMCs at 30 days PD4 for the 13 shared serotypes were generally comparable for participants administered mixed regimens and for participants administered a complete dosing regimen of Prevnar 13 as assessed by IgG GMC ratios. Serotype-specific immune responses at 30 days PD3 were generally comparable across intervention groups for the 13 shared serotypes as assessed by IgG response rates and IgG GMCs. Serotype-specific immune responses varied for the 2 unique serotypes (22F and 33F) across the mixed regimens at 30 days PD3.

- The immunogenicity results appear to be similar for the overall study population as well as the subjects who received Pentacel.
- Responses to the assessed concomitant antigens met noninferiority criteria for V114 and Prevnar 13 recipients in the overall study population. Note that among the subjects who received Pentacel, the responses to mumps antigen missed the prespecified noninferiority margin of -5% (the lower bound of the 2-sided 95% CI for the difference in response rates was -5.4%). Nevertheless, the difference appears to be numerically small and might be caused by the smaller sample size due to exclusion of the subjects who received Pentavac. Hence, the results from V114-029 and V114-027 generally support the administration of V114 concomitantly with licensed pediatric vaccines Pentacel, VAQTA, M-M-RII, VARIVAX, HIBERIX, RECOMBIVAX HB, and RotaTeq as part of recommended pediatric vaccination schedules.

Study V114-024 evaluated healthy infants and children 7 months through 17 years of age administered catch-up vaccination regimens. Catch-up vaccination with V114 elicited serotype-specific immune responses, as assessed by IgG GMCs at 30 days after the last dose of study intervention for all 15 serotypes contained in the vaccine. Serotype-specific IgG GMCs and response rates at 30 days after the last dose of study intervention were generally comparable between the V114 and Prevnar 13 intervention groups for the 13 shared serotypes and higher in the V114 group than in the Prevnar 13 group for the 2 unique V114 serotypes.

The applicant evaluated the vaccine in specific populations with increased risk of pneumococcal disease.
- Preterm Infants: the analysis of the preterm infants from study V114-031 and the integrated immunogenicity analysis showed that V114 elicited immune responses in preterm infants (<37 weeks gestational age at birth) administered with a 4-dose series that were generally comparable to Prevnar 13 for the shared serotypes and higher than Prevnar 13 for 2 serotypes unique to V114 (22F and 33F).
- Children with Sickle Cell Disease (SCD): study V114-023 showed that a single dose of V114, administered to children 5 through 17 years of age with SCD, elicited immune responses that were generally comparable to Prevnar 13 for the 13 shared serotypes and higher than Prevnar 13 for 2 serotypes unique to V114 (22F and 33F) at 30 days postvaccination.
- Children with HIV: study V114-030 showed that a single dose of V114, administered to children 6 through 17 years of age with HIV, elicited immune responses (IgG and OPA) that were generally comparable to Prevnar 13 for the 13 shared serotypes and higher than Prevnar 13 for 2 serotypes unique to V114 (22F and 33F) at 30 days postvaccination.

Safety:
- In healthy infants receiving a 4-dose regimen of PCV starting at 6 to 12 weeks of age, the safety profile was generally comparable between V114 and Prevnar 13.
- Among participants 7 to 11 months of age, 12 to 23 months of age, and 2 through 17 years of age who received catch-up vaccination, the safety profiles of 1, 2, or 3-dose catch-up regimens of V114 were generally comparable to those of Prevnar 13.

- V114 was generally tolerated when changing from Prevnar 13 to V114 at Doses 2, 3 or 4 during a 4-dose PCV dosing regimen. The proportions of participants with AEs, including injection-site, systemic, and vaccine-related AEs, and SAEs were generally comparable across mixed PCV regimens and complete V114 or Prevnar 13 regimens.
- The proportions of preterm infants with AEs after any dose, including injection-site AEs, systemic AEs, vaccine-related AEs, and SAEs were generally comparable in both intervention groups.
- In children 5 through 17 years of age with SCD, the overall proportions of participants with AEs and SAEs were generally comparable across intervention groups. However, there was a higher proportion of vaccine-related systemic AEs reported in the V114 group compared to the Prevnar 13 group.
- In children 6 through 17 years of age with HIV, the proportions of participants with 1 or more AEs were generally comparable in both intervention groups. Vaccine-related injection-site and systemic AEs were reported for a higher proportion of participants in the V114 group compared with the Prevnar 13 group.

Overall, the studies showed that V114 met the majority of the pre-specified immunogenicity criteria. Although IgG response to serotype 6A, as assessed by serotype specific IgG GMCs at 30 days PD3, missed the prespecified noninferiority criterion (the lower bound of the 2-sided 95% CI for the GMC ratio being 0.48 versus >0.5) in Study V114-029, this difference appears to be relatively small. Hence, the immunogenicity results appear to be adequate to support the proposed indication. Regarding safety evaluation, the studies showed that the safety profiles are generally comparable between the V114 and Prevnar 13 groups among healthy infants and children. However, in Studies V114-023 and V114-030, the vaccine-related systemic AEs were reported for a higher proportion of participants in the V114 group compared with the Prevnar 13 group among children with SCD and children with HIV. I defer to the clinical reviewers on whether the safety results are adequate to support the proposed indication based on the totality of the evidence.

10.2 Conclusions and Recommendations

Overall, the immunogenicity results appear to be adequate to support the proposed indication. Regarding safety evaluation, the proportion of vaccine-related systemic AEs was higher in the V114 group than the Prevnar 13 group among children with SCD and children with HIV. I defer to the clinical reviewers on whether the safety results are adequate to support the proposed indication.