BLA Clinical Review Memorandum

Application Type	sBLA
STN	125814/428
CBER Received Date	18 August 2025
PDUFA Goal Date	18 June 2026
Division / Office	DCTR/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Nicholas Geagan, D.O. Physician CRB1/DCTR/OVRR
Review Completion Date / Stamped Date	12 June 2026
Supervisory Concurrence	Joohee Lee, MD Branch Chief CRB1/DCTR/OVRR
Applicant	Merck & Co., Inc
Proper Name	Pneumococcal 21-valent Conjugate Vaccine
Trade Name	CAPVAXIVE
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	A 0.5 mL dose contains 4 µg of each pneumococcal capsular polysaccharide antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B, and deOAc15B). The antigens are individually conjugated to CRM197 carrier protein.
Dosage Form(s) and Route(s) of Administration	Solution, intramuscular
Dosing Regimen	Single Dose
Indication(s) and Intended Population(s)	CAPVAXIVE is indicated for:

	• active immunization for the prevention of invasive disease caused by Streptococcus pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 2 through 17 years of age who are at increased risk for pneumococcal disease. • active immunization for the prevention of pneumonia caused by S. pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older.
Orphan Designated (Yes/No)	No

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GLOSSARY

ABCs	Active Bacterial Core Surveillance
AE	Adverse Event
AESI	Adverse Events of Special Interest
APaT	All Participants as Treated
AR	Adverse Reaction
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
CAP	Community-Acquired Pneumonia
CDC	Centers for Disease Control and Prevention
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CKD	Chronic Kidney Disease
CMC	Chemistry, Manufacturing, and Controls
CPR	Cardiopulmonary Resuscitation
CRB	Clinical Review Branch
CSF	Cerebrospinal Fluid
DCTR	Division of Clinical Trial Review
deOAc15B	De-O-acetylated polysaccharide from serotype 15B
eDMC	External Data Monitoring Committee
ER	Emergency Room
ES	Exposed Set
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
IgG	Immunoglobulin G
IM	Intramuscular
IPD	Invasive Pneumococcal Disease
IR	Information Request
MedDRA	Medical Dictionary for Regulatory Activities
OPA	Opsonophagocytic Activity
OVRR	Office of Vaccines Research and Review
PCV	Pneumococcal Conjugate Vaccine
PCV7	Pneumococcal 7-valent Conjugate Vaccine
PCV10	Pneumococcal 10-valent Conjugate Vaccine
PCV13	Pneumococcal 13-valent Conjugate Vaccine
PCV15	Pneumococcal 15-valent Conjugate Vaccine
PCV20	Pneumococcal 20-valent Conjugate Vaccine
PD	Pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMR	Postmarketing Requirement
PnPs	Pneumococcal Polysaccharide
PP	Per-Protocol
PPSV23	Pneumococcal Polysaccharide Vaccine (23-valent)

PPS	Per-Protocol Set
PREA	Pediatric Research Equity Act
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
sBLA	Supplemental Biologics Licensing Application
SD	Standard Deviation
SOC	System Organ Class
STN	Submission Tracking Number
U.S.	United States
USPI	United States Prescribing Information
YOA	Years of Age

1. EXECUTIVE SUMMARY

Merck & Co., Inc (the Applicant) submitted a supplemental Biologics License Application (sBLA) for the licensed pneumococcal 21-valent conjugate vaccine, CAPVAXIVE, for the purpose of extending the indication to children and adolescents 2 through 17 years of age (YOA) with chronic medical conditions putting them at increased risk for invasive pneumococcal disease (IPD) (i.e. chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and/or chronic kidney disease) and updating the prescribing information (PI) to include safety and immunogenicity data from one study in this population. This is the second efficacy sBLA following the original approval of CAPVAXIVE on June 17, 2024. CAPVAXIVE is currently indicated for individuals 18 years of age and older for:

- prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B[1], 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B; and
- prevention of pneumonia caused by *S. pneumoniae serotypes* 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B.

The pneumonia indication was approved via the accelerated approval pathway with a confirmatory real-world evidence study currently underway to confirm effectiveness. The first sBLA, 125814/149, included data from special populations including individuals living with HIV and adults with chronic medical conditions putting them at increased risk for pneumococcal disease.

CAPVAXIVE consists of 4µg of each pneumococcal capsular polysaccharide antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B, and deOAc15B) conjugated to CRM197 carrier protein and is administered as a single dose.

This sBLA contains data from one Phase 3, double-blind, active comparator-controlled, parallel-group study, V116-013 (Study 13). The Applicant is not proposing any changes to the dosage and administration sections of the United States Prescribing Information (USPI). Study 13 evaluated the immunogenicity of CAPVAXIVE compared with PPSV23 in children and adolescents 2 through 17 YOA with prespecified chronic medical conditions (i.e., underlying chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and/or chronic kidney disease). The study enrolled 874 participants into 2 groups: CAPVAXIVE group (527 participants) and PPSV23 group (347 participants).

The primary immunogenicity objectives were to evaluate serotype-specific opsonophagocytic (OPA) geometric mean titers (GMTs) at 30 days postvaccination with

[1] CAPVAXIVE contains de-O-acetylated polysaccharide from serotype 15B [deOAc15B], which induces OPA to serotypes 15B (crossreactive) and 15C (see original BLA 125814/0). The antibody response to deOAc15B is measured as serotype 15C. CAPVAXIVE does not contain unmodified polysaccharide from serotype 15B. Cross-reactive serotype 15B is not included in the pneumonia indication as it was not evaluated in the confirmatory real-world evidence study.

CAPVAXIVE compared with OPA GMTs at 30 days postvaccination with pneumococcal 23-valent polysaccharide vaccine (PPSV23). The predefined success criterion for noninferiority for the OPA GMT ratio (CAPVAXIVE over PPSV23) was met with the lower bound of the 95% CI of the OPA GMT ratio > 0.5 for each of the 12 common serotypes between CAPVAXIVE and PPSV23. The predefined success criterion for superiority for the OPA GMT ratio (CAPVAXIVE over PPSV23) was met with the lower bound of 95% confidence interval (CI) of the OPA GMT ratio > 2.0 for each of the 9 unique serotypes in CAPVAXIVE.

Safety was evaluated as a primary objective in participants who received CAPVAXIVE. Solicited adverse reactions within 5 days of vaccination were reported at higher rates in the CAPVAXIVE group compared with the PPSV23 group (76.9% versus 67.1%). The most frequently reported local reaction in both groups was pain at the injection site, and the most frequently reported systemic reaction was fatigue. The percentage of participants reporting at least 1 unsolicited, nonserious adverse event through 1 month following vaccination was 30.7% in the CAPVAXIVE group and 28.0% in the PPSV23 group. The percentage of participants reporting at least 1 nonfatal serious adverse event (SAE) was 5.5% in the CAPVAXIVE group and 7.2% in the PPSV23 group. None of the nonfatal SAEs were considered as related to study vaccination by this clinical reviewer. No deaths were reported in the CAPVAXIVE group and 2 deaths in the PPSV23 group. None of the deaths were considered as related to study vaccination by this clinical reviewer.

The safety and immunogenicity data from children and adolescents 2 through 17 years of age at increased risk for IPD provided in this sBLA support inclusion in the USPI for use of CAPVAXIVE in pediatric age groups 2 through 17 years of age. The Pediatric Research Equity Act requirements for this age group would be fulfilled with approval of STN 125814.428.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

In Study V116-013, the overall median age of study participants was 8 years. Overall, 59.6% were White, 14.6% were Multiple race categories, 10.4% were American Indian or Alaska Native, 9.6% were Asian, and 5.7% were Black or African American. Most participants were Not Hispanic or Latino (55.5%). The demographic characteristics were similar between the vaccine groups.

1.2 Patient Experience Data

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

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Streptococcus pneumoniae is an encapsulated bacterium that causes significant disease in older adults. Pneumococcal infections can range from invasive disease, defined as infection from a normally sterile site such as meningitis, bacteremia, osteomyelitis, or septic joint, to non-invasive infections such as pneumonia (without bacteremia), sinusitis, or otitis media (CDC, 2024b). *S. pneumoniae* causes pneumonia, which results in approximately 150,000 hospitalizations annually in adults in the United States (U.S.) (CDC, 2024b). It is also the most common cause of bacterial pneumonia in children younger than 5 years of age. Symptoms of pneumonia may include fever, cough, chest

pain with breathing or coughing, shortness of breath and fatigue (CDC, 2021). In cases of pneumonia with bacteremia, case fatality ratio is approximately 10%. Symptoms of meningitis may include headache, fever, nuchal rigidity, seizures, photophobia, neurologic deficits, altered mental status, nausea, and vomiting (Hersi, et al., 2023). *S. pneumoniae* is the most common cause of bacterial meningitis in adults and the second most common cause in children (Oligbu, et al., 2019). Older adults are at highest risk of invasive pneumococcal disease (IPD) if they have certain medical conditions including hematologic cancer, immunosuppressive conditions due to disease or medications, functional or anatomic asplenia, renal disease, chronic heart disease, lung disease (including asthma), liver disease, smoking history, alcoholism, cerebrospinal fluid (CSF) leak or cochlear implants (CDC, 2024c).

Approximately 100 different serotypes of pneumococci have been identified. Some are more invasive when compared with others (Scelfo, et al., 2021). Invasive potential and virulence factors contribute to the pathogenicity of *S. pneumoniae*. A polysaccharide capsule interferes with phagocytosis by inhibiting binding of complement C3b to the cell surface (Dion, et al., 2023). Other pneumococcal proteins interfere with host defenses, allow for adherence to cells, and play a role in host inflammation.

In 2022, preliminary Active Bacterial Core Surveillance (ABCs) data indicated that there were an estimated 27,790 total cases of IPD overall, including 3,220 deaths (CDC, 2024a). Age-specific rates of disease and deaths were applied from the aggregate surveillance area to the age distribution of the United States (U.S.) population for the given year. In 2022, there were 8.3 cases of IPD per 100,000 population. Within the specific ABCs surveillance areas, there were 2,644 cases in adults 18 years of age and older out of a total of 2,922 cases.

It is estimated that in the year 2019, in children <5 years of age, there were approximately 300,000 deaths worldwide due to pneumococcal disease (CDC, 2024d). Among at-risk children from the years 2007 to 2010, rate ratios for IPD (versus children without at-risk/high-risk conditions) were 1.8 (95% CI; 1.4, 2.3) in children <5 years of age and 3.3 (95% CI; 2.4, 4.4) in children 5 to 17 years of age (Pelton, 2014). The risk of IPD is increased further in individuals considered high-risk or immunocompromised (Lynch, 2010).

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

Invasive pneumococcal disease and community-acquired pneumonia (CAP) are treated with antibiotics and supportive care measures, such as respiratory support, if necessary. However, other than vaccines, there are no interventions or treatments currently available for the prevention of invasive disease or community-acquired pneumonia caused by pneumococcal infections.

2.3 Safety and Efficacy of Pharmacologically Related Products

Four pneumococcal vaccines (1 unconjugated, 3 conjugate) are licensed and available in the U.S. Pneumovax 23 (PPSV23; Merck Sharp & Dohme) is administered as a single dose in persons ≥50 years of age and persons ≥2 years of age who are at increased risk for disease. Pneumococcal conjugate vaccines (PCV) Prevnar 13 (PCV13; Wyeth Pharmaceuticals) (No longer licensed in the US), Vaxneuvance (PCV15; Merck Sharp & Dohme), and Prevnar 20 (PCV20; Wyeth Pharmaceuticals) are approved for prevention

of vaccine-serotype IPD in individuals ≥6 weeks of age; PCV13 and PCV20 are also approved for prevention of otitis media (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) in individuals 6 weeks to <6 years of age and vaccine-serotype *S. pneumoniae* pneumonia in individuals ≥18 years of age. Clinical data to support the safety and effectiveness for the indications and populations described above are described in the USPI linked above.

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

CAPVAXIVE is licensed for use in the U.S. for active immunization for the prevention of invasive disease caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older and for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older.

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

Major Regulatory Activity

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

- 17 June 2024 – CAPVAXIVE was initially approved under original BLA 125814 for prevention of invasive pneumococcal disease caused by 22 serotypes and pneumococcal pneumonia caused by 21 serotypes in individuals 18 years of age and older.
- 31 July 2025 – CAPVAXIVE prescribing information was updated to include data in individuals at increased risk for pneumococcal disease and individuals living with HIV

2.6 Other Relevant Background Information

CAPVAXIVE contains de-O-acetylated polysaccharide from serotype 15B [deOAc15B], which induces OPA to serotypes 15B and 15C. The antibody response to deOAc15B is measured as serotype 15C. CAPVAXIVE does not contain unmodified polysaccharide from serotype 15B.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of this sBLA was complete and adequately organized for review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Study V116-013 was conducted in accordance with Good Clinical Practice (GCP). Bioresearch Monitoring (BIMO) inspection did not reveal substantive issues that impact the data submitted in the sBLA. Please see the BIMO review for further details.

3.3 Financial Disclosures

Covered clinical study (name and/or number): V116-013

Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 391
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Reviewer Comment
Upon independent review of the single investigator with a disclosable financial interest this clinical reviewer finds the steps taken to minimize potential bias acceptable and there was no impact on the study. The study was designed as a large multi-site blinded study to minimize bias and the financial interest reported for the investigator was a grant for research of a non-pneumococcal disease.

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

4.1 Chemistry, Manufacturing, and Controls

CAPVAXIVE is a licensed product and no new chemistry, manufacturing, and control (CMC) information was provided in this sBLA.

4.2 Assay Validation

No new assays were submitted for validation to this sBLA.

4.3 Nonclinical Pharmacology/Toxicology

No additional nonclinical pharmacology/toxicology information was submitted to this sBLA.

4.4 Clinical Pharmacology

No additional clinical pharmacology information was submitted to this sBLA.

4.4.1 Mechanism of Action

Protection against invasive pneumococcal disease is conferred mainly by opsonophagocytic killing of *S. pneumoniae*. CAPVAXIVE is a 21-valent vaccine that induces OPA against 22 *S. pneumoniae* serotypes. The de-O-acetylated polysaccharide from serotype 15B has a molecular structure similar to serotype 15C and induces OPA to serotype 15C. The deOAc15B also induces cross-reactive OPA against serotype 15B. An OPA titer that is predictive of protection against invasive pneumococcal disease or pneumococcal pneumonia has not been established.

4.5 Statistical

No major statistical issues were identified. Success criteria for the primary immunogenicity objectives of V116-013 were met and no notable imbalances in safety results across groups were identified. Please see the Statistical Review Memo for further details.

4.6 Pharmacovigilance

No changes to the Applicant's proposed pharmacovigilance plan were submitted to this sBLA and no changes are recommended to the proposed pharmacovigilance plan.

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

5.1 Review Strategy

Clinical data from one study (V116-013) were submitted in this sBLA to support the safety and effectiveness of CAPVAXIVE for the proposed indications in children 2 through 17 years of age with chronic medical conditions (chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and/or chronic kidney disease).

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

The following amendments were reviewed in support of this application (listed by module and section):

- Amendment 0: module 1.1, 1.2, 1.3, 1.4, 1.9 (financial certification and disclosure, Applicant meeting and other correspondence, package insert, pediatric administrative information); module 2.2, 2.5, 2.7 (clinical overview and summaries); module 5.2, 5.3, 5.4 (clinical study reports)
- Amendment 5: module 1.11.3 (response to information request [IR] regarding the applicability of foreign data)
- Amendment 7: module 1.11.3 (response to IR regarding adverse event datasets)
- Amendment 11: module 1.11.3 (response to IR regarding subset analysis of solicited adverse reactions by age)
- Amendments 12, 13, 14: module 1.14 (updated draft prescribing information and carton)

5.3 Table of Studies/Clinical Trials

Table 1. Overview of Clinical Study

Study Number	Description	Study Groups	Number of Participants
V116-013	Randomized, double-blind, active comparator-controlled, parallel group safety and immunogenicity study	CAPVAXIVE (2 through 17 YOA) PPSV23 (2 through 17 YOA)	CAPVAXIVE: 527 PPSV23: 347

Source: adapted from 125814.428 tabular-listing.pdf
Abbreviations: PPSV23=23-valent pneumococcal polysaccharide vaccine

5.4 Consultations

5.4.1 Advisory Committee Meeting

Not applicable

5.4.2 External Consults/Collaborations

Study V116-013 results were presented to the Pediatric Review Committee (PeRC) on April 21, 2026. PeRC agreed that the data are adequate to support the use of CAPVAXIVE in children 2 through 17 years of age and approval of this sBLA fulfills Pediatric Research Equity Act (PREA) Post Marketing Requirement (PMR) #2 from the original BLA 125814.0.

5.5 Literature Reviewed

Centers for Disease Control and Prevention (CDC). 2024a. ABCs Bact Facts Interactive Data Dashboard. https://www.cdc.gov/abcs/bact-facts/data-dashboard.html?CDC_AAref_Val=https://www.cdc.gov/abcs/bact-facts-interactive-dashboard.html.

CDC. 2024b. Clinical Features of Pneumococcal Disease. https://www.cdc.gov/pneumococcal/hcp/clinical-signs/?CDC_AAref_Val=https://www.cdc.gov/pneumococcal/clinicians/clinical-features.html.

CDC. 2024c. Pneumococcal Disease: Causes and How it Spreads. https://www.cdc.gov/pneumococcal/causes/?CDC_AAref_Val=https://www.cdc.gov/pneumococcal/about/risk-transmission.html.

CDC.2024d. Washington (DC): Department of Health and Human Services (HHS). Pneumococcal disease surveillance and trends; 2024 Sep 9 [cited 2025 Feb 12]; [about 12 screens]. Available from: https://www.cdc.gov/pneumococcal/php/surveillance/index.html.

CDC. Epidemiology and Prevention of Vaccine-Preventable Diseases. Gierke R, Wodi AP, and Kobayashi M. 14th ed. Washington, D.C. Public Health Foundation, 2021.

Dion CF, Ashurst JV. Streptococcus pneumoniae. 2023 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 29261971.

Hersi K, Gonzalez FJ, Kondamudi NP. Meningitis. 2023 Aug 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 29083833.

Lynch JP, III, Zhanel GG. Streptococcus pneumoniae: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. Curr Opin Pulm Med 2010;16:217-25.

Oligbu G, Fry NK, Ladhani SN. The Epidemiology and Biostatistics of Pneumococcus. Methods Mol Biol. 2019;1968:215-224. doi: 10.1007/978-1-4939-9199-0_18. PMID: 30929218.

Pelton SI, Weycker D, Farkouh RA, Strutton DR, Shea KM, Edelsberg J. Risk of pneumococcal disease in children with chronic medical conditions in the era of pneumococcal conjugate vaccine. Clin Infect Dis. 2014 Sep 1;59(5):615-23.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study V116-013

NCT06177912
"A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Children and Adolescents With Increased Risk of Pneumococcal Disease"

6.1.1 Objectives

Primary Objectives and Endpoints

1. To evaluate the safety and tolerability of CAPVAXIVE with respect to the percentage of participants with adverse events (AEs).
    a. Solicited injection-site AEs Day 1 through Day 5 postvaccination
    b. Solicited systemic AEs Day 1 through Day 5 postvaccination
    c. Vaccine-related serious AEs (SAEs) Day 1 through the duration of participation in the study
2. To compare the serotype-specific opsonophagocytic (OPA) geometric mean titers (GMTs) at 30 days postvaccination with CAPVAXIVE versus PPSV23
    a. CAPVAXIVE is noninferior to PPSV23 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 12 common serotypes in CAPVAXIVE and PPSV23
        i. Success criteria: the lower bound of the 2-sided 95% confidence interval (CI) of the OPA GMT ratio (CAPVAXIVE/PPSV23) > 0.5
    b. CAPVAXIVE is superior to PPSV23 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 9 unique serotypes in CAPVAXIVE
        i. Success criteria: the lower bound of the 2-sided 95% CI of the OPA GMT ratio (CAPVAXIVE/PPSV23) > 2.0

Secondary Objectives and Endpoints

1. To evaluate the serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days postvaccination with CAPVAXIVE compared with PPSV23
    a. Serotype-specific IgG responses
2. To evaluate the serotype-specific geometric mean fold rises (GMFRs) and percentages of participants with a ≥ 4-fold rise in serotype-specific OPA responses and IgG responses from baseline to 30 days postvaccination within each vaccination group.
    a. Serotype-specific OPA and IgG responses

6.1.2 Design Overview

Study V116-013 is a randomized, double-blind, active comparator-controlled, parallel-group, multi-site, multinational study of CAPVAXIVE in children and adolescents 2 through 17 years of age who have completed a primary pneumococcal vaccination regimen and are at increased risk for pneumococcal disease due to chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and/or chronic kidney disease.

Participants were randomized in a 3:2 ratio to receive a single dose of either CAPVAXIVE or PPSV23 on Day 1. Randomization was stratified by the number of increased-risk conditions for pneumococcal disease (1 increased-risk condition, or ≥2 increased-risk conditions), by prior pneumococcal vaccination (prior PCV7 alone, prior PCV7 and 1 prior PPSV23 dose, prior PCV10 alone, prior PCV10 and 1 prior PPSV23 dose, prior PCV13 alone, or prior PCV13 and 1 prior PPSV23 dose), and age (≥2 through 5 years or ≥6 through 17 years).

Safety evaluation included the following parameters: solicited injection site/systemic adverse events (AEs) and daily body temperature from postvaccination Day 1 through Day 5, unsolicited AEs through postvaccination Day 30, and SAEs/deaths to the end of study.

An external data monitoring committee (eDMC) conducted a periodic review of safety and tolerability data.

Reviewer Comment
The design for this study includes 6 different strata for prior pneumococcal vaccination. As this was an international study, different countries have different standards of care regarding pneumococcal vaccine regimens. Despite including prior pneumococcal vaccine regimens that are not standard of care in the U.S. the results of this study are still applicable.

6.1.3 Population

Individuals were eligible to be included if they met all the following inclusion criteria:

- Children and adolescents 2 years through 17 years of age, at the time of providing the informed consent/assent.
- Documented diagnosis of ≥1 of the following increased-risk conditions for pneumococcal disease: diabetes mellitus, chronic liver disease, chronic lung disease, chronic heart disease, or chronic kidney disease.
- Receiving stable medical management for the risk conditions listed above for ≥3 months with no anticipated major change in treatment expected for the duration of the study and with ≤1 hospitalization directly related to the risk condition within 3 months before study vaccination.
- Completed primary PCV regimen with PCV7, PCV10, or PCV13 at least 8 weeks prior to enrollment, with either a 2+1 or 3+1 regimen according to local recommendations; all doses of the primary regimen must be of the same vaccine.
- Was PPSV23 vaccine-naïve or had not received more than 1 dose of PPSV23 ≥5 years before study vaccination.

- Persons of childbearing potential were not pregnant or breastfeeding.

Individuals were not eligible to be included if they met any of the following exclusion criteria:

- Had a curative procedure/surgery for chronic heart disease and did not require medication, follow-up, additional interventions, or further management per local guidelines.
- Had a history of active hepatitis within 3 months before study vaccination (Day 1).
- Had a history of diabetic ketoacidosis or 2 or more episodes of severe, symptomatic hypoglycemia within 3 months before study vaccination (Day 1).
- Had a history of severely decreased kidney function, dialysis, autoimmune related chronic kidney disease, nephrotic syndrome of any cause, or an acute/reversible cause of kidney disease.
- Had a history of severe pulmonary hypertension or a history of Eisenmenger syndrome.
- Had a history of IPD or known history of other culture-positive pneumococcal disease within 3 years before study vaccination (Day 1).
- Had a known or suspected impairment of immunological function including congenital or acquired immunodeficiency, documented HIV infection, functional or anatomic asplenia, or autoimmune disease.
- Receipt of systemic corticosteroids or immunosuppressive therapy.

6.1.4 Study Treatments or Agents Mandated by the Protocol

All study interventions were administered intramuscularly as a single dose.

CAPVAXIVE

- Composition: 4 µg of each pneumococcal polysaccharide (PnPs) antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B, and deOAc15B)
- Dose Volume: 0.5 mL
- Presentation: Pre-filled syringe

PPSV23

- Composition: 25µg of each PnPs antigen (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F)
- Dose Volume: 0.5 mL
- Presentation: Pre-filled syringe

6.1.5 Directions for Use

Personnel who prepared and administered all study vaccines were not blinded to the vaccine assignment. Study vaccine was administered as a single IM injection, preferably in the deltoid region of the participant's arm.

6.1.6 Sites and Centers

This study was conducted at 92 centers in 13 countries (in descending order: Colombia, United States, Turkey, Chile, Spain, Canada, Finland, Japan, Poland, Thailand, Israel, France, Sweden) (See Table 3 for details).

6.1.7 Surveillance/Monitoring

Safety Monitoring

- Clinical assessments: physical exam before vaccination (Day 1)
- A pregnancy test consistent with local requirements performed before vaccination at Visit 1 in women of childbearing potential.
- AE Monitoring:
  - All participants were observed for 30 mins after vaccination for any immediate reactions
  - Solicited local reactions: postvaccination Days 1-5
    - Injection site pain, erythema, swelling
    - Grading scale:
      - Pain: Grade 1: Does not interfere with activity; Grade 2: Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity; Grade 3: Any use of narcotic pain reliever or prevents daily activity; Grade 4: Emergency room (ER) visit or hospitalization.
      - Erythema/Swelling: Grade 1: Size measured as ≤ 5 cm; Grade 2: 5.1-10 cm; Grade 3: >10 cm; Grade 4: Necrosis or exfoliative dermatitis or ER visit or hospitalization.
  - Solicited systemic ARs: postvaccination Days 1-5
    - Arthralgia, fatigue, headache, malaise, myalgia, pyrexia, somnolence urticaria
    - Grading scale:
      - Arthralgia, fatigue, headache, malaise, myalgia, pyrexia, somnolence urticaria: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant interference with activity, prevents daily activity; Grade 4: ER visit or hospitalization.
      - Pyrexia: Grade 1: 38.0-38.4°C; Grade 2: 38.5-38.9°C; Grade 3: 39.0-40.0°C, Grade 4: > 40.0°C
  - Unsolicited AEs: postvaccination Days 1-30
  - SAEs, deaths, AEs leading to withdrawal from the study: postvaccination Day 1 through postvaccination Month 6

Withdrawals/Discontinuation

A participant was withdrawn from the study if the participant or participant's legally acceptable representative withdrew consent from the study.

If a participant withdrew from the study, they no longer received study intervention nor were they followed at scheduled protocol visits.

If a participant failed to return to the clinic for a required study visit and/or if the site was unable to contact the participant, the following procedures were to be performed:

- The site attempted to contact the participant and reschedule the missed visit. If the participant was contacted, the participant should have been counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee made every effort to regain contact with the participant at each missed visit. These contact attempts were documented in the participant's medical record.

External Data Monitoring Committee (eDMC): A periodic review of safety and tolerability data across the CAPVAXIVE Phase 3 program will be conducted by an independent, unblinded, external DMC. The DMC was responsible for ongoing safety reviews and recommendations for continuation or discontinuation of the study.

6.1.8 Endpoints and Criteria for Study Success

See section 6.1.1

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary Endpoints/Hypotheses (H1 and H2)
For the 12 common serotypes, the primary noninferiority hypothesis (H1) regarding OPA GMT levels between recipients of V116 and PPSV23 is:

H0: GMT1/GMT2 ≤ 0.50 versus
H1: GMT1/GMT2 > 0.50

where GMT1 is the serotype-specific OPA GMT for the CAPVAXIVE group and GMT2 is the serotype-specific OPA GMT for the PPSV23 group. A ratio of 0.50 corresponds to an OPA GMT that is 2.0-fold lower in the V116 group compared with the PPSV23 group. Rejecting the null hypothesis (H0) at the 1-sided $\alpha = 0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (V116/PPSV23) being > 0.50 and would lead to the conclusion that the OPA response to V116 for the common serotype is noninferior to that of PPSV23.

For the 9 serotypes that are unique to V116, the primary superiority hypothesis (H2) regarding OPA GMT levels between recipients of V116 and PPSV23 is:

H0: GMT1/GMT2 ≤ 2.0 versus
H1: GMT1/GMT2 > 2.0

where GMT1 is the serotype-specific OPA GMT for the CAPVAXIVE group, and GMT2 is the serotype-specific OPA GMT for the PPSV23 group. A ratio of 2.0 corresponds to an OPA GMT that is 2.0-fold higher in the V116 group compared with the PPSV23 group. Rejecting the null hypothesis (H0) at the 1-sided $\alpha = 0.025$ level corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (V116/PPSV23) being > 2.0 and would lead to the conclusion that the OPA response to V116 for the unique serotype is superior to that of PPSV23.

A sample size of approximately 820 participants provides the study < 90% power to declare noninferiority to PPSV23 of CAPVAXIVE for the 12 common serotypes and superiority to PPSV23 for the 9 unique serotypes at an overall 1-sided 2.5% alpha-level

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Analysis Populations

Populations used for the study analyses are displayed in Table 2. The primary estimand immunogenicity analysis was performed on the Per-Protocol Set (PPS). The Exposed set (ES) was the primary population for safety analysis.

Table 2. Analysis Populations

Population	Description
Screened Set	All participants who were screened for eligibility.
All Participants as Treated (APaT)	All participants who received the study intervention. Analysis per group is based on the administered intervention.
Per-Protocol (PP) Population	All eligible who received the study intervention as per protocol, had immunogenicity results pre-and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. Analysis per group is based on the administered intervention.

Source: Adapted from STN 125814/428 Study V116-013 Protocol: Section 9.4

6.1.10.1.1 Demographics, Children and Adolescents 2 Through 17 Years of Age

In the APaT, the overall median age of study participants was 8 years. The demographics of participants in the APaT are shown in Table 3. Overall, 59.6% were White, 14.6% were Multiple race categories, 10.4% were American Indian or Alaska Native, 9.6% were Asian, and 5.7% were Black or African American. 44.4% of participants were Hispanic or Latino. The demographic characteristics were similar between the vaccine groups.

Table 3. Demographic and Baseline Characteristics, APaT

Characteristic	CAPVAXIVE N=527	PPSV23 N=347	Total N=874
Sex, n (%)	--	--	--
Male	308 (58.4)	207 (59.7)	515 (58.9)
Female	219 (41.6)	140 (40.3)	359 (41.1)

Characteristic	CAPVAXIVE N=527	PPSV23 N=347	Total N=874
Age, years	--	--	--
Mean age (SD)	8.2 (4.1)	7.8 (3.8)	8.0 (4.0)
Median age	8.0	7.0	8.0
Race, n (%)	--	--	--
American Indian or Alaska Native	48 (9.1)	43 (12.4)	91 (10.4)
Asian	47 (8.9)	37 (10.7)	84 (9.6)
Black or African American	31 (5.9)	19 (5.5)	50 (5.7)
White	321 (60.9)	200 (57.6)	521 (59.6)
Multiple Race Categories	80 (15.2)	48 (13.8)	128 (14.6)
Ethnicity, n (%)	--	--	--
Hispanic/Latino	231 (43.8)	157 (45.2)	388 (44.4)
Not Hispanic/Latino	296 (56.2)	189 (54.5)	485 (55.5)
Unknown	0 (0.0)	1 (0.3)	1 (0.1)
Country, n (%)	--	--	--
Canada	36 (6.8)	21 (6.1)	57 (6.5)
Chile	72 (13.7)	53 (15.3)	125 (14.3)
Columbia	120 (22.8)	83 (23.9)	203 (23.2)
Finland	37 (7.0)	18 (5.2)	55 (6.3)
France	9 (1.7)	7 (2.0)	16 (1.8)
Israel	13 (2.5)	7 (2.0)	20 (2.3)
Japan	23 (4.4)	25 (7.2)	48 (5.5)
Poland	22 (4.2)	19 (5.5)	41 (4.7)
Spain	37 (7.0)	25 (7.2)	62 (7.1)
Sweden	0 (0.0)	2 (0.6)	2 (0.2)
Turkey	43 (8.2)	29 (8.4)	72 (8.2)
Thailand	21 (4.0)	10 (2.9)	31 (3.5)
United States	94 (17.8)	48 (13.8)	142 (16.2)

Characteristic	CAPVAXIVE N=527	PPSV23 N=347	Total N=874
Prior Pneumococcal Vaccination, n (%)	--	--	--
Prior PCV7 alone	31 (5.9)	24 (6.9)	55 (6.3)
Prior PCV7 and one prior PPSV23 dose	2 (0.4)	2 (0.6)	4 (0.5)
Prior PCV10 alone	176 (33.4)	111 (32.0)	287 (32.8)
Prior PCV10 and one prior PPSV23 dose	4 (0.8)	2 (0.6)	6 (0.7)
Prior PCV13 alone	302 (57.3)	195 (56.2)	497 (56.9)
Prior PCV13 and one prior PPSV23 dose	5 (0.9)	4 (1.2)	9 (1.0)
Others	6 (1.1)	9 (2.6)	15 (1.7)
Missing	1 (0.2)	0 (0.0)	1 (0.1)
Number of increased-risk conditions for pneumococcal disease at randomization	--	--	--
1 increased-risk condition	508 (96.4)	330 (95.1)	838 (95.9)
≥2 increased-risk conditions	19 (3.6)	17 (4.9)	36 (4.1)
Prior PCV primary regimen[a]	--	--	--
3+1 regimen	201 (38.1)	140 (40.3)	341 (39.0)
2+1 regimen	303 (57.5)	189 (54.5)	492 (56.3)
Others	22 (4.2)	18 (5.2)	40 (4.6)
Missing	1 (0.2)	0 (0.0)	1 (0.1)

Source: Adapted from STN 125814/428, V116-013 Clinical Study Report: Table 10-2
[a] 2+1 regimen refers to the administration of 2 priming doses followed by 1 booster dose prior to 2 years of age according to local recommendations. 3+1 regimen refers to the administration of 3 priming doses followed by 1 booster dose prior to 2 years of age according to local recommendations. Others include any regimen other than the 3+1 or 2+1 regimen.
APaT= all participants as treated: Participants who received at least the first dose of the study intervention. Analyses were performed according to the study product administered.
Abbreviations: N=number of participants; n/%=number / percentage of participants in a given category; SD=standard deviation PCV7= pneumococcal 7-valent conjugate vaccine; PCV10= pneumococcal 10-valent conjugate vaccine; PCV13= pneumococcal 13-valent conjugate vaccine; PPSV23=pneumococcal vaccine, polyvalent (23-valent); SD=standard deviation.

6.1.10.1.2 Subject Disposition

A total of 882 participants were randomized and 876 received study intervention (528 received CAPVAXIVE and 348 received PPSV23). Overall, 867 (98.3%) of participants completed the study. The disposition of the participants who contributed to the analyses is presented in Table 4.

Table 4. Subject Disposition, Study 13

Population	Number of Participants N (%)
CAPVAXIVE	--
Randomized	531 (100)
Exposed Set (ES)	528 (99.4)
Per Protocol Set (PPS) at least one timepoint	488 (91.9
PPSV23	--
Randomized	351 (100)
ES	348 (99.1)
PPS at least one timepoint	315 (89.7)

Source: Adapted from STN 125814.428 Table 10-1
N=total number of subjects; PPSV23=pneumococcal vaccine, polyvalent (23-valent)

By the end of study, 73 (8.3%) participants (40 [7.5%] in the CAPVAXIVE group and 33 [9.4%] in the PPSV23 group) were excluded from the PPS. The most common reasons for exclusions from analysis include: Pneumococcal vaccine naïve or prior pneumococcal vaccination prohibited by protocol (25 participants [4.7%] CAPVAXIVE, 20 participants [5.7%] PPSV23); Missing serology results (19 participants [4.3%] CAPVAXIVE, 17 participants [4.8%] PPSV23); Missing results for intrinsic killing test (23 participants [4.3%] CAPVAXIVE, 17 participants [4.8%] PPSV23).

Fifteen participants discontinued the study: 8 participants due to withdrawal by parent/guardian (5 CAPVAXIVE recipients, 3 PPSV23 recipients), 2 participants due to death (2 PPSV23 recipients), 2 participants due to lost to follow-up (2 CAPVAXIVE recipients), 2 randomized by mistake without study treatment (1 CAPVAXIVE recipient, 1 PPSV23 recipient), and 1 CAPVAXIVE recipient for other reasons.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

CAPVAXIVE met the predefined criterion for noninferiority compared with PPSV23 (lower bound of 95% CI of the OPA GMT ratio [CAPVAXIVE/PPSV23] > 0.5) for each of the 12 common serotypes at 30 days postvaccination and the predefined criterion for superiority compared with PPSV23 (lower bound of 95% CI of the OPA GMT ratio [CAPVAXIVE/PPSV23] > 2.0) for each of the 9 serotypes unique to CAPVAXIVE at 30 days postvaccination (Table 5).

Table 5. Serotype-Specific OPA GMTs, Per-Protocol Population

Pneumococcal Serotype	CAPVAXIVE N=488 GMT (n)	PPSV23 N=315 GMT (n)	GMT Ratio (CAPVAXIVE/PPSV23) (95% CI)
12 common serotypes	--	--	--
3	526.6 (488)	517.0 (314)	1.02 (0.89, 1.17)
7F	20,618.1 (486)	14,207.2 (315)	1.45 (1.24, 1.70)
8	12,294.5 (485)	8,966.9 (313)	1.37 (1.20, 1.56)
9N	35,556.8 (485)	18,587.8 (315)	1.91 (1.64, 2.23)
10A	13,719.7 (485)	5,363.8 (311)	2.56 (2.18, 3.00)
11A	10,396.3 (486)	3,129.8 (312)	3.32 (2.80, 3.95)
12F	14,752.0 (486)	4,820.1 (314)	3.06 (2.62, 3.58)
17F	40,011.8 (481)	11,267.4 (312)	3.55 (3.02, 4.17)
19A	9,009.8 (486)	9,797.6 (314)	0.92 (0.78, 1.08)
20A	37,532.2 (480)	14,787.0 (311)	2.54 (2.13, 3.02)
22F	20,162.7 (487)	7,770.3 (313)	2.59 (2.21, 3.04)
33F	73,201.8 (488)	40,609.0 (314)	1.80 (1.54, 2.11)
9 serotypes unique to CAPVAXIVE	--	--	--
6A	16,910.9 (480)	5,653.8 (311)	2.99 (2.46, 3.64)
15A	69,527.8 (485)	5,332.2 (315)	13.04 (11.13, 15.27)

Pneumococcal Serotype	CAPVAXIVE N=488 GMT (n)	PPSV23 N=315 GMT (n)	GMT Ratio (CAPVAXIVE/PPSV23) (95% CI)
15C	34,539.1 (480)	4,398.4 (308)	7.85 (6.29, 9.81)
16F	31,544.9 (485)	5,449.7 (313)	5.79 (5.01, 6.69)
23A	28,591.7 (474)	4,882.0 (296)	5.86 (4.88, 7.03)
23B	5,988.2 (485)	370.5 (312)	16.16 (12.03, 21.72)
24F	11,102.2 (478)	2,771.8 (297)	4.01 (3.40, 4.72)
31	46,163.7 (484)	2,563.0 (311)	18.01 (15.09, 21.50)
35B	40,102.8 (482)	7,812.5 (311)	5.13 (4.45, 5.93)

Source: Adapted from STN 125814.428 V116-013 Clinical Study Report: Tables 11-1, 11-2
Abbreviations: OPA=opsonophagocytic activity; GMT=geometric mean titer; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis. PPSV23=23-valent pneumococcal vaccine (Pneumovax 23)
Notes: Per-protocol: defined as all randomized participants without deviations from the protocol that would substantially affect immunogenicity. n=maximum number of participants (across all serotypes) with serology result contributing to the primary (OPA) immunogenicity analysis and secondary (IgG) analyses, respectively.

Reviewer Comment

CAPVAXIVE met all the predefined noninferiority and superiority criteria for both common and unique serotypes, although the immune responses against serotype 3 were numerically lower compared with all other serotypes and noninferiority compared with PPSV23 was met by a smaller margin. This is notable as serotype 3 is the leading cause of pediatric IPD despite inclusion in standard-of-care pneumococcal vaccines. However, this reviewer considers overall effectiveness based on OPA GMT responses supportive of an age expansion down to 2 through 17 YOA.

6.1.11.2 Analyses of Secondary Endpoints

The distribution of serotype-specific IgG concentrations at 30 days postvaccination was numerically similar between the intervention groups for the 12 common serotypes between CAPVAXIVE and PPSV23; GMC ratios were > 1 for some serotypes (10A, 11A, 12F, 17F, 20A, and 22F) and < 1 for the other common serotypes. The distribution of serotype-specific IgG concentrations at 30 days postvaccination was numerically higher in the CAPVAXIVE group for the 9 serotypes unique to CAPVAXIVE, compared with the PPSV23 group (Table 6); GMC ratios ranged from 1.92 (6A) to 17.38 (31).

Table 6. IgG Geometric Mean Concentrations at 30 Days Postvaccination, Per-Protocol Set

Pneumococcal Serotype	CAPVAXIVE N=527 GMC (n)	PPSV23 N=347 GMC (n)	GMC Ratio (CAPVAXIVE/PPSV23) (95% CI)
12 common serotypes	--	--	--
3	1.56 (462)	1.88 (299)	0.83 (0.72, 0.95)
7F	7.33 (462)	7.37 (299)	0.99 (0.86, 1.15)
8	13.68 (462)	17.86 (299)	0.77 (0.67, 0.87)
9N	7.11 (462)	9.41 (299)	0.76 (0.65, 0.88)
10A	8.47 (462)	4.69 (299)	1.81 (1.50, 2.17)
11A	7.47 (462)	4.32 (299)	1.73 (1.49, 2.01)
12F	1.78 (462)	1.38 (299)	1.28 (1.07, 1.54)
17F	14.75 (462)	6.13 (298)	2.41 (2.06, 2.81)
19A	13.50 (462)	15.97 (299)	0.85 (0.71, 1.00)
20A	9.09 (462)	5.75 (299)	1.58 (1.34, 1.87)

Pneumococcal Serotype	CAPVAXIVE N=527 GMC (n)	PPSV23 N=347 GMC (n)	GMC Ratio (CAPVAXIVE/PPSV23) (95% CI)
22F	14.20 (462)	10.23 (299)	1.39 (1.17, 1.64)
33F	6.75 (462)	9.34 (299)	0.72 (0.61, 0.85)
9 serotypes unique to CAPVAXIVE	--	--	--
6A	11.98 (462)	6.25 (299)	1.92 (1.59, 2.31)
15A	12.00 (462)	1.24 (299)	9.67 (8.07, 11.60)
15C	13.54 (462)	2.55 (299)	5.32 (4.35, 6.50)
16F	2.35 (462)	0.18 (299)	12.97 (11.04, 15.24)
23A	7.17 (462)	1.05 (299)	6.84 (5.56, 8.43)
23B	6.47 (462)	1.29 (299)	5.03 (4.18, 6.04)
24F	2.39 (462)	0.22 (299)	10.72 (8.83, 13.01)
31	4.67 (462)	0.27 (299)	17.38 (14.92, 20.24)
35B	8.96 (462)	0.89 (299)	10.10 (8.72, 11.70)

Source: Adapted from STN 125814.428 V116-013 Clinical Study Report: Tables 14.2-5, 14.2-6
Abbreviations: GMC=geometric mean concentration; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis; PPSV23=23-valent pneumococcal vaccine (Pneumovax 23)
Per-Protocol (PP): defined as all randomized participants without deviations from the protocol that would substantially affect immunogenicity

The distribution of serotype-specific GMFRs and % ≥ 4-fold rise in OPA responses from baseline to 30 days postvaccination were generally numerically higher in the CAPVAXIVE group compared with PPSV23 for the 12 common serotypes except for serotype 19A. For the 9 serotypes unique to CAPVAXIVE, these two endpoints were numerically higher in the CAPVAXIVE group compared with the PPSV23 group (Table 7).

Table 7. Serotype-specific OPA GMFRs at 30 Days Postvaccination, Per-Protocol Set

Pneumococcal Serotype	CAPVAXIVE N=527 GMFR (n)	CAPVAXIVE N=527 % ≥ 4-fold rise (n)	PPSV23 N=347 GMFR (n)	PPSV23 N=347 % ≥ 4-fold rise (n
12 common serotypes	--	--	--	--
3	7.9 (413)	64.6% (413)	7.6 (274)	66.1% (274)
7F	15.8 (417)	84.2% (417)	10.5 (271)	79.7% (271)
8	30.5 (391)	92.3% (391)	21.7 (255)	90.6% (255)
9N	13.9 (412)	82.8% (412)	8.0 (265)	71.7% (265)
10A	15.4 (373)	73.5% (373)	6.0 (255)	47.5% (255)
11A	18.6 (387)	76.2% (387)	5.9 (249)	46.2% (249)
12F	452.7 (420)	96.7% (420)	149.3 (275)	96.0% (275)
17F	33.3 (395)	92.4% (395)	9.9 (258)	74.0% (258)
19A	6.6 (408)	57.8% (408)	7.2 (272)	64.0% (272)
20A	10.4 (361)	77.8% (361)	4.1 (256)	48.0% (256)
22F	22.2 (402)	84.1% (402)	8.4 (262)	65.3% (262)
33F	18.2 (416)	88.9% (416)	10.0 (267)	74.2% (267)
9 serotypes unique to CAPVAXIVE	--	--	--	--
6A	22.1 (380)	76.3% (380)	7.1 (246)	55.7% (246)
15A	26.6 (400)	91.3% (400)	2.0 (268)	22.8% (268)
15C	124.5 (365)	90.7% (365)	13.4 (241)	68.9% (241)
16F	7.6 (400)	67.5% (400)	1.5 (259)	13.5% (259)
23A	14.2 (323)	75.2% (323)	2.2 (219)	27.4% (219)
23B	92.9 (390)	78.2 (390)	6.2 (241)	42.7% (241)

Pneumococcal Serotype	CAPVAXIVE N=527 GMFR (n)	CAPVAXIVE N=527 % ≥ 4-fold rise (n)	PPSV23 N=347 GMFR (n)	PPSV23 N=347 % ≥ 4-fold rise (n
24F	4.4 (357)	47.6% (357)	1.1 (214)	7.9% (214)
31	28.8 (386)	89.9% (386)	1.6 (250)	13.6% (250)
35B	6.0 (387)	60.7% (387)	1.3 (256)	7.8% (256)

Source: Adapted from STN 125814.428 V116-013 Clinical Study Report: Tables 14.2-7, 14.2-8
Abbreviations: GMC=geometric mean concentration; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis; PPSV23=23-valent pneumococcal vaccine (Pneumovax 23)
Per-Protocol (PP): defined as all randomized participants without deviations from the protocol that would substantially affect immunogenicity

Reviewer Comment
PPSV23 recipients were observed to have GMFRs up to 13.4 and increased seroresponse rates for the 9 serotypes unique to CAPVAXIVE. These measurable responses are potentially due to low baseline GMCs and cross-reactivity between biochemically similar serotypes contained in PPSV23.

6.1.11.3 Subpopulation Analyses

For the primary immunogenicity endpoint, serotype-specific OPA GMT ratios at 30 days postvaccination with CAPVAXIVE, within each of the subgroup categories analyzed (age, sex, race, ethnicity, number of risk factors) were generally consistent with results observed in the overall population.

6.1.11.4 Dropouts and/or Discontinuations

See Section 6.1.10.1.2

6.1.11.5 Exploratory and Post Hoc Analyses

CAPVAXIVE elicited OPA responses based on GMTs to cross-reactive serotype 6C and serotype 15B at 30 days postvaccination in a descriptive analysis. The distribution of serotype-specific OPA titers with CAPVAXIVE were numerically similar between serotype 15B and serotype 15C; the distribution of serotype-specific OPA titers at 30 days postvaccination was higher for serotype 6A compared with serotype 6C.

In a post hoc analysis, serotype 15B was evaluated using the same methodology conducted for the primary immunogenicity analyses. The estimated GMT ratio (CAPVAXIVE/PPSV23) for serotype 15B was 3.78 (95% CI: 3.03, 4.73) which met the primary noninferiority criterion for the common serotypes between CAPVAXIVE and PPSV23 of a lower bound > 0.5.

Reviewer comment
Cross-reactivity of serotypes 15B and 6C was initially evaluated in the original BLA 125814/0 based on the structural similarity to those covered by CAPVAXIVE, 15C and 6A, respectively. Serotype 6C did not meet the prespecified success criteria for non-inferiority. Although this was not a prespecified endpoint, CBER requested a post hoc analysis based on the same methodology performed as the primary immunogenicity analysis (GMT ratio with a lower bound 95% CI >0.5) to determine if the immune response to 15B was comparable with the serotypes covered by CAPVAXIVE. This analysis was repeated for the age group studied in this sBLA (2 through 17 years of age).

6.1.12 Safety Analyses

6.1.12.1 Methods

See Section 6.1.7

6.1.12.2 Overview of Adverse Events

A total of 874 participants received 1 dose of CAPVAXIVE (n=527) or PPSV23 (n=347). Table 8 provides an overview of the rates of adverse events in the CAPVAXIVE group compared with the PPSV23 group during the study period. The overall rates of solicited adverse reactions were numerically similar between the two groups (CAPVAXIVE 76.9; PPSV23 67.1%). The rates of participants reporting unsolicited events were numerically similar between the two groups (CAPVAXIVE 30.7%; PPSV23 28.0%).

Table 8. Overview of Adverse Events, Study 13, All Participants as Treated

Event	CAPVAXIVE N=527 n (%)	PPSV23 N=347 n (%)
Solicited injection site reaction within 5 days	382 (72.5)	202 (58.2)
Solicited systemic adverse reaction within 5 days	313 (59.4)	204 (58.8)
Unsolicited nonserious AE up to 30 days	162 (30.7)	97 (28.0)
SAEs up to 6 months	29 (5.5)	25 (7.2)
Deaths	0	2 (0.6)

Source: Adapted from STN 125814.428 V116-013 Clinical Study Report: Table 12-1, 12-2
Abbreviations: PPSV23=23-valent pneumococcal vaccine (Pneumovax 23).N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis; AE=adverse event, SAE=serious adverse event
All Participants as Treated: defined as all randomized participants who received the study intervention.

Solicited Adverse Reactions (AR)

Within 5 days postvaccination, the percentage of participants reporting any injection site reaction was higher in the CAPVAXIVE group (72.5%) compared with the PPSV23 group (58.2%) (Table 9). This discrepancy was primarily driven by pain at the injection site which was also the most frequently reported injection site reaction in both groups (CAPVAXIVE 67.7%, PPSV23 54.5%).

Table 9. Solicited Local and Systemic Adverse Reactions, Within 5 Days Postvaccination, Study 13, All Participants as Treated

Adverse Events	CAPVAXIVE N=527 n (%)	PPSV23 N=347 n (%)
One or more solicited adverse events	405 (76.9)	233 (67.1)
Local adverse reactions[b] (injection site): Severity	--	--
Pain	--	--
Any	357 (67.7)	189 (54.5)
Mild	243 (46.1)	127 (36.6)
Moderate	109 (20.7)	55 (15.9)
Severe	5 (0.9)	7 (2.0)
Erythema[c]	--	--
Any	128 (24.3)	57 (16.4)
Mild	79 (15.0)	45 (13.0)
Moderate	40 (7.6)	10 (2.9)
Severe	9 (1.7)	2 (0.6)
Swelling[c]	--	--
Any	99 (18.8)	63 (18.2)

Adverse Events	**CAPVAXIVE N=527 n (%)**	**PPSV23 N=347 n (%)**
Mild	64 (12.1)	49 (14.1)
Moderate	26 (4.9)	13 (3.7)
Severe	9 (1.7)	1 (0.3)
Systemic adverse events: Severity	--	--
Arthralgia	--	--
Any	23 (4.4)	19 (5.5)
Mild	20 (3.8)	11 (3.2)
Moderate	2 (0.4)	7 (2.0)
Severe	1 (0.2)	1 (0.3)
Fatigue	--	--
Any	106 (20.1)	73 (21.0)
Mild	70 (13.3)	43 (12.4)
Moderate	32 (6.1)	28 (8.1)
Severe	4 (0.8)	2 (0.6)
Headache	--	--
Any	90 (17.1)	53 (15.3)
Mild	66 (12.5)	40 (11.5)
Moderate	24 (4.6)	13 (3.7)
Severe	0	0
Irritability	--	--
Any	61 (11.6)	38 (11.0)
Mild	37 (7.0)	25 (7.2)
Moderate	23 (4.4)	12 (3.5)
Severe	1 (0.2)	1 (0.3)
Malaise	--	--
Any	70 (13.3)	32 (9.2)
Mild	43 (8.2)	16 (4.6)
Moderate	27 (5.1)	15 (4.3)
Severe	0	1 (0.3)
Myalgia	--	--
Any	33 (6.3)	18 (5.2)
Mild	19 (3.6)	10 (2.9)
Moderate	14 (2.7)	8 (2.3)
Severe	0	0
Somnolence	--	--
Any	50 (9.5)	32 (9.2)
Mild	38 (7.2)	18 (5.2)
Moderate	9 (1.7)	14 (4.0)
Severe	3 (0.6)	0
Urticaria	--	--
Any	14 (2.7)	6 (1.7)
Mild	9 (1.7)	5 (1.4)
Moderate	5 (0.9)	1 (0.3)
Severe	0	0
Pyrexia[d]	--	--
≥38.0°C (100.4°F)	24 (4.6)	20 (5.8)
≥38.0°C (100.4°F) to <38.5°C (101.3°F)	14 (2.7)	7 (2.0)
≥38.5°C (101.3°F) to <39.0°C (102.2°F)	8 (1.5)	12 (3.5)
≥39.0°C (102.2°F) to <40.0°C (104.0°F)	2 (0.4)	1 (0.3)

Source: Adapted from STN 125814.428 V116-013 Clinical Study Report: Table 12-2, 14.3-11
Abbreviations: N=number of participants in particular cohort; n (%)=number and percentage of participants with specified adverse event; PPSV23=23-valent pneumococcal vaccine [Pneumovax 23]
All Participants as Treated: defined as all randomized participants who received the study intervention.
Notes: Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity
a: Every individual is counted a single time for each applicable row and column.
b: Injection-site erythema, injection-site pain, injection-site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination.
c: Injection site erythema and injection site swelling from Day 1 through Day 5 postvaccination are graded according to size and presented as intensity grade as follows: 0 to ≤5.0 cm=Mild; >5.0 to ≤10.0 cm=Moderate; >10.0 cm=Severe.
d: Pyrexia was defined as temperature ≥38.0°C (100.4°F) solicited from Day 1 through Day 5 postvaccination. Percentages are based on the number of individuals with temperature data.

The majority of participants with solicited ARs had events of short duration (≥3 days) with 61.3% in the CAPVAXIVE group and 53.6% in the PPSV23 group.

Reviewer Comment
In the opinion of this reviewer, the numerically higher rates of reactogenicity with CAPVAXIVE compared with PPSV23 is not a major safety concern. The major driver in the difference of rates was primarily local reactions (injection site pain and erythema). The majority of these events lasted less than 3 days (pain: 88.5% CAPVAXIVE, 83.6% PPSV23; erythema: 80.4% CAPVAXIVE, 82.5% PPSV23). This trend was observed in the original BLA 125775/0 in pneumococcal vaccine-naïve adults 18 through 49 years of age (CAPVAXIVE 78.2% versus PPSV23 71.5%), which was determined to be an acceptable reactogenicity profile. Despite numerically higher rates of reactogenicity with CAPVAXIVE, the overall rates of Grade 3 solicited reactions were low (CAPVAXIVE 4.6% versus PPSV23 3.5%).

Unsolicited Adverse Events (AE): 30 Days Postvaccination
Rates of non-serious unsolicited AEs within 30 days postvaccination were similar between the CAPVAXIVE group (30.7%) and the PPSV23 group (28.0%). The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) included: *Infections and infestations* (CAPVAXIVE 15.0% versus PPSV23 11.8%; most commonly *nasopharyngitis and upper respiratory tract infection), Respiratory, thoracic, and mediastinal disorders* (CAPVAXIVE 6.5% versus PPSV23 5.8%; most commonly *asthma*), and *Gastrointestinal disorders* (CAPVAXIVE 4.4% versus PPSV23 6.6%; most commonly *diarrhea and vomiting*).

At least 1 Grade 3 unsolicited AE was reported in 2.3% of participants in the CAPVAXIVE group and 2.9% in the PPSV23 group.

Reviewer Comment
Except for nasopharyngitis and upper respiratory tract infections, there was no clustering of PTs for unsolicited adverse events (reported rates > 2.0%). For these two events the reporting rates were similar between CAPVAXIVE and PPSV23 (nasopharyngitis 5.1% CAPVAXIVE versus 3.5% PPSV23, and upper respiratory tract infections 2.8% CAPVAXIVE versus 1.4% PPSV23). No clustering was noted for any Grade 3 unsolicited AEs.

6.1.12.3 Deaths

No deaths were reported in participants in the CAPVAXIVE group and 2 deaths were reported in the PPSV23 group (*septic shock* and *cardiopulmonary failure*). The narratives for these deaths are included below:

Subject (b) (6) *(Septic shock):* Participant was a 5-year-old male with a significant past medical history of CKD, anorectal malformation status post colostomy who was hospitalized on Day 35 postvaccination due to a scheduled surgical procedure and developed symptoms concerning for sepsis on Day 42 (post-operative Day 5) and was diagnosed with peritonitis. No organisms were identified through culture results during his hospital course. Participant had further worsening of symptoms despite appropriate treatment and died on Day 48 with the cause of death being septic shock.

Subject (b) (6) *(Cardiopulmonary failure):* Participant was a 4-year-old male with a significant past medical history of congenital heart disease and bronchopulmonary dysplasia who presented on Day 47 postvaccination with unresponsiveness requiring 30 minutes of CPR. An autopsy was declined by the participant's caregivers. Participant died on Day 47 with the reported cause of death being cardiopulmonary failure.

Reviewer Comment
Case narratives were provided and reviewed. The fatal serious adverse events were not considered by the Applicant, study investigator, or this clinical reviewer as related to the active control vaccine due to more plausible alternative causes of death and lack of close temporal association.

6.1.12.4 Nonfatal Serious Adverse Events

The frequency of nonfatal serious adverse events reported 6 months after any vaccination was 5.5% in the CAPVAXIVE group and 7.2% in the PPSV23 group. The most frequently reported events by MedDRA SOC included: *Infections and infestations* (CAPVAXIVE 3.0% versus PPSV23 4.0%; most commonly *urinary tract infection and pneumonia)* and *Respiratory, thoracic and mediastinal disorders* (CAPVAXIVE 1.1% versus PPSV23 0.6%; most commonly *asthma*). Three SAEs were considered as vaccine related by the study investigator: 1 participant with an SAE of syncope in the CAPVAXIVE group and 2 participants with an SAE of anaphylactic reaction in the PPSV23 group. The narratives for these events are included below:

CAPVAXIVE

Subject (b) (6) (*Syncope*): Participant was a 5-year-old male with a past medical history of asthma who developed short-term loss of consciousness and increased muscle tension approximately 3 mins after vaccination with CAPVAXIVE with resolution of symptoms approximately 4 mins after the event. Participant was hospitalized for further evaluation and had no recurrence of symptoms.

PPSV23

Subject (b) (6) (*Anaphylactic reaction*): Participant was a 6-year-old male with a past medical history of mite, animal allergies, and asthma who developed abdominal discomfort, nausea, respiratory distress with bronchospasm and lip cyanosis, rash, and uneasiness immediately following vaccination with PPSV23. Treatment included epinephrine and cetirizine hydrochloride with resolution of symptoms after 3 mins.

Subject (b) (6) (*Anaphylactic reaction*): Participant was an 11-year-old male with a past medical history of cardiac valve disease that developed intense weakness, severe nausea, breathing difficulty, rash, and swallowing difficulty 2 to 3 minutes

postvaccination with PPSV23. He received epinephrine with rapid improvement in symptoms.

Reviewer Comment
The case of syncope in the participant who received CAPVAXIVE appears likely due to a vasovagal response based on onset and rapid recovery. Although the participant did have reported increased muscle tension which would be concerning for seizure activity all seizure workup (including EEG and brain imaging was negative). This reviewer agrees with the investigator and Applicant that the case of syncope is related to vaccination based on biologic plausibility and temporal association. Although this is only a single case of syncope, it is a clinically significant adverse reaction. Postvaccination syncope has been reported more commonly in adolescents, so it is not an unexpected adverse reaction.

This reviewer also agrees with the investigator and Applicant that the two cases of anaphylaxis in PPSV23 recipients are secondary to vaccination due to temporal association.

6.1.12.5 Adverse Events of Special Interest (AESI)

No AEs of special interest were predefined for this study.

6.1.12.6 Clinical Test Results

Clinical laboratory evaluations were not prespecified or performed in this study.

6.1.12.7 Dropouts and/or Discontinuations

See section 6.1.10.1.2.

6.1.13 Study Summary and Conclusions

Study 13 is a Phase 3, randomized, double-blind, controlled study to evaluate the safety and immunogenicity of CAPVAXIVE in individuals 2 through 17 years of age with medical conditions that increase their risk for invasive pneumococcal disease (IPD), including diabetes mellitus, chronic liver disease, chronic lung disease, chronic heart disease, and chronic kidney disease. A total of 874 participants who had completed a primary pneumococcal conjugate vaccination regimen were randomized to receive a single dose of CAPVAXIVE (n=527) or a 23-valent pneumococcal polysaccharide vaccine (PPSV23; n=347). The primary statistical criteria for serotype-specific immunogenicity at 30 days postvaccination were met as described below:

- noninferiority: the lower bound of 95% CI of the OPA GMT ratio [CAPVAXIVE/PPSV23] was > 0.5 for each of the 12 common serotypes
- superiority: the lower bound of 95% CI of the OPA GMT ratio was > 2.0 for each of the 9 unique serotypes

Adverse events (AEs) (comprising solicited, unsolicited and SAEs) were reported in 80.8% of CAPVAXIVE recipients and 76.1% of PPSV23 recipients. The most commonly reported solicited adverse reactions were injection-site pain (67.7%), injection-site erythema (24.3%), fatigue (20.1%), injection-site swelling (18.8%), and headache (17.1%). Overall, the percentage of participants reporting injection site reactions were higher in the CAPVAXIVE group compared with the PPSV23 group (72.5 % versus 58.2%), primarily due to pain at the injection site. The percentages of participants

reporting solicited systemic adverse reactions up through 5 days postvaccination and unsolicited AEs up through 30 days postvaccination were numerically similar between the two study groups (solicited systemic ARs: CAPVAXIVE 59.4% and PPSV23 58.8%, unsolicited AEs: CAPVAXIVE 30.7% versus PPSV23 28.0%). During the 6-month postvaccination period, serious adverse events (SAEs) were reported in 5.5% of CAPVAXIVE recipients and 7.2% of PPSV23 recipients. One SAE of syncope in a CAPVAXIVE recipient (see narrative in Section 6.1.12.4) was considered by the study investigator and the clinical reviewer as related to the vaccine. Overall, although there were trends towards higher local reactogenicity with CAPVAXIVE compared with PPSV23, the overall reactogenicity and tolerability profile in children and adolescents 2 through 17 years of age for CAPVAXIVE is acceptable.

7. INTEGRATED OVERVIEW OF EFFICACY

Immunogenicity data were from a single study. Therefore, an integrated summary of immunogenicity could not be conducted. Please see Section 6.1.11 for clinical review of immunogenicity.

8. INTEGRATED OVERVIEW OF SAFETY

Safety data were from a single study. Therefore, an integrated summary of safety could not be conducted. Please see Section 6.1.12 for clinical review of safety data.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Currently, there are no adequate and well-controlled studies of CAPVAXIVE in pregnant individuals. No cases of pregnancy were identified in Study 13.

9.1.2 Use During Lactation

Human data are not available to assess the impact of CAPVAXIVE on milk production, its presence in breast milk, or its effects on the breastfed child.

9.1.3 Pediatric Use and PREA Considerations

The immunogenicity and safety data presented in this sBLA support the use of CAPVAXIVE in children 2 through 17 years of age at increased risk for pneumococcal disease due to certain chronic medical conditions. Study V116-013 fulfills PREA PMR #2 from the original BLA 125814.0 (Deferred pediatric study under PREA to evaluate the safety and immunogenicity of CAPVAXIVE in pediatric patients ages 2 to <18 years). The study results were presented to the PeRC on April 21, 2026. PeRC agreed that the data are adequate to support the use of CAPVAXIVE in children 2 through 17 years of age and approval of this sBLA fulfills PREA PMR #2.

The safety and effectiveness of CAPVAXIVE in individuals younger than 2 years of age have not been established.

9.1.4 Immunocompromised Patients

No new data evaluating CAPVAXIVE in immunocompromised were submitted with this sBLA. For details on data in immunocompromised individuals please see the CAPVAXIVE USPI.

9.1.5 Geriatric Use

No new data evaluating CAPVAXIVE in geriatric individuals were submitted with this sBLA. For further information on this population please see the original BLA 125775 and the CAPVAXIVE USPI.

10. CONCLUSIONS

This sBLA contains clinical data from a single study, Study 13, providing evidence of immunogenicity and safety of CAPVAXIVE in 874 children and adolescents 2 through 17 years of age at increased risk for pneumococcal disease to support lowering the age indication for this subpopulation.

Immunogenicity
A primary objective of Study 13 was to evaluate OPA GMTs 1 month after CAPVAXIVE administration compared with OPA GMTs 1 month after PPSV23 administration. For each of the 12 common serotypes, the predefined success criterion for noninferiority for the OPA GMT ratio (CAPVAXIVE over PPSV23) was met with the lower bound of the 95% CI of the OPA GMT ratio > 0.5. For each of the 9 unique serotypes, the predefined success criterion for superiority for the OPA GMT ratio (CAPVAXIVE over PPSV23) was met with the lower bound of 95% CI of the OPA GMT ratio was > 2.0.

Safety
The safety profile of CAPVAXIVE compared with PPSV23 was also evaluated as a primary objective. Solicited adverse reactions within 5 days of vaccination were reported at higher rates in the CAPVAXIVE group compared with the PPSV23 group (76.9% versus 67.1%). The most frequently reported local reaction in both groups was pain at the injection site and the most frequently reported systemic reaction was fatigue. The percentage of participants reporting at least 1 unsolicited, nonserious adverse event through 1 month postvaccination was 30.7% in the CAPVAXIVE group and 28.0% in the PPSV23 group. The percentage of participants reporting at least 1 nonfatal SAE was 5.5% in the CAPVAXIVE group and 7.2% in the PPSV23 group. None of the nonfatal SAEs were considered as related to study vaccination by CBER. No deaths were reported in the CAPVAXIVE group and 2 deaths in the PPSV23 group. None of the deaths were considered related to study vaccination by this reviewer.

Overall Conclusions
The safety and immunogenicity data submitted in this sBLA from 874 children and adolescents at increased risk for IPD (527 CAPVAXIVE recipients and 347 PPSV23 recipients) enrolled in Study 13 support inclusion in the USPI for CAPVAXIVE in sections 6.1 (clinical trials experience) and 14.1 (clinical studies) in support of lowering the age indication to include children 2 through 17 years of age at increased risk for IPD due to pneumococcal disease. The Pediatric Research Equity Act requirements for this age group would be fulfilled with approval of STN 125814.428.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 14. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pneumococcal disease continues to be a major cause of vaccine-preventable disease worldwide. • Individuals with certain medical conditions, such as functional or anatomic asplenia, renal disease, chronic heart disease, lung disease (including asthma), liver disease, smoking history, and alcoholism are at risk to develop IPD.	• Invasive pneumococcal disease is a significant cause of morbidity and mortality in children and adolescents at increased risk for pneumococcal disease.
Unmet Medical Need	• CAPVAXIVE has 13 serotypes in common with PCV15 + PPSV23. There are 8 serotypes for which CAPVAXIVE is indicated that are not covered by PCV15 + PPSV23. • CAPVAXIVE is indicated against eight unique serotypes not covered by currently licensed pneumococcal vaccines, which were responsible for approximately 30% of IPD in individuals 65 years of age and older. • Serotypes covered by CAPVAXIVE are responsible for approximately 83% of IPD in individuals 65 years of age and older. • There is effective antibiotic therapy for treatment of IPD, however, there is also increasing resistance which can make timely and effective treatment more difficult.	• There is unmet medical need for effective prevention of IPD caused by serotypes that are not included in PCV15 or PPSV23 in children and adolescents at increased risk for pneumococcal disease.
Clinical Benefit	• Effectiveness of CAPVAXIVE was evaluated based on OPA which is the primary mechanism for prevention of pneumococcal disease.	• The immunogenicity data from Study 13 submitted in this sBLA are informative and warrant inclusion in the prescribing information.
Risk	• The most commonly reported (>10%) solicited adverse reactions in individuals ≥18 years of age living with HIV who received CAPVAXIVE were: injection site pain (48.4%), fatigue (21.3%), and headache (16.8%) • The most commonly reported (>10%) solicited adverse reaction in individuals 18 through 65 years of age with at least one prespecified chronic medical condition were: injection site pain (49.5%), fatigue (24.6%), and headache (15.8%). • The percentage of individuals reported 1 or more SAEs within 6 months postvaccination was comparable between individuals vaccinated with CAPVAXIVE (Study 007: 1.9%; Study 008: 2.6%) and individuals vaccinated with an active comparator (Study 007: 3.9%; Study 008: 5.4%)	• No new safety signals were identified in Study 13 • The safety of CAPVAXIVE is acceptable for its intended use • The results described in the USPI adequately mitigate the risks of CAPVAXIVE
Risk Management	• No changes to the risk management plan were submitted to this sBLA	• Routine pharmacovigilance is considered adequate to monitor safety in the postmarketing setting.

11.2 Risk-Benefit Summary and Assessment

The data submitted in this sBLA demonstrate the immunogenicity of CAPVAXIVE administered as a single dose in individuals 2 through 17 years of age living with one or more prespecified chronic medical conditions.

To adequately describe the safety of CAPVAXIVE in children and adolescents, we recommend changes to Section 6 (Clinical Trials Experience) in the prescribing information to incorporate data from Study 13.

11.3 Discussion of Regulatory Options

The totality of the clinical data supports the safety, immunogenicity, and a favorable benefit-risk assessment for individuals 2 through 17 years of age who are at increased risk for IPD. The clinical data in this sBLA are sufficiently informative to update the USPI.

11.4 Recommendations on Regulatory Actions

The clinical review team recommends inclusion of data from Study V116-013 in the prescribing information in Section 6.1 and Section 14.1.

11.5 Labeling Review and Recommendations

The USPI was reviewed and CBER's proposed language is included in this memo.

11.6 Recommendations on Postmarketing Actions

No changes to the Applicant's proposed pharmacovigilance plan were submitted to this sBLA and no changes are recommended to the proposed pharmacovigilance plan. Study V116-013 fulfills PREA PMR #2 from the original BLA 125814.0 (Deferred pediatric study under PREA to evaluate the safety and immunogenicity of CAPVAXIVE in pediatric patients ages 2 to <18 years).