

BLA Clinical Review Memorandum

Application Type	BLA
STN	125814/0
CBER Received Date	October 18, 2023
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Division / Office	DCTR/OVRR
Priority Review (Yes/No)	Yes
Reviewer Names	Nicholas Geagan, D.O. Medical Officer CRB1/DCTR/OVRR Sarah Benke, D.O. Clinical Fellow CRB1/DCTR/OVRR
Review Completion Date / Stamped Date	June 12, 2024
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Applicant	Merck & Co., Inc
Proper Name	Pneumococcal 21-valent Conjugate Vaccine
(Proposed) Trade Name	CAPVAXIVE
Pharmacologic Class	Vaccine
Formulation	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, Route of Administration	Solution, intramuscular
Dosing Regimen	Single dose
Indications and Intended Population	<ul style="list-style-type: none"> active immunization for the prevention of invasive disease caused by <i>Streptococcus pneumoniae</i> serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B active immunization for the prevention of pneumonia caused by <i>S. pneumoniae</i> serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B <p>Population: individuals 18 years of age and older</p>
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
APaT	All-Participants-as-Treated
BLA	biologics license application
CAP	community-acquired pneumonia
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
cLDA	constrained longitudinal data analysis
CSF	cerebrospinal fluid
DMC	data monitoring committee
eVRC	electronic vaccination report card
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
HAI	hemagglutination inhibition
IgG	immunoglobulin G
IM	intramuscular
IPD	invasive pneumococcal disease
LB	lower bound
MedDRA	Medical Dictionary for Regulatory Activities
MOPA	multiplex opsonophagocytic assay
NI	noninferior(ity)
OPA	opsonophagocytic activity
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
Pn ECL	pneumococcal electrochemiluminescence
PnPs	pneumococcal polysaccharide
PP	per-protocol
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	preferred term
SAE	serious adverse event
SD	standard deviation
SOC	System Organ Class
US	United States
USPI	United States Prescribing Information
V116	pneumococcal 21-valent conjugate vaccine (investigational formulation of CAPVAXIVE)
YOA	years of age

1. EXECUTIVE SUMMARY

An original biologics license application (BLA) has been submitted by Merck & Co., Inc. for a candidate pneumococcal 21-valent conjugate vaccine (CRM₁₉₇ protein), (proposed tradename CAPVAXIVE, investigational product name V116) with a proposed indication 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 18 years of age and older.
- 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.

CAPVAXIVE was developed to target key serotypes common to currently licensed vaccines and 8 unique serotypes not contained in any U.S.-licensed vaccine. The serotypes covered by CAPVAXIVE account for approximately 30% more cases of invasive pneumococcal disease than PCV20 in adults ≥18 years of age ([CDC, 2019](#)). The Applicant has submitted data from 5 clinical studies as part of this BLA, including 4 Phase 3 trials which provided the principal data to support the safety and effectiveness of V116 (throughout the review the investigational drug is referred to as CAPVAXIVE) for the intended indication for use in individuals 18 years of age and older, as well as clinical data to support manufacturing consistency (lot consistency). These 4 trials (V116-003, V116-004, V116-006, and V116-005) enrolled adults with and without prior history of pneumococcal vaccination. Study V116-003 (Study 003), which enrolled pneumococcal vaccine-naïve participants ≥18 years of age, evaluated immunogenicity and safety of a single dose of CAPVAXIVE compared with [Pneumovax 23](#) (PCV20; Wyeth Pharmaceuticals) and immunobridging for participants 18 through 49 years of age with participants ≥50 years of age. Study V116-004 (Study 004) evaluated lot-to-lot consistency in pneumococcal vaccine-naïve adults 18 through 49 years of age. Study V116-006 (Study 006) enrolled pneumococcal vaccine-experienced adults 50 years of age and older and evaluated safety and immunogenicity of CAPVAXIVE compared to active control ([Vaxneuvance](#) [PCV15; Merck Sharp & Dohme] or [Pneumovax 23](#) [PPVS23; Merck Sharp & Dohme]). Study V116-005 (Study 005) evaluated the safety and immunogenicity of CAPVAXIVE when administered concomitantly with a quadrivalent influenza vaccine compared with sequential administration in pneumococcal vaccine-naïve adults 50 years of age and older.

Immunogenicity Analyses

Immunogenicity of CAPVAXIVE was evaluated in Study 003, a Phase 3, randomized, active comparator-controlled, double-blind, international clinical trial. A total of 2663 participants (1382 CAPVAXIVE, 1281 PCV20) enrolled in the study. The co-primary objectives were to establish effectiveness of CAPVAXIVE in adults ≥50 years of age through serotype-specific opsonophagocytic activity (OPA) and to establish effectiveness in adults 18 through 49 years of age by comparison with adults ≥50 years of age through OPA. The primary endpoint in adults ≥50 years of age was serotype-specific OPA geometric mean titers (GMTs) at 30 days postvaccination. The predefined noninferiority success criteria (lower bound of 95% CI of the OPA GMT ratio [CAPVAXIVE/PCV20] >0.5) was met for the 10 common serotypes. The predefined criteria for statistically significantly higher OPA responses (LB of the 95% CI of the OPA GMT ratio >2.0) compared to PCV20 were met for 10 of 11 serotypes unique to CAPVAXIVE. For serotype 15C, the LB of the 95% CI of the OPA GMT ratio was 1.77. The predefined criteria for immunobridging were met for CAPVAXIVE in participants 18 through 49 years of age compared with CAPVAXIVE in participants 50 through 64 years of age for all 21

serotypes as assessed by serotype-specific OPA GMTs (lower bound of the 95% CI of the OPA GMT >0.5) at 30 days postvaccination.

Analyses of secondary outcomes included evaluations of OPA responses for serotypes 15B and 6C, which are not included in the vaccine formulation, but for which OPA responses to CAPVAXIVE were assessed based on antigenic similarity with vaccine serotypes (i.e., 15C¹ and 6A). For serotype 15B, CAPVAXIVE met the predefined criterion for antibody response. For serotype 6C, CAPVAXIVE did not meet the predefined criterion for antibody response.

Study 004 was designed as a lot-to-lot consistency, immunogenicity, and safety study in adults 18 through 49 years of age. Pneumococcal vaccine-naïve adults 18 through 49 years of age received a single dose from one of three CAPVAXIVE lots or PPSV23. The equivalence criteria were met for all 21 serotypes in CAPVAXIVE, demonstrating lot-to-lot equivalency and providing clinical evidence of manufacturing consistency.

Study 006 was designed to descriptively evaluate the safety and immunogenicity of CAPVAXIVE in pneumococcal vaccine-experienced adults ≥50 years of age compared with an active U.S.-licensed control vaccine (PCV15 or PPSV23) for 2 of the 3 cohorts. In each of the 3 cohorts, immune responses were based on serotype-specific OPA GMTs and the proportion of individuals with ≥4-fold rise in OPA responses from baseline to 1-month postvaccination. In Cohort 1, CAPVAXIVE elicited immune responses that were comparable to VAXNEUVANCE for the 6 common serotypes, and higher for the 15 unique serotypes and serotype 15B. In Cohort 2, CAPVAXIVE elicited immune responses comparable to Pneumovax 23 for the 12 common serotypes and serotype 15B, and higher for the 9 unique serotypes. Immune responses to CAPVAXIVE were similar across the 3 cohorts of participants who previously received one or more pneumococcal vaccines.

Study 005 was a Phase 3, randomized, double-blind, placebo-controlled study in which immunogenicity was assessed for CAPVAXIVE when administered concomitantly with QIV compared with when administered sequentially. Except for pneumococcal serotype 23B and influenza strain A/H3N2, the primary objectives to demonstrate non-inferiority of concomitant administration of CAPVAXIVE and QIV were met (LB of the 95% CI of the GMT ratio >0.5 and >0.67, respectively) compared with pneumococcal and influenza antibody responses following sequential administration. For pneumococcal serotype 23B and influenza strain A/H3N2, the LB of the 95% CI of the group GMT ratio was 0.44 and 0.67, respectively.

CAPVAXIVE demonstrated effectiveness for prevention of IPD for 22 pneumococcal serotypes based on OPA responses. Across the Phase 3 studies, CAPVAXIVE was noninferior to active, U.S.-licensed comparators for the shared serotypes and 15B, and statistically superior to the unique serotypes with the exception of 15C which marginally missed the pre-defined success criteria. The totality of data supports licensure of CAPVAXIVE for the indication of active immunization for the prevention of IPD caused by the specified serotypes.

Safety

The safety of CAPVAXIVE after a single dose was evaluated in 4 Phase 3 studies (4,020 study participants received CAPVAXIVE, 2018 received active control). Solicited adverse reactions within 5 days of vaccination (Study 003) occurred at similar rates between CAPVAXIVE and PCV20 (55.3% CAPVAXIVE, 61.3% PCV20). In both groups there was a trend towards higher

¹ CAPVAXIVE contains de-O-acetylated polysaccharide from serotype 15B [deOAc15B], which is similar in structure to polysaccharide from 15C. The antibody response to deOAc15B is measured as serotype 15C.

rates of reactions in the 18 through 49 years of age group. The most frequently reported local reaction in all groups was pain at the injection site (≥ 50 years of age: 39.4% CAPVAXIVE, 51.7% PCV20; 18 through 49 years of age: 71.5% CAPVAXIVE, 74.0% PCV20) and the most frequently reported systemic reaction was fatigue (≥ 50 years of age: 20.1% CAPVAXIVE, 19.6% PCV20; 18 through 49 years of age: 40.5% CAPVAXIVE, 34.0% PCV20). Severe (Grade 3) solicited local and systemic reactions were reported in 0.5% of CAPVAXIVE recipients ≥ 50 years of age, 1.0% of PCV20 recipients ≥ 50 years of age, 4.5% of CAPVAXIVE recipients 18 through 49 years of age, and 3.0% of PCV20 recipients 18 through 49 years of age. The percentage of vaccine recipients that reported at least 1 unsolicited, non-serious adverse event (AE) through 1-month postvaccination was 22.3% in CAPVAXIVE recipients and 22.2% in active control recipients.

The percentage of participants reporting at least 1 non-fatal serious adverse event (SAE) in the 4 Phase 3 studies was 1.4% among CAPVAXIVE recipients and 2.0% of comparator recipients. Two SAEs were assessed to be related to the study vaccination: one participant in Study 005 with reported bronchospasm and one participant in Study 006 who reported injection-site cellulitis (See individual studies in [section 6](#) for narrative details). Deaths were reported for 6 CAPVAXIVE recipients (0.1%) and 3 active comparator recipients (0.1%). Based on independent review of event narratives, FDA considers the deaths to be attributable to the participants underlying medical conditions, risk factors, or events that are not physiologically plausible to be attributed to vaccination. There were no SAEs or deaths observed in the phase 1/2 study that could be attributed to vaccination.

The data submitted to this BLA support the safety of CAPVAXIVE when administered to adults ≥ 18 years of age. The SAE rates among CAPVAXIVE and active comparators (PCV20, PPSV23, or PCV15) were similar and were $\leq 2.0\%$. Two SAEs (bronchospasm, injection site cellulitis) were assessed to be related to CAPVAXIVE vaccination. No additional safety concerns were identified when a single dose of CAPVAXIVE was administered to adults ≥ 18 years of age, with or without prior pneumococcal vaccine exposure.

Pneumococcal Pneumonia Indication

Vaccine effectiveness of CAPVAXIVE to prevent pneumococcal pneumonia in individuals ≥ 18 years of age was based on an immunological surrogate endpoint (OPA GMT) reasonably likely to predict clinical benefit in preventing bacteremic and non-bacteremic pneumonia (21 CFR 601.41). As a condition of accelerated approval, the Applicant will conduct a postmarketing real-world effectiveness study as a required confirmatory study to verify and describe clinical benefit of CAPVAXIVE for the prevention of serotype-specific pneumococcal pneumonia.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed individually.

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 bacteria 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, 2022](#)). *S. pneumoniae* causes pneumonia, which results in approximately 150,000 hospitalizations annually in adults in the United States (U.S.) ([CDC, 2022](#)). 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, 2023](#)).

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 *Streptococcus 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.

The serotypes increasing in incidence post-PCV13, but not included in any currently available vaccines, included serotypes 15A, 23A, 23B, and 35B in adults. ([Løchen et al., 2020](#)).

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

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 United States. [Pneumovax 23](#) (PPVS23; 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) [Prenar 13](#) (PCV13; Wyeth Pharmaceuticals), [Vaxneuvance](#) (PCV15; Merck Sharp & Dohme), and [Prenar 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 US prescribing information linked above.

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

Currently, CAPVAXIVE (pneumococcal 21-valent conjugate vaccine) is not licensed in any country.

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

2.5.1 Demonstration of Vaccine Effectiveness

IPD

Vaccine effectiveness of CAPVAXIVE to prevent IPD in individuals ≥ 18 years of age was inferred from demonstration of immunological noninferiority, based on an OPA GMT endpoint, to a US vaccine that is approved for IPD due to the vaccine-specific pneumococcal serotypes. Protection against pneumococcal disease *in vivo* is conferred mainly by opsonophagocytic killing of *S. pneumoniae* and OPA measured *in vitro* reflects this mechanism of protection. Because there is no established immune correlate of protection in adults (i.e., a threshold level of an immune parameter predictive of protection), effectiveness for each vaccine serotype was evaluated by comparisons of OPA titer following CAPVAXIVE to those following PCV20, a licensed vaccine for which effectiveness for the prevention of IPD caused by 20 vaccine serotypes was demonstrated in adults.

Pneumonia

Immunogenicity data alone were not considered sufficient to support a traditional approval for a pneumonia indication, because 1) there is no scientific consensus regarding serologic criteria for assessing effectiveness of new pneumococcal conjugate vaccines against noninvasive disease, and 2) antibody levels have not been found to be indicative of prevention of non-invasive pneumococcal disease.

CBER agreed to the Applicant's proposal to consider approval of CAPVAXIVE for prevention of pneumonia under the accelerated approval regulations (21 CFR 601.41). Since pneumococcal pneumonia is a serious condition and CAPVAXIVE would provide meaningful therapeutic benefit over existing treatments due to additional serotypes (see [section 2.1](#)), these qualifying criteria would be met. Approval under the accelerated approval regulations requires demonstration of an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The Applicant proposed use of OPA as the immunologic surrogate, which had previously been accepted by FDA/CBER as a surrogate endpoint for prevention of pneumococcal pneumonia with the approvals of PCV13 (December 30, 2011) and PCV20 (June 10, 2021) for prevention of pneumococcal pneumonia. Opsonophagocytosis, mediated by antibodies and complement, is thought to be the main protective mechanism against pneumococcal disease *in vivo*. As a condition of accelerated approval, the Applicant proposed to conduct a postmarketing real-world effectiveness study as a required confirmatory study to verify and describe clinical benefit of CAPVAXIVE for the prevention of pneumonia caused by 21 vaccine-specific serotypes. Serotype 15B is not being studied in the proposed real-world effectiveness study and thus will not be included in the indication for pneumococcal pneumonia.

2.5.2 Other Pre-submission Regulatory Activity

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

- December 13, 2019: Fast track designation granted.
- December 2, 2021: Type B End-of-Phase 2 Meeting re: discussion on Phase 3 program; agreement on studies to support indication for vaccine serotypes.
- January 10, 2022: Breakthrough designation granted (IPD only)
- May 5, 2022: Proposed design of the RWE/TND case-control study in support of the pneumococcal pneumonia indication via an AA pathway
- June 21, 2023: Pre-BLA request - The Applicant sought to obtain CBER concurrence on the clinical data supporting review of the BLA; CBER recommended removal of serotypes (b) (4) from proposed indication

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 BLA was complete and adequately organized for review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

In this BLA, the five studies (V116-001, V116-003, V116-004, V116-005, and V116-006) were conducted in accordance with Good Clinical Practice (GCP) and International Committee on Harmonization (ICH) guidelines. The Applicant conducted audits at 12 clinical sites to assess adherence to the protocol and applicable GCP regulations and guidelines; the audits did not reveal substantive issues that impact the data submitted in this BLA.

Bioresearch monitoring (BIMO) inspections were issued for four clinical study sites, two of which were domestic and two were foreign sites. At one of the sites, the inclusion/exclusion eligibility for 16 study participants were assessed and signed by a nurse practitioner sub-investigator, however, the protocol stated “All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualified for the study.” A form FDA-483 was issued at the site and the CBER BIMO reviewer concluded that results at this site were not issues that would substantively impact the data submitted in this BLA; the inspection was classified as Voluntary Action indicated (VAI). For the other 3 sites, BIMO inspections determined that the sites were in compliance with GCP and ICH guidelines.

3.3 Financial Disclosures

Covered clinical study (name and/or number): V116-001, V116-003, V116-004, V116-005, and V116-006
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from Applicant)
Total number of investigators identified: <u>1304</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <div style="margin-left: 20px; padding-left: 20px;"> Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>1</u> Is an attachment provided with details of the disclosable financial interests/arrangements? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request details from Applicant) Is a description of the steps taken to minimize potential bias provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request information from Applicant) </div>
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>1302</u> <div style="margin-left: 20px; padding-left: 20px;"> Is an attachment provided with the reason? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from Applicant) The Applicant certified that 1,302 investigators had absence of financial interests and/or arrangements. One (1) investigator had an equity interest with disclosure that their spouse, who was an MSD employee, had stock options. One (1) sub-investigator did not return the form with requested information despite due diligence attempts. An internal search was performed for proprietary or financial interests and significant payments of other sorts. The Applicant reported that no financial interests or arrangements were identified. </div>

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

4.1 Chemistry, Manufacturing, and Controls

Manufacturing process development, in-process testing, release and stability testing were reviewed and support licensure. The data support the proposed expiry dating for Drug Product. Facility information and data provided in the BLA were reviewed by CBER reviewers and found to be sufficient and acceptable.

4.2 Assay Validation

(b) (4) developed the multiplexed opsonophagocytosis assay (MOPA) and the pneumococcal electrochemiluminescence (Pn-ECL) assay to assess clinical samples for

primary and secondary endpoints, respectively, to support the immunogenicity of CAPVAXIVE. They validated MOPA in terms of ruggedness and precision, relative accuracy/dilutional linearity, analytical specificity, and matrix interference. (b) (4) also developed the (b) (4) assay to screen serum samples from clinical studies for (b) (4) prior to the evaluation of functional antibodies of serum samples in MOPA. They validated Pn-ECL in terms of precision, assay ruggedness, selectivity, specificity, and dilutional linearity. All assays are adequate for their intended uses to evaluate primary and secondary clinical endpoints, and data support that the assays were stable throughout the clinical testing period. Please see Dr. Jiro Sakai's memo for additional details.

4.3 Nonclinical Pharmacology/Toxicology

Merck evaluated immunogenicity of CAPVAXIVE in mice and adult (b) (4) monkeys. CAPVAXIVE was immunogenic, generated functional antibodies, and had comparable immunogenicity to all three comparator vaccines for shared serotypes.

The Applicant submitted study reports of a 22-day intramuscular toxicity study in rats. There was no V116-related mortality. There were no test article-related clinical observations during the study except transient hindlimb swelling was observed in control (11/42) and CAPVAXIVE-treated (18/41) females in both cohorts following dose administration and/or the following day in the hindlimb. Slightly higher incidence was likely treatment-related although being transient.

In a developmental toxicity study in female rats, there were no embryofetal deaths or fetal malformations, and no adverse effects on female fertility and preweaning development were observed.

4.4 Mechanism of Action

Protection against invasive pneumococcal disease is conferred mainly by opsonophagocytic killing of *S. pneumoniae*. CAPVAXIVE 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 that would impact the clinical reviewer's interpretation of the data and conclusions. Please see statistical review memo (Dr. Ross Peterson) for additional details.

4.6 Pharmacovigilance

Since CAPVAXIVE is not available in any other countries there are no pharmacovigilance data available.

The Applicant's PVP adequately reflects the safety concerns based on the clinical trial experience. There are no important identified or potential risks in the Applicant's proposed PVP. This risk assessment is consistent with the safety profile observed in the clinical trials, for which there were no concerning differences in rates of SAEs, very few SAEs (one event each of bronchospasm and injection site cellulitis) and no deaths that were attributed to vaccination with

V116. Other populations discussed (other immunocompromised, pregnancy/lactating women) do no warrant inclusion in the PVP at this time. The reviewed data do not indicate a safety signal which would require either a Risk Evaluation and Mitigation Strategy (REMS), or a postmarketing commitment (PMC) or postmarketing requirement (PMR) study that is specifically designed to evaluate safety as a primary endpoint.

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

5.1 Review Strategy

Clinical data from 5 studies (V116-001, V116-003, V116-004, V116-005, and V116-006) were submitted in this BLA to support the safety and effectiveness of CAPVAXIVE for the proposed indications in individuals 18 years and older.

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 6: module 1.11 (response to IR re: dataset discrepancies)
- Amendment 9: module 1.11 (response to IR re: TND study design and timing of final report)
- Amendment 12: module 1.11 (response to IR re: TND estimated milestones)
- Amendments 14, 15: module 1.11 (responses to IR re: removal of serotypes (b) (4) from pneumonia indication)
- Amendment 16: module 1.11 (response to IR re: OPA responses to serotype 15B)
- Amendment 28: module 1.9 (updated agreed iPSP)
- Amendments 45, 73, 94: module 1.14 (draft package insert and revisions)

5.3 Table of Studies/Clinical Trials

Table 1. Overview of Clinical Studies

Study Number	Study Site Location	Description	APaT Analysis Set
V116-001	U.S.	Phase 1/2 randomized, double-blind, safety and immunogenicity study in pneumococcal vaccine-naïve adults ≥18 years of age	CAPVAXIVE: 254 PPSV23: 254
V116-003	Australia, Belgium, Chile, Germany, New Zealand, Puerto Rico, South Korea, Sweden, Taiwan, Turkey, and U.S.	Phase 3, randomized, double-blind, safety, and immunogenicity of CAPVAXIVE in pneumococcal vaccine-naïve adults ≥18 years of age	Cohort 1 (≥50 YOA) CAPVAXIVE: 1177 PCV20: 1175 Cohort 2 (18 to <50 YOA) CAPVAXIVE: 200 PCV20: 100
V116-004	Austria, Canada, Denmark, Finland, Israel, Poland, Spain, and U.S.	Phase 3, randomized, double-blind, lot consistency study in pneumococcal vaccine-naïve adults 18 through 49 years of age	CAPVAXIVE Lot 1: 539 CAPVAXIVE Lot 2: 536 CAPVAXIVE Lot 3: 541 PPSV23: 540

Study Number	Study Site Location	Description	APaT Analysis Set
V116-005	U.S.	Phase 3, randomized, concomitant administration with quadrivalent influenza vaccine (QIV; Fluzone) in pneumococcal vaccine-experienced adults ≥50 years of age	Concomitant group: 534 Sequential group: 535
V116-006	Canada, France, Israel, Italy, Japan, South Korea, Spain, Taiwan, and U.S.	Phase 3, randomized (cohorts 1 and 2 only) to evaluate the safety and immunogenicity of CAPVAXIVE in pneumococcal vaccine-experienced adults ≥50 years of age <ul style="list-style-type: none"> ○ Cohort 1: double-blind; adults with prior PPSV23 vaccination ○ Cohort 2: double-blind, adults with prior PCV13 vaccination ○ Cohort 3: open-label; adults with prior pneumococcal vaccination (PCV13 + PPSV23, PCV15 + PPSV23, PCV15, PCV20, or PPSV23 + PCV13) 	Cohort 1 (prior PPSV23) CAPVAXIVE: 230 PCV15: 117 Cohort 2 (prior PCV13) CAPVAXIVE: 174 PPSV23: 85 Cohort 3 (prior other pneumococcal regimen) CAPVAXIVE: 105

Abbreviations: U.S.=United States; PCV13=13-valent pneumococcal conjugate vaccine; PCV15=15-valent pneumococcal conjugate vaccine; PCV20=20-valent pneumococcal conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine; APaT=All Participants as Treated

5.4 Consultations

5.4.1 Advisory Committee Meeting

Not applicable

5.4.2 External Consults/Collaborations

Not applicable

5.5 Literature Reviewed

Centers for Disease Control and Prevention (CDC, 2019). Active Bacterial Core Surveillance Report, Emerging Infections Program Network, *Streptococcus pneumoniae*, 2019.

www.cdc.gov/abcs/downloads/SPN_Surveillance_Report_2019.pdf

Centers for Disease Control and Prevention (CDC, 2021) [Pinkbook: Pneumococcal Disease | CDC](#)

Centers for Disease Control and Prevention (CDC, 2022) [Clinical Features of Pneumococcal Disease | CDC](#)

Centers for Disease Control and Prevention (CDC, 2023) [Pneumococcal Disease: Risk Factors and How It Spreads | CDC](#)

Centers for Disease Control and Prevention (CDC, 2024) [ABCs Bact Facts Interactive Data Dashboard | CDC](#)

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study V116-003

NCT 05425732

“A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of CAPVAXIVE in Pneumococcal Vaccine-naïve Adults.”

6.1.1 Objectives

Primary Objectives, Endpoints, and Statistical Criteria

≥50 years of age group (Cohort 1) and 18 through 49 years of age group (Cohort 2) (separately)
To evaluate the safety and tolerability of CAPVAXIVE.

- Solicited injection site and systemic adverse events (AEs) postvaccination Days 1-5.

- Vaccine-related serious adverse events (SAEs) from postvaccination Day 1 through the duration of participation in the study.

Cohort 1

1. To compare the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination with CAPVAXIVE versus PCV20
 - Hypothesis 1 (H1): CAPVAXIVE is noninferior to PCV20 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 10 common serotypes
 - Lower bound (LB) of the 2-sided 95% confidence interval (CI) (hereafter LB of 95% CI) of the OPA GMT ratio (CAPVAXIVE/PCV20) is >0.5
 - Hypothesis 2 (H2): CAPVAXIVE is superior to PCV20 as assessed by serotype-specific OPA GMTs at 30 days postvaccination for the 11 unique serotypes
 - LB of 95% CI of the OPA GMT ratio (CAPVAXIVE/PCV20) is >2.0
2. To compare the percentage of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from baseline with 30 days postvaccination for the unique serotypes in CAPVAXIVE
 - Hypothesis 3 (H3): CAPVAXIVE is superior to PCV20 as assessed by proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA responses for the 11 unique serotypes in CAPVAXIVE
 - LB of 95% CI of the differences (V116-PCV20) between the proportions of participants with ≥ 4 -fold rise is >0.1 .

Cohort 2

To compare the serotype-specific OPA GMTs in adults 18 through 49 years of age from Cohort 2 to adults 50 through 64 years of age from Cohort 1 at 30 days postvaccination with CAPVAXIVE.

- Hypothesis 4 (H4): CAPVAXIVE in participants 18 through 49 years of age immunobridges to CAPVAXIVE in participants 50 through 64 years of age as assessed by serotype-specific OPA GMTs at 30 days postvaccination for all 21 serotypes in CAPVAXIVE
 - LB of 95% CI of the OPA GMT ratio (CAPVAXIVE_{18 through 49 group}/CAPVAXIVE_{50 through 64 group}) is >0.5

Reviewer Comment: Since OPA responses in participants 18 through 49 years of age were immunobridged to OPA responses in participants 50 through 64 years of age, instead of being compared to a randomized control group, the term ‘immunobridging’ rather than ‘noninferiority’ was used by the Applicant to describe the comparisons.

Secondary Objectives, Endpoints, and Statistical Criteria

Cohort 1 and Cohort 2

To evaluate serotype-specific OPA responses at 30 days postvaccination with CAPVAXIVE in adults ≥ 50 years of age from Cohort 1 and adults 18 through 49 years of age from Cohort 2 for serotypes (i.e., serotype 6C, serotype 15B) within a serogroup.

- Hypothesis 5 (H5): CAPVAXIVE induces an antibody response in adults ≥ 50 years of age as assessed by the percentages of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from baseline (pre-vaccination) to 30 days postvaccination for serotypes within a serogroup in CAPVAXIVE.
 - LB of 95% CI of percentages of participants with a ≥ 4 -fold rise from baseline to 30 days postvaccination for CAPVAXIVE is >0.5 .

- Hypothesis 6 (H6): Post-vaccination OPA GMTs in CAPVAXIVE participants 18 through 49 years of age immunobridges to OPA GMTs in CAPVAXIVE participants 50 through 64 years of age as assessed by serotype-specific OPA GMTs at 30 days postvaccination for serotypes within a serogroup in CAPVAXIVE.
 - LB of 95% CI of the OPA GMT ratio (CAPVAXIVE_{18 through 49 group}/CAPVAXIVE_{50 through 64 group}) is >0.5.

Reviewer Comment: The de-O-acetylated polysaccharide from serotype 15B (contained in CAPVAXIVE) [deOAc15B] induces OPA to serotypes 15B and 15C. The OPA response to deOAc15B is measured as serotype 15C.

Cohort 1

1. To evaluate the serotype-specific IgG geometric mean concentrations (GMCs) at 30 days postvaccination with CAPVAXIVE compared with PCV20
2. To evaluate the percentages of participants with a ≥4-fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination with CAPVAXIVE and separately for PCV20

6.1.2 Design Overview

Study 003 is a randomized, double-blind, controlled study designed to evaluate the immunogenicity and safety of a single dose of CAPVAXIVE in pneumococcal vaccine-naïve adults ≥18 years of age. The study was conducted in 11 countries (Australia, Belgium, Chile, Germany, New Zealand, Puerto Rico, South Korea, Sweden, Taiwan, Turkey, and US). A total of 2,663 participants were enrolled into 1 of 2 cohorts based on age at the time of enrollment. In Cohort 1, 2,362 participants ≥50 years of age were randomized in a 1:1 ratio to receive a single dose of either CAPVAXIVE or PCV20 on Day 1. In Cohort 2, 301 participants 18 through 49 years of age were randomized in a 2:1 ratio to receive a single dose of either CAPVAXIVE or PCV20 on Day 1.

Safety evaluation included the following parameters: solicited injection site/systemic 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 (DMC) conducted a periodic review of safety and tolerability data.

6.1.3 Study Population

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

- Male or female ≥18 years of age, at the time of informed consent.
- A female participant was eligible to participate if she was not pregnant or breastfeeding, and at least one of the following conditions applied:
 - Not a woman of childbearing potential, OR
 - A woman of childbearing potential who uses an acceptable contraceptive method; has a negative highly sensitive pregnancy test within 24 hrs before the first dose of study intervention; medical history, menstrual history, and recent sexual activity has been reviewed by the investigator.
- Provided documented informed consent for the study.
- Able to complete the electronic vaccination card (eVRC) without assistance.
- The participant may have underlying chronic conditions if they were assessed to be stable as per the investigator's judgment.

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

- History of IPD or known history of other culture-positive pneumococcal disease within 3 years of Visit 1.
- Known hypersensitivity to any component of CAPVAXIVE or PCV20.
- Known or suspected impairment of immunological function or history of autoimmune disease.
- Coagulation disorder contraindicating an intramuscular (IM) vaccination.
- Recent febrile illness or received antibiotic therapy for any acute illness occurring <72 hrs before receipt of study vaccine.
- Known malignancy that is progressing or has required active treatment <3 years before enrollment.
- Received prior administration of any pneumococcal vaccine or was expected to receive any pneumococcal vaccine during the study outside of protocol.
- Received systemic corticosteroids for ≥ 14 consecutive days and had not completed intervention ≥ 14 days before receipt of study vaccine.
- Currently receiving immunosuppressive therapy.
- Received any non-live vaccine ≤ 14 days before receipt of study vaccine or was scheduled to receive any non-live vaccine ≤ 30 days after receipt of study vaccine.
- Received any live virus vaccine ≤ 30 days before receipt of study vaccine or was scheduled to receive any live virus vaccine ≤ 30 days after receipt of study vaccine.
- Received a blood transfusion or blood products, including immunoglobulin ≤ 6 months before receipt of study vaccine or was scheduled to receive a blood transfusion or blood product before the postvaccination Day 30 blood draw was complete.
- Currently participating in or has participated in an interventional clinical study with an investigational compound or device within 2 months of participating in this current study.
- History of clinically relevant drug or alcohol use that would interfere with participation in protocol-specified activities.
- History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might expose the participant to risk by participating in the study, confound the results of the study, or interfere with the participants participation for the full duration of the study.
- Is or has an immediate family member who is investigational site or Sponsor staff directly involved with the study.

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
- Lot #: W013259

PCV20 (comparator)

- Composition: 2.2 μg of each PnPs antigen (1, 3, 4, 5, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F) and 4.4 μg of PnPs antigen 6B.

- Dose Volume: 0.5 mL
- Presentation: Pre-filled syringe
- Lot# 0001442724, 0001494099, 0001506444

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

The study was conducted at 112 centers in 11 countries.

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:
 - 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
 - Headache, myalgia, fatigue, fever
 - Grading scale:
 - Headache, fatigue, myalgia: 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.
 - Fever: 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 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 attempt 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 adult 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.

Immunogenicity (methods)

Pneumococcal OPA responses to 21 vaccine serotypes (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B) and 2 serotypes not included in the vaccine (6C and 15B) were measured using a multiplex opsonophagocytic assay (MOPA). Sera tested by the MOPA assay was performed at (b) (4).

6.1.8 Endpoints and Criteria for Study Success

See [section 6.1.1](#).

6.1.9 Statistical Considerations and Statistical Analysis Plan

For the primary immunogenicity hypotheses:

- H1: CAPVAXIVE was considered noninferior to PCV20 if the LB of 95% CI of the OPA GMT ratio (CAPVAXIVE/PCV20) for each of the 10 common serotypes was >0.50 .
- H2: CAPVAXIVE was considered superior to PCV20 if the LB of 95% CI of the OPA GMT ratio (CAPVAXIVE/PCV20) for each of the 11 unique serotypes contained in CAPVAXIVE was >2.0 .

For the hypotheses H1 and H2, estimation of the serotype-specific OPA GMT ratios and 95% CIs was calculated using the constrained longitudinal data analysis (cLDA) method.

- H3: CAPVAXIVE was considered superior to PCV20 if the LB of 95% CI of the difference (CAPVAXIVE – PCV20) between proportions of participants with a ≥ 4 -fold rise from baseline to 30 days postvaccination was >0.1 for each of the 11 unique serotypes in CAPVAXIVE. The between-group difference (CAPVAXIVE – PCV20), its 95% CI was calculated using the stratified M&N method.
- H4: CAPVAXIVE in participants 18 through 49 years of age was considered immunobridged to CAPVAXIVE in participants 50 through 64 years of age if the LB of 95% CI of the OPA GMT ratio (CAPVAXIVE 18 through 49 group/CAPVAXIVE 50 through 64 group) for each of the 21 serotypes was >0.5 . For H4, estimation of the serotype-specific OPA GMT ratios and 95% CIs was calculated using the LDA method.

For the overall safety evaluation, safety parameters will be summarized via descriptive statistics.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All Participants as Treated (APaT): defined as all randomized participants who received at least 1 dose of study vaccination. Safety analyses were based on the APaT set. Analyses were performed according to the vaccine administered.

Full Analysis Set (FAS): defined as randomized participants who received at least 1 vaccination and had at least 1 serology result.

Per-protocol (PP): defined as all randomized participants without deviations from the protocol that would substantially affect immunogenicity. Final determination of all protocol deviations was made prior to the final unblinding of the database. Participants were analyzed according to the vaccine group to which they were randomized. Deviations that may result in exclusion of a participant from the PPS included:

- Failure to receive any study vaccine at Visit 1 Day 1
- Failure to receive correct study vaccine as per randomization schedule on Day 1
- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination
- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of a blood sample outside of the pre-specified windows (Day 1 and Day 30 to 44)

6.1.10.1.1 Demographics

The demographic characteristics were similar between the CAPVAXIVE and PCV20 groups. The median age at the time of vaccination was 63 years; 300 (11.3%) participants were 18 through 49 years of age, 1,176 (44.3%) participants were 50 through 64 years of age, 928 (34.9%) participants were 65 through 74 years of age, 225 (8.5%) participants were 75 through 84 years of age, and 27 (1.0%) participants were ≥85 years of age. Overall, 72.0% of participants were White, 13.9% were Asian, 9.7% were Black or African American, 2.7% were characterized as “multiple”, 1.4% were Native Hawaiian or Other Pacific Islander, 0.3% were American Indian or Alaska Native and 1 participant was characterized as missing; 22.0% were of Hispanic or Latino ethnicity; 58.7% were female.

Table 2. Participant Demographics, All Participants as Treated, Study 003

Characteristic	CAPVAXIVE N=1379	PCV20 N=1277
Sex, n (%)	--	--
Male	555 (40.2)	543 (42.5)
Female	824 (59.8)	734 (57.5)
Age (Years)	--	--
Mean age (SD)	59.7 (13.2)	61.6 (11.5)
Median age	62	63
18 through 49, n (%)	200 (14.5)	100 (7.8)
50 through 64, n (%)	589 (42.7)	587 (46.0)
65 through 74, n (%)	464 (33.6)	464 (36.3)
75 through 84, n (%)	112 (8.1)	113 (8.8)
≥85, n (%)	14 (1.0)	13 (1.0)

Characteristic	CAPVAXIVE N=1379	PCV20 N=1277
Race, n (%)	--	--
American Indian or Alaska Native	4 (0.3)	5 (0.4)
Asian	186 (13.5)	183 (14.3)
Black or African American	129 (9.4)	129 (10.1)
Multiple	35 (2.5)	36 (2.8)
Native Hawaiian or Other Pacific Islander	18 (1.3)	18 (1.4)
White	1006 (73.0)	906 (70.9)
Missing	1 (0.1)	0 (0.0)
Ethnicity, n (%)	--	--
Hispanic or Latino	317 (23.0)	266 (20.8)
Not Hispanic or Latino	1050 (76.1)	998 (78.2)
Not Reported	8 (0.6)	10 (0.8)
Unknown	4 (0.3)	3 (0.2)
Country, n (%)	--	--
Australia	49 (3.6)	46 (3.6)
Belgium	84 (6.1)	71 (5.6)
Chile	76 (5.5)	59 (4.6)
Germany	48 (3.5)	31 (2.4)
New Zealand	134 (9.7)	156 (12.2)
Puerto Rico	75 (5.4)	80 (6.3)
South Korea	101 (7.3)	99 (7.8)
Sweden	60 (4.4)	50 (3.9)
Taiwan	65 (4.7)	58 (4.5)
Turkey	26 (1.9)	28 (2.2)
United States	661 (47.9)	599 (46.9)

Source: Adapted from STN 125814.0, V116-003 Clinical Study Report: Table 10-2

All participants as treated defined as all randomized participants who received the study intervention.

Abbreviations: N=number of participants; n (%)=number and percentage of participants in a given category; PCV20= 20-valent pneumococcal conjugate vaccine [Prevna[®] 20]; SD=standard deviation

6.1.10.1.2 Participant Disposition

A total of 2,663 participants were randomized and 2,656 received the study intervention. Two participants were randomized into the study twice with each individual being randomized at two different study sites and received a dose of PCV20 at the first study site and a dose of CAPVAXIVE at the second study site.

Disposition of 2656 participants who contributed to the analyses of safety and immunogenicity are presented in Table 3. 97.7% of participants completed the study and the number of participants who discontinued the study were generally comparable between intervention groups.

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

Population	CAPVAXIVE n (%^a)	PCV20 n (%^a)
Enrolled	1382	1281
Randomized	1382	1281
Vaccinated	1379 (99.8)	1277 (99.7)
Completed study	1355 (98.0)	1248 (97.4)
Safety Analysis ^a	1377 (99.6)	1275 (99.5)
FAS Set ^b	1379 (99.8)	1277 (99.7)
Per-Protocol OPA ^c	1080 (91.4)	1063 (90.0)
Per-Protocol IgG ^c	1102 (93.3)	1077 (91.2)

Population	CAPVAXIVE n (%^a)	PCV20 n (%^a)
≥1 Important Protocol Deviation	113 (8.2)	109 (8.5)

Source: Adapted from STN 125814.0 V116-003 Clinical Study Report: Tables 10-1, 14.1-4, 14.1-5 14.1-6, 14.1-10,

≥1 Important Protocol Deviation: participants with one or more important protocol deviations.

a. Denominator used to calculate percentage was randomized population.

b. Full Analysis Set (FAS): All randomized participants who received the intervention and had at least 1 serology result. n= maximum number of participants (across all serotypes) with serology result contributing to the primary immunogenicity analysis.

c. Per-Protocol (PP): 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.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The noninferiority criteria (LB of 95% CI of the OPA GMT ratio [CAPVAXIVE/PCV20] >0.5) were met for the 10 common serotypes (Table 4). The predefined criteria for statistically significantly higher OPA responses (LB of the 95% CI of the OPA GMT ratio >2.0) compared to PCV20 were met for 10 of 11 serotypes unique to CAPVAXIVE (Table 4). For serotype 15C, the LB of the 95% CI of the OPA GMT ratio was 1.77.

Reviewer Comment: For CAPVAXIVE 15C did not meet the predefined success criterion for statistical superiority. The breadth of data suggests that CAPVAXIVE induces an effective OPA response to serotype 15C. Serotype 15C missed superiority criteria possibly due to OPA response to serotype 15B in Prevnar 20 also inducing a response to serotype 15C, suggested by the relatively high GMT for 15C seen with Prevnar 20 compared to the other unique serotypes. GMTs for 15C in CAPVAXIVE, are comparable to those of the other unique serotypes.

Table 4. Serotype-Specific OPA GMTs, Pneumococcal Vaccine-Naïve Adults ≥50 Years of Age, Per-Protocol Set

Pneumococcal Serotype	CAPVAXIVE N=1179 GMT^a (n)	Prevnar 20 N=1177 GMT^a (n)	GMT Ratio^a (CAPVAXIVE/ Prevnar 20) (95% CI)^a
10 common serotypes ^b	--	--	--
3	274.0 (1154)	176.7 (1161)	1.55 (1.40, 1.72)
6A	2302.0 (1148)	2972.5 (1153)	0.77 (0.68, 0.88)
7F	3637.4 (1152)	3429.9 (1158)	1.06 (0.95, 1.18)
8	2501.3 (1155)	1811.1 (1158)	1.38 (1.25, 1.53)
10A	3893.4 (1161)	4678.0 (1159)	0.83 (0.75, 0.93)
11A	3232.6 (1145)	2092.8 (1150)	1.54 (1.39, 1.72)
12F	2641.2 (1160)	2499.6 (1161)	1.06 (0.92, 1.21)
19A	2136.1 (1159)	2817.8 (1162)	0.76 (0.69, 0.84)
22F	3874.5 (1147)	4770.1 (1154)	0.81 (0.72, 0.92)
33F	13558.9 (1154)	11742.1 (1157)	1.15 (1.01, 1.32)

Pneumococcal Serotype	CAPVAXIVE N=1179 GMT^a (n)	Prevnam 20 N=1177 GMT^a (n)	GMT Ratio^a (CAPVAXIVE/ Prevnam 20) (95% CI)^a
11 serotypes unique to CAPVAXIVE ^c	--	--	--
9N	7470.7 (1147)	1640.4 (1150)	4.55 (4.12, 5.04)
15A	5237.2 (1107)	1589.0 (1102)	3.30 (2.91, 3.74)
15C	4216.2 (1153)	2072.3 (1158)	2.03 (1.77, 2.34)
16F	4868.2 (1151)	846.3 (1153)	5.75 (5.16, 6.41)
17F	7764.9 (1148)	460.4 (1156)	16.86 (14.90, 19.09)
20A	6099.2 (1161)	631.1 (1155)	9.66 (8.66, 10.79)
23A	3737.2 (1132)	461.5 (1104)	8.10 (6.86, 9.55)
23B	1082.5 (1160)	107.3 (1160)	10.09 (8.48, 12.00)
24F	2728.6 (1153)	70.5 (1130)	38.71 (33.87, 44.25)
31	3132.5 (1153)	144.4 (1154)	21.69 (18.68, 25.18)
35B	8527.8 (1153)	1383.0 (1159)	6.17 (5.59, 6.80)

Source: Adapted from STN 125814.0 V116-003 Clinical Study Report: Figure 11-1; Figure 11-2 Abbreviations: GMT=geometric mean titer; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis. PCV20=20-valent pneumococcal conjugate vaccine [Prevnam 20]

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.

a: GMTs, GMT ratio, and 95% CI were estimated from a constrained Longitudinal Data Analysis model.

b: Noninferiority criteria for the common serotypes: the lower bound of the 2-sided 95% CI for the estimated GMT ratio (CAPVAXIVE/PCV20) was >0.5.

c: Statistically significantly greater OPA responses for the unique serotypes in CAPVAXIVE compared to PCV20 were based on the lower bound of the 2-sided 95% CI for the estimated GMT ratio (CAPVAXIVE/PCV20) was >2.0.

CAPVAXIVE met the predefined criteria for superiority to PCV20 (lower bound of 95% CI of the differences >10%) for 10 of 11 serotypes unique to CAPVAXIVE based on the percentage of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination (Table 5). CAPVAXIVE did not meet the predefined criterion for superiority to PCV20 for serotype 15C as the lower bound of 95% CI of the percentage point difference between the percentage of participants with ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination was 5.6%.

Table 5. ≥4-Fold Rise in OPA Responses, Serotypes Unique to CAPVAXIVE, Pneumococcal Vaccine-Naïve Individuals ≥50 Years of Age, Per-Protocol Set

Pneumococcal Serotype	CAPVAXIVE N=1179 Observed Response % (m/n)	Prevnam 20 N=1177 Observed Response % (m/n)	Percentage Point Difference^a CAPVAXIVE–Prevnam 20 Estimate^b (95% CI)
9N	64.7 (595/920)	19.9 (195/978)	44.7 (40.7, 48.6)
15A	66.7 (462/693)	35.8 (253/706)	30.9 (25.8, 35.8)
15C	83.4 (794/952)	74.2 (695/937)	9.2 (5.6, 12.9)
16F	71.9 (654/910)	20.8 (200/961)	51.1 (47.1, 54.9)
17F	75.8 (653/862)	9.5 (90/952)	66.3 (62.8, 69.6)
20A	67.3 (675/1003)	9.6 (97/1011)	57.7 (54.2, 61.1)
23A	78.9 (598/758)	36.8 (270/734)	42.2 (37.6, 46.6)
23B	85.5 (873/1021)	49.6 (506/1021)	35.9 (32.1, 39.6)
24F	80.5 (745/925)	6.3 (55/872)	74.2 (71.1, 77.1)
31	76.5 (698/912)	17.9 (171/954)	58.6 (54.8, 62.1)

Pneumococcal Serotype	CAPVAXIVE N=1179 Observed Response % (m/n)	Pevnar 20 N=1177 Observed Response % (m/n)	Percentage Point Difference^a CAPVAXIVE–Pevnar 20 Estimate^b (95% CI)
35B	60.0 (550/917)	6.8 (67/988)	53.2 (49.6, 56.6)

Source: Adapted from STN 125814.0 V116-003 Clinical Study Report: Table 11-1

Abbreviations: m=number of individuals with the indicated response; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis

Per-Protocol (PP): defined as all randomized participants without deviations from the protocol that would substantially affect immunogenicity

a: Statistically significantly greater OPA responses were based on the lower bound of the 2-sided 95% CI of the differences (CAPVAXIVE – Pevnar 20) between the percentages of individuals with a ≥ 4 -fold rise from prevaccination to 1-month postvaccination being >10 % points

b: Estimated difference and CI were based on the stratified Miettinen & Nurminen method.

The predefined criteria for immunobridging were met for CAPVAXIVE in participants 18 through 49 years of age (Cohort 2) compared with CAPVAXIVE in participants 50 through 64 years of age (Cohort 1) for all 21 serotypes as assessed by serotype-specific OPA GMTs (lower bound of the 95% CI of the OPA GMT >0.5) at 30 days postvaccination (Table 6).

Table 6. Postvaccination OPA GMT Ratios, Participants 18 through 49 Years of Age and 50 through 64 Years of Age, 21 Serotypes in CAPVAXIVE, Per-Protocol Set, Study 003

Pneumococcal Serotype	18 through 49 YOA N=200 GMT (n)	50 through 64 YOA N=589 GMT (n)	GMT Ratio^{*,†} (18 through 49 YOA / 50 through 64 YOA) (95% CI)*
3	308.6 (194)	282.7 (572)	1.1 (0.9, 1.3)
6A	5289.6 (196)	2572.9 (569)	2.1 (1.6, 2.6)
7F	6447.2 (198)	4278.8 (571)	1.5 (1.2, 1.8)
8	4516.0 (197)	3004.7 (571)	1.5 (1.3, 1.8)
9N	17283.2 (197)	8791.4 (570)	2.0 (1.6, 2.4)
10A	6808.1 (197)	4382.6 (575)	1.6 (1.3, 1.9)
11A	5871.6 (196)	3785.8 (564)	1.6 (1.3, 1.9)
12F	6150.4 (196)	3561.2 (574)	1.7 (1.4, 2.2)
15A	11319.2 (184)	5901.2 (550)	1.9 (1.6, 2.4)
15C	10194.0 (195)	5708.0 (570)	1.8 (1.4, 2.4)
16F	8877.0 (193)	5720.0 (571)	1.6 (1.3, 1.9)
17F	16070.6 (194)	10068.0 (568)	1.6 (1.3, 2.0)
19A	2773.2 (198)	2374.6 (574)	1.2 (1.0, 1.4)
20A	13150.0 (197)	7562.7 (575)	1.7 (1.4, 2.2)
22F	9299.6 (198)	4683.6 (568)	2.0 (1.6, 2.5)
23A	8848.7 (192)	4739.5 (561)	1.9 (1.4, 2.4)
23B	2140.1 (198)	1420.9 (575)	1.5 (1.1, 2.0)
24F	4137.6 (197)	3047.2 (570)	1.4 (1.1, 1.7)
31	8005.6 (195)	3820.7 (570)	2.1 (1.6, 2.7)
33F	34805.5 (197)	17607.4 (570)	2.0 (1.5, 2.6)
35B	13933.4 (198)	9053.9 (573)	1.5 (1.3, 1.9)

Source: Adapted from STN 125814.0 V116-003 Clinical Study Report: Figure 11-3

Abbreviations: CI=confidence interval; GMT=geometric mean titer; n=number of participants; N=number of participants in cohort; YOA=years of age

Notes: GMTs, GMT ratio, and 95% CI were estimated from a constrained Longitudinal Data Analysis model.

Per-Protocol (PP): defined as all randomized participants without deviations from the protocol that would substantially affect immunogenicity

6.1.11.2 Analyses of Secondary Endpoints

Serotypes not included in CAPVAXIVE

For serotype 15B, CAPVAXIVE met the predefined criterion for antibody response (lower bound of 95% CI of the percentage of participants with a ≥ 4 -fold rise in OPA responses $> 50\%$ with the percentage of participants with a ≥ 4 -fold rise in OPA responses from baseline to 30 days postvaccination being 64.7% (95% CI: 61.4, 67.8). CAPVAXIVE in participants 18 through 49 years of age (Cohort 2) met the predefined criterion for immunobridging to CAPVAXIVE in participants 50 through 64 years of age (Cohort 1) (lower bound of the 95% CI of the OPA GMT ratio > 0.5) at 30 days postvaccination with the OPA GMT ratio being 2.02 (95% CI: 1.57, 2.60)

For serotype 6C, CAPVAXIVE did not meet the predefined criterion for antibody response with the percentage of participants with a ≥ 4 -fold rise in OPA responses from baseline to 30 days postvaccination being 49.3% (95% CI: 46.0, 52.6). For serotype 6C (cross reactive to serotype 6A), the immunobridging hypothesis was not tested.

A post-hoc analysis was performed to assess OPA GMTs for serotype 15B at 30 days postvaccination. The OPA GMT for serotype 15B following administration of CAPVAXIVE was 4400.6 and following PCV20 was 4640.0. The estimated GMT ratio (CAPVAXIVE/PCV20) was 0.95 (95% CI: 0.84, 1.07).

Additional Immunogenicity

In a descriptive analysis in Cohort 2, the distribution of serotype-specific IgG concentrations at 30 days postvaccination was generally comparable between the intervention groups for the 10 common serotypes and higher in the CAPVAXIVE group for the 11 serotypes unique to CAPVAXIVE, compared with the PCV20 group (See Table 7).

Table 7. IgG Geometric Mean Concentrations at 30 days postvaccination, Per-Protocol Set, Participants 18 through 49 YOA, Study 003

Pneumococcal Serotype	CAPVAXIVE N=200 GMC (n)	Pevnar 20 N=100 GMC (n)
10 common serotypes	--	--
3	0.78 (183)	0.56 (90)
6A	6.82 (183)	7.80 (90)
7F	5.83 (183)	4.13 (89)
8	11.25 (183)	5.72 (90)
10A	11.34 (183)	11.19 (90)
11A	6.64 (183)	4.61 (89)
12F	1.65 (183)	0.87 (90)
19A	6.84 (183)	9.69 (90)
22F	7.88 (183)	6.77 (90)
33F	9.74 (183)	7.38 (89)

Pneumococcal Serotype	CAPVAXIVE N=200 GMC (n)	Pprevnar 20 N=100 GMC (n)
11 serotypes unique to CAPVAXIVE	--	--
9N	6.56 (183)	0.91 (90)
15A	12.28 (183)	2.70 (89)
15C	5.5 (183)	4.77 (90)
16F	1.76 (183)	0.26 (90)
17F	12.38 (183)	0.79 (90)
20A	15.70 (183)	1.85 (90)
23A	3.91 (183)	0.59 (90)
23B	5.66 (183)	1.84 (90)
24F	5.85 (183)	0.39 (90)
31	3.45 (183)	0.34 (90)
35B	12.72 (183)	1.77 (90)

Source: Adapted from STN 125814.0 V116-003 Clinical Study Report: Table 14.2-16

Abbreviations: GMC=geometric mean concentration; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis

Per-Protocol (PP): defined as all randomized participants without deviations from the protocol that would substantially affect immunogenicity

Reviewer Comment: In the younger adult population (18 through 49 YOA) serotype-specific serum IgG concentrations appear generally comparable between CAPVAXIVE and PCV20 for the common serotypes and higher in CAPVAXIVE for the unique serotypes. However, this descriptive analysis is of limited significance because IgG is not a reliable indicator of effectiveness in adult populations due to the presence of non-specific antibody to pneumococcus in older individuals.

6.1.11.3 Subpopulation Analyses

For primary immunogenicity endpoints, serotype-specific OPA GMT ratios and proportion of participants with a ≥ 4 -fold rise in serotype-specific OPA responses at 30 days postvaccination with CAPVAXIVE in Cohort 1 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. A trend toward lower immune responses (OPA GMTs) was observed in the older age groups (i.e., 65 through 74 years of age, and ≥ 75 years of age) compared with the younger age group (50 through 64 years of age) in Cohort 1.

For the primary immunogenicity endpoint, OPA GMTs in adults 18 through 49 years of age (Cohort 2) to 50 through 64 years of age (Cohort 1) for all serotypes at 30 days postvaccination with CAPVAXIVE within each of the subgroup categories analyzed (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](#).

6.1.12 Safety Analyses

6.1.12.1 Methods

See [section 6.1.2](#).

6.1.12.2 Overview of Adverse Events

A total of 2652 participants received 1 dose of CAPVAXIVE [n=1377 (n=200 18 through 49 years of age; n=1177 ≥50 years of age)] or PCV20 (n=1275). Table 8 provides an overview of the rates of adverse events in the CAPVAXIVE groups separated by age cohort compared to the placebo group during the study period. The rates of solicited and unsolicited reactions were similar between CAPVAXIVE and PCV20. In both groups there was a trend towards higher rates of events in the 18 through 49 years of age group.

Table 8. Overview of Adverse Events, Study 003, All Participants as Treated

Event	CAPVAXIVE ≥50 YOA N=1177 n (%)	PCV20 ≥50 YOA N=1175 n (%)	CAPVAXIVE 18 through 49 YOY N=200 n (%)	PCV20 18 through 49 YOY N=100 n (%)
Solicited injection site reaction within 5 days	505 (42.9)	642 (54.6)	146 (73.0)	75 (75.0)
Solicited systemic adverse reaction within 5 days	461 (39.2)	470 (40.0)	118 (59.0)	50 (50.0)
Unsolicited non-serious AE within 30 days	251 (21.3)	252 (21.4)	52 (26.0)	20 (20.0)
SAEs	--	--	--	--
up to 6 months	19 (1.6)	24 (2.0)	1 (0.5)	3 (3.0)
Deaths	4 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)

Source: Adapted from STN 125814.0 V116-003 Clinical Study Report: Table 12-1

Abbreviations: YOA=years of age; PCV20=20-valent pneumococcal conjugate vaccine [Prevnar 20]; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis; SAE=serious adverse event
All Participants as Treated (APaT): defined as all randomized participants who received the study intervention.

Solicited Adverse Reactions.

Within 5 days postvaccination, the percentage of participants reporting any local reaction was similar between the CAPVAXIVE groups (Cohort 1: 51.0%; Cohort 2 80.5%) and PCV20 groups (Cohort 1: 60.3%; Cohort 2 78.0%) (Table 9). The most frequently reported local reaction in all groups was pain at the injection site.

Severe (Grade 3) solicited local and systemic reactions were rare, reported in 0.5% of CAPVAXIVE recipients in Cohort 1, 1.0% of PCV20 recipients in Cohort 1, 4.5% of CAPVAXIVE recipients in Cohort 2, and 3.0% of PCV20 recipients in Cohort 2. One participant in the CAPVAXIVE Cohort 1 group was reported to have a potentially life-threatening (Grade 4) event of pyrexia. The participant was asymptomatic and there were no other AEs reported relating to elevated temperature.

Reviewer Comment: Based on the clinical details provided in BLA, the severity of pyrexia in the participant was likely erroneous as the participant had no additional clinical findings.

Table 9. Solicited Local and Systemic Adverse Events, Within 5 Days Postvaccination, Pneumococcal Vaccine-Naïve Adults 18 through 49 and ≥50 Years of Age, Study 003, All Participants as Treated

Adverse Events	CAPVAXIVE 18 through 49 YOA N=200^a n (%)	PCV20 18 through 49 YOA N=100^a n (%)	CAPVAXIVE ≥50 YOA N=1177^a n (%)	PCV20 ≥50 YOA N=1175^a n (%)
One or more solicited adverse events	161 (80.5)	78 (78.0)	600 (51.0)	708 (60.3)

Adverse Events	CAPVAXIVE 18 through 49 YOA N=200^a n (%)	PCV20 18 through 49 YOA N=100^a n (%)	CAPVAXIVE ≥50 YOA N=1177^a n (%)	PCV20 ≥50 YOA N=1175^a n (%)
No solicited adverse events	39 (19.5)	22 (22.0)	577 (49.0)	467 (39.7)
Local adverse reactions ^b (injection site):				
Severity	--	--	--	--
Pain	--	--	--	--
Any	143 (71.5)	74 (74.0)	464 (39.4)	607 (51.7)
Mild	95 (47.5)	49 (49.0)	361 (30.7)	504 (42.9)
Moderate	46 (23.0)	25 (25.0)	102 (8.7)	102 (8.7)
Severe	2 (1.0)	0	1 (0.1)	1 (0.1)
Erythema ^c	--	--	--	--
Any	31 (15.5)	13 (13.0)	64 (5.4) ±	74 (6.3) ±
Mild	23 (11.5)	10 (10.0)	51 (4.3)	59 (5.0)
Moderate	7 (3.5)	3 (3.0)	10 (0.8)	12 (1.0)
Severe	1 (0.5)	0	2 (0.2)	2 (0.2)
Swelling ^c	--	--	--	--
Any	28 (14.0)	14 (14.0)	71 (6.0)	98 (8.3)
Mild	20 (10.0)	9 (9.0)	53 (4.5)	79 (6.7)
Moderate	7 (3.5)	5 (5.0)	15 (1.3)	17 (1.4)
Severe	1 (0.5)	0	3 (0.3)	2 (0.2)
Systemic adverse events ^d : Severity	--	--	--	--
Fatigue	--	--	--	--
Any	81 (40.5)	34 (34.0)	237 (20.1)	230 (19.6)
Mild	50 (25.0)	21 (21.0)	167 (14.2)	153 (13.0)
Moderate	29 (14.5)	11 (11.0)	70 (5.9)	72 (6.1)
Severe	2 (1.0)	2 (2.0)	0	5 (0.4)
Headache	--	--	--	--
Any	59 (29.5)	24 (24.0)	135 (11.5)	152 (12.9)
Mild	44 (22.0)	17 (17.0)	102 (8.7)	106 (9.0)
Moderate	14 (7.0)	7 (7.0)	33 (2.8)	45 (3.8)
Severe	1 (0.5)	0	0	1 (0.10)
Myalgia	--	--	--	--
Any	33 (16.5)	14 (14.0)	70 (5.9)	79 (6.7)
Mild	15 (7.5)	9 (9.0)	40 (3.4)	42 (3.6)
Moderate	15 (7.5)	4 (4.0)	30 (2.5)	36 (3.1)
Severe	3 (1.5)	1 (1.0)	0	1 (0.1)
Pyrexia ^e	--	--	--	--
≥38.0°C (100.4°F)	7 (3.5)	1 (1.0)	15 (1.3)	15 (1.3)
≥38.0°C (100.4°F) to <38.5°C (101.3°F)	3 (1.5)	0	7 (0.6)	7 (0.6)
≥38.5°C (101.3°F) to <39.0°C (102.2°F)	2 (1.0)	0	6 (0.5)	5 (0.4)
≥39.0°C (102.2°F)	2 (1.0)	1 (1.0)	2 (0.2)	3 (0.3)

Source: Adapted from STN 125814.0 V116-003 Clinical Study Report: Table 14.3-21, 14.3-23

Abbreviations: N=number of participants in particular cohort; n (%)=number and percentage of participants with specified adverse event; YOA=years of age; PCV20=20-valent pneumococcal conjugate vaccine [Prevnar 20]

All Participants as Treated (APaT): 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: Includes one individual with an event of unknown intensity.

e: 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 AEs had events of short duration (≤3 days) with 41.8% in the CAPVAXIVE group and 49.7% in the PCV20 group.

Unsolicited AEs (Non-Serious): 30 Days Postvaccination

Rates on non-serious unsolicited AEs within 30 days postvaccination were similar between the CAPVAXIVE group and the PCV20 group (CAPVAXIVE 21.3% vs PCV20 21.4%). The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) for cohort 1 included: *General disorders and administration site conditions* (CAPVAXIVE 18.5% vs PCV20 18.9%; most commonly *fatigue*), *Nervous system disorders* (CAPVAXIVE 11.0% vs PCV20 11.9%; most commonly *headache*), and *Musculoskeletal and connective tissue disorders* (CAPVAXIVE 6.2% vs PCV20 6.7%; most commonly *myalgia*).

At least 1 Grade 3 unsolicited AE was reported in 2.3% of participants in the CAPVAXIVE group and 3.4% of participants in the PCV20 group. The most frequent types reported by SOC were similar to those reported as any grade AEs.

6.1.12.3 Deaths

Deaths were reported in 4 participants in the CAPVAXIVE group and 2 participants in the PCV20 intervention group, all of which occurred in cohort 1 (≥50 years of age). Deaths in the CAPVAXIVE group were due to sepsis (Day 28), cerebrovascular accident (Day 44), myocardial infarction (Day 179), and hepatic cirrhosis and hepatic encephalopathy (Day 20). Deaths in the PCV20 group were due to cardiac arrest (Day 10) and abdominal abscess (Day 14).

Reviewer Comment: Case narratives were provided and reviewed. None of the fatal serious adverse events are considered by the Applicant, study investigator or this clinical reviewer as related to vaccination due to either timing of event, comorbid conditions/age of participants, or pathologic implausibility.

6.1.12.4 Nonfatal Serious Adverse Events

The frequency of non-fatal serious adverse events (SAEs) reported within 6 months after vaccination in Cohort 1 was 1.6% in the CAPVAXIVE group and 2.0% in the PCV 20 group. The frequency of SAEs in Cohort 2 was 0.5% in the CAPVAXIVE group and 3.0% in the PCV20 group. The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) for cohort 1 included: *Infections and infestations* (CAPVAXIVE 0.6% vs PCV20 0.3%; most commonly *sepsis*), and *Nervous system disorders* (CAPVAXIVE 0.3% vs PCV20 0.3%; most commonly *cerebrovascular accident*).

Reviewer Comment: None of the nonfatal serious adverse events are considered by the Applicant, study investigator or this clinical reviewer as related to vaccination due to lack of temporal association, comorbid conditions/age of participants, or pathologic plausibility.

6.1.12.6 Dropouts and/or Discontinuations

See [section 6.1.10.1.2](#).

6.1.13 Study Summary and Conclusions

Study 003 was designed to demonstrate the immunogenicity and safety of CAPVAXIVE compared to PCV20, a licensed pneumococcal conjugate vaccine for use in adults ≥ 50 years of age. The primary objectives evaluated the immunologic noninferiority of CAPVAXIVE to PCV 20 for the 10 shared serotypes and the statistical superiority of CAPVAXIVE to PCV20 for 10 of the 11 unique serotypes in CAPVAXIVE based on OPA responses. The OPA primary endpoint for serotype 15C, which is contained in CAPVAXIVE but not PCV20, marginally missed the success criteria for statistical superiority. Following the review of data from all immunogenicity parameters, the immunogenicity data indicate that CAPVAXIVE induces an effective immune response to serotype 15C. The predefined criteria for immunobridging were met for CAPVAXIVE in participants 18 through 49 years of age compared with CAPVAXIVE in participants 50 through 64 years of age for all 21 serotypes as assessed by serotype-specific OPA GMTs. The secondary objectives also evaluated the immune response against serotype 15B following vaccination with CAPVAXIVE. The study met the prespecified criteria for success for immune response to serotype 15B based on ≥ 4 -fold rise in OPA responses.

The percentages of participants with AEs were generally comparable between the CAPVAXIVE and PCV20 intervention groups. Solicited adverse reactions following administration of CAPVAXIVE lasted a median of 2 days with 81.3% of reactions lasting ≤ 3 days for individuals 18 through 49 years of age and a median of 1 day with 86.5% of reactions lasting ≤ 3 days for individuals 50 years of age and older. The percentage of participants with solicited AEs of moderate (Grade 2) intensity grade were $\leq 15\%$ in Cohort 1 and $\leq 35\%$ in Cohort 2. The percentage of participants with solicited AEs of severe (Grade 3) intensity grade were $\leq 1\%$ in Cohort 1 and $< 5\%$ in Cohort 2 in each intervention group. The percentages of participants with SAEs were low (0.5% to 1.6% in CAPVAXIVE recipients vs 2.0% to 3.0% in PCV20 recipients) with none assessed as related to vaccination.

The data from this study support the safety and effectiveness of CAPVAXIVE for use as a single dose in individuals ≥ 18 years of age for 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.

6.2 Study V116-004

NCT 05464420

“A Phase 3 Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of CAPVAXIVE in Adults 18 through 49 Years of Age.”

6.2.1 Objectives

Primary Objectives, Endpoints, and Statistical Criteria

- To evaluate the safety and tolerability profile of CAPVAXIVE as assessed by the proportion of participants with AEs.
 - Solicited injection site AEs from postvaccination Day 1-Day 5
 - Solicited systemic AEs from Day 1 through Day 5 postvaccination
 - Vaccine-related SAEs from postvaccination Day 1 through the duration of participation in the study

- To compare the serotype-specific OPA GMTs at 30 days postvaccination across 3 different lots of CAPVAXIVE for all serotypes included in CAPVAXIVE.
 - Hypothesis: All 3 lots of CAPVAXIVE are equivalent as assessed by the serotype-specific OPA GMTs at 30 days postvaccination for all serotypes included in CAPVAXIVE.
 - Bounds of the 95% CI of the OPA GMT ratio for each pairwise CAPVAXIVE lot-to-lot comparison to be within 0.5 to 2.0

Secondary Objectives, Endpoints, and Statistical Criteria

- To evaluate the serotype-specific OPA GMTs at 30 days postvaccination separately for 3 different lots of CAPVAXIVE for immune responses to serotypes within a serogroup not included in the vaccine (i.e., 15B and 6C).

6.2.2 Design Overview

Study 004 is a randomized, active comparator-controlled, parallel-group, multisite, double-blind study to establish lot-to-lot consistency and evaluate safety, tolerability, and immunogenicity of a single dose of CAPVAXIVE in pneumococcal vaccine-naïve adults 18 through 49 years of age. The study was conducted in 8 countries. A total of 2,157 participants were randomized in a 1:1:1:1 ratio to receive a single dose of either CAPVAXIVE Lot 1, CAPVAXIVE Lot 2, CAPVAXIVE Lot 3 or PPSV23 on Day 1. PPSV23 was chosen as the comparator for safety evaluation.

Safety monitoring and data collection methods were the same as for Study 003 (see [section 6.1.7](#)). Blood samples were collected at 30 days after vaccination for immunologic evaluations.

6.2.3 Population

Except for the age inclusion of 18 through 49 years of age, the inclusion and exclusion criteria are the same as Study 003 (see [section 6.1.3](#)).

6.2.4 Study Treatments or Agents Mandated by the Protocol

All study interventions were administered intramuscularly as a single dose.

CAPVAXIVE: vaccine composition and presentation are the same as for Study 003 (see [section 6.1.4](#)) Lot #s 0001471935, 0001482963, 0001491024.

PPSV23 (comparator)

- Composition: 25 µg 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 for injection
- Lot# 0001432932

6.2.5 Directions for Use

Same as for Study 003 (see [section 6.1.5](#))

6.2.6 Sites and Centers

72 centers in 8 countries: Austria, Canada, Denmark, Finland, Israel, Poland, Spain, and United States

6.2.7 Surveillance/Monitoring

Safety Monitoring

Same as Study 003 (see [section 6.1.7](#)).

Immunogenicity

Sera from participants was used to measure vaccine-induced OPA and IgG responses. The multiplex opsonophagocytic assay (MOPA) was used for measuring OPA responses, and serotype-specific IgG was measured using the pneumococcal electrochemiluminescence (Pn ECL) assay to assess the concentration of binding antibodies to capsular polysaccharide of *S. pneumoniae*.

6.2.8 Endpoints and Criteria for Study Success

See [section 6.2.1](#).

6.2.9 Statistical Analysis Plan

Primary hypothesis: the bounds of the 95% CI on the pairwise lot-to-lot comparison of the CAPVAXIVE GMT ratios is between 0.5 and 2.0.

Each possible pairwise comparison of lots was made (Lot 1 to Lot 2, Lot 1 to Lot 3, and Lot 2 to Lot 3), with a type 1 error = 0.025 level. Estimation of the GMT ratios, 95% CIs, and the hypothesis test will be conducted using a cLDA method proposed by Liang and Zeger.

Descriptive statistics with point estimates and within-group 95% CIs were provided for the secondary immunogenicity endpoints and safety endpoints.

For the primary hypothesis based on an enrollment of 510 participants, this study had >90% power to demonstrate equivalent immunogenicity across the 3 CAPVAXIVE lots as assessed by the OPA GMTs at 30 days postvaccination for all serotypes contained in CAPVAXIVE at an overall type 1 error = 0.05 (2- sided). The power and sample size are based on the following assumptions:

- 90% evaluability rate (approximately 459 evaluable participants in each of 3 manufactured lots of CAPVAXIVE)
- The underlying serotype-specific OPA GMT ratios are 1.0 for all serotypes
- The variabilities for OPA titers in the CAPVAXIVE vaccination groups are the same as those observed in V116-001 Phase 2 for all serotypes. That is, the standard deviations of the natural log titers range from 1.06 to 1.95

6.2.10 Study Population and Disposition

Important protocol deviations were reported for 164 (7.6%) participants, 134 of which were considered to be clinically important. Participants with important protocol deviations were excluded from the lot consistency analysis. The most frequently reported clinically important protocol deviations were due to:

- Immunogenicity blood sample drawn outside the protocol-defined window (n=68)
- Immunogenicity samples not drawn or samples unable to be tested due to an error by the site in processing and/or handling of the sample (n=36).

6.2.10.1 Populations Enrolled/Analyzed

Per-Protocol (PP) population is defined as all randomized participants 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) consists of all randomized participants who received at least one study vaccination and have at least one serology result. All-Participants-as-Treated (APaT) set consists of all randomized participants who received at least one dose of study vaccination.

6.2.10.1.1 Demographics

The demographics of participants in the APaT set are shown in Table 10.

The median age of participants was 35.0 years. 57.6% of participants were female, 79.7% were non-Hispanic or Latino ethnicity, 84.6% were White, 9.0% were Black or African American, and 3.8% were multiple races. Demographics were comparable between the intervention groups.

Table 10. Demographic Characteristics, All-Participants-as-Treated Set, Study 004

Characteristic	CAPVAXIVE Lot 1 N=539	CAPVAXIVE Lot 2 N=538	CAPVAXIVE Lot 3 N=540	PPSV3 N=540
Sex, n (%)	--	--	--	--
Male	235 (43.6)	219 (40.7)	230 (42.6)	230 (42.6)
Female	304 (56.4)	319 (59.3)	310 (57.4)	310 (57.4)
Age (Years)	--	--	--	--
Mean age (SD)	34.8 (9.3)	34.8 (9.2)	34.3 (9.3)	34.4 (9.2)
Median age	35.0	35.5	35.0	34.0
18 through 49, n (%)	539 (100.0)	538 (100.0)	540 (100.0)	540 (100.0)
Race, n (%)	--	--	--	--
American Indian or Alaska Native	6 (1.1)	2 (0.4)	4 (0.7)	4 (0.7)
Asian	9 (1.7)	12 (2.2)	6 (1.1)	8 (1.5)
Black or African American	48 (8.9)	43 (8.0)	55 (10.2)	48 (8.9)
Multiple	16 (3.0)	23 (4.3)	16 (3.0)	26 (4.8)
Native Hawaiian or Other Pacific Islander	2 (0.4)	1 (0.2)	0 (0.0)	1 (0.2)
White	457 (84.8)	457 (84.9)	457 (84.6)	453 (83.9)
Missing	1 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
Ethnicity, n (%)	--	--	--	--
Hispanic or Latino	98 (18.2)	104 (19.3)	113 (20.9)	107 (19.8)
Not Hispanic or Latino	438 (81.3)	432 (80.3)	419 (77.6)	430 (79.6)
Not Reported	3 (0.6)	1 (0.2)	7 (1.3)	3 (0.6)
Unknown	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
Country, n (%)	--	--	--	--
Austria	34 (6.3)	22 (4.1)	30 (5.6)	27 (5.0)
Canada	31 (5.8)	25 (4.6)	30 (5.6)	25 (4.6)
Denmark	27 (5.0)	36 (6.7)	27 (5.0)	30 (5.6)
Finland	32 (5.9)	37 (6.9)	33 (6.1)	35 (6.5)
Israel	74 (13.7)	71 (13.2)	64 (11.9)	71 (13.1)
Poland	35 (6.5)	29 (5.4)	28 (5.2)	29 (5.4)
Spain	52 (9.6)	56 (10.4)	58 (10.7)	61 (11.3)
United States	254 (47.1)	262 (48.7)	270 (50.0)	262 (48.5)

Source: Adapted from STN 125814.0, V116-004 Clinical Study Report: Table 10-2

Abbreviations: N=number of participants; n (%)=number and percentage of participants in a given category; PPSV23=23-valent pneumococcal polysaccharide vaccine; SD=standard deviation; CAPVAXIVE=Pneumococcal 21-valent conjugate vaccine

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Approximately 25% of vaccinated participants had ≥ 1 prespecified medical history condition. The five most commonly reported medical history conditions (by Preferred Term) were seasonal allergy (9.9%), anxiety (9.6%), depression (9.2%), asthma (7.8%), and obesity (7.5%).

6.2.10.1.3 Participant Disposition

Of 2,162 randomized participants (n=541 CAPVAXIVE Lot 1, n=540 CAPVAXIVE Lot 2, n=541 CAPVAXIVE Lot 3 n= 540 PPSV23), 2,157 participants were vaccinated, and 2092 (96.8%) (n=521 CAPVAXIVE Lot 1, n=520 CAPVAXIVE Lot 2, n=525 CAPVAXIVE Lot 3 n= 526 PPSV23) completed the study. Of the participants randomized, 1,950 (90.2%) of participants were included in the Per Protocol population (n=478 CAPVAXIVE Lot 1, n=490 CAPVAXIVE Lot 2, n=491 CAPVAXIVE Lot 3, n=491 PPSV23).

The most commonly reported protocol deviations that resulted in exclusion from the PP were:

- Immunogenicity blood sample drawn outside the protocol-defined window (n=68)
- Immunogenicity samples not drawn or samples unable to be tested due to an error by the site in processing and/or handling of the sample (n=36)

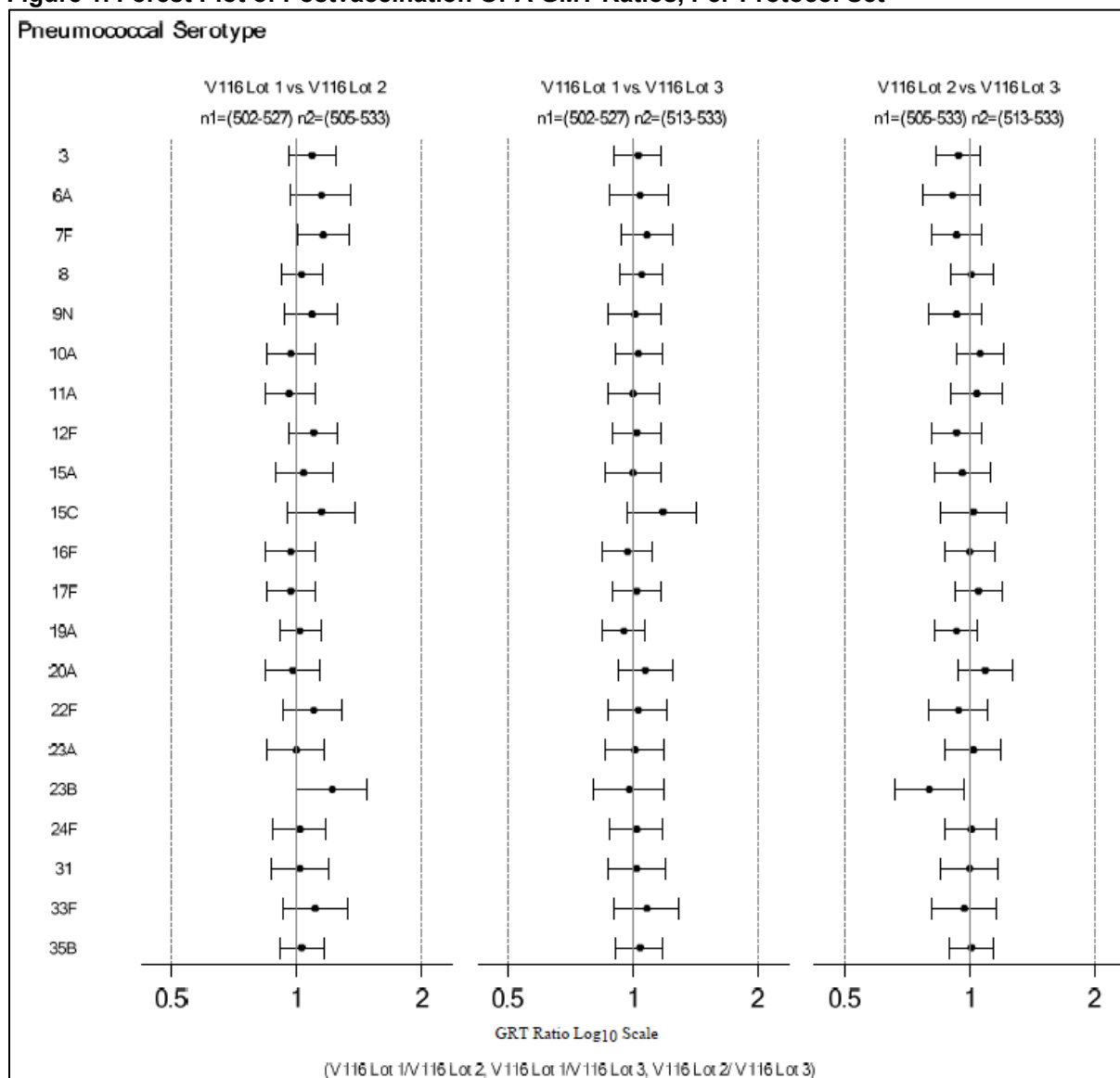
The main reasons for discontinuation from the study were lost to follow-up (n=49) and withdrawal by participants (n=16).

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Lot-to-lot consistency was demonstrated across the 3 CAPVAXIVE vaccine lots, as measured by serotype-specific OPA GMTs at 1-month postvaccination. The 2-sided 95% CI for pair-wise comparisons of CAPVAXIVE serotype-specific OPA GMT ratios for the 3 vaccine lots were within the pre-defined limit of [0.5, 2.0] (Figure 2).

Figure 1. Forest Plot of Postvaccination OPA GMT Ratios, Per-Protocol Set



Source: adapted from Study V116-004 report.pdf, Figure 11-1

Per-Protocol (PP): 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.

n1=Number of participants contributing to analysis from Lot 1, Lot 1, Lot 2 respectively;

n2=Number of participants contributing to analysis from Lot 2, Lot 3, Lot 3 respectively.

6.2.11.2 Dropouts and/or Discontinuations

The number of participants with at least 1 important protocol deviation leading to elimination from any analyses was 20 (3.7%), 20 (3.7%), and 16 (3.0%) in CAPVAXIVE Lot 1 group, Lot 2, group, and Lot 3 group respectively. Most of the protocol deviation were related to lost to follow-up (3.0%, 2.0%, and 2.0% in the Lot 1, Lot 2, and Lot 3 study groups, respectively).

6.2.12 Safety Analyses

6.2.12.1 Methods

See [section 6.4.1](#).

6.2.12.2 Overview of Adverse Events

Overall (3 lots combined),

- Solicited local and systemic adverse reactions (Day 1-5)
 - Solicited local adverse reactions were reported by 80.4% of participants (Table 11). The most frequently reported event was injection site pain (73.3%).
 - Solicited systemic adverse reactions were reported by 48.1% of CAPVAXIVE combined lot recipients and 43.3% of PPSV23 recipients (Table 11). The most frequently reported event for both groups was fatigue (35.5% CAPVAXIVE, 34.0% PPSV23).
 - Grade 3 solicited adverse reactions were reported in 5.4% of participants.

Table 11. Solicited Local and Systemic Adverse Events, Within 5 Days Postvaccination, Pneumococcal Vaccine-Naïve Adults 18 through 49 Years of Age, Study 004, All Participants as Treated

Adverse Events	CAPVAXIVE (Combined Lots) N=1616 n (%)	PPSV23 N=541 n (%)
One or more solicited adverse events	1,263 (78.2)	387 (71.5)
Local adverse event [†]	--	--
Pain	--	--
Any	1,184 (73.3)	328 (60.6)
Mild	759 (47.0)	234 (43.3)
Moderate	395 (24.4)	86 (15.9)
Severe	30 (1.9)	8 (1.5)
Erythema ^a	--	--
Any	219 (13.6)	41 (7.6)
Mild	143 (8.8)	30 (5.5)
Moderate	57 (3.5)	8 (1.5)
Severe	19 (1.2)	3 (0.6)
Swelling ^a	--	--
Any	213 (13.2)	41 (7.6)
Mild	148 (9.2)	29 (5.4)
Moderate	55 (3.4)	10 (1.8)
Severe	10 (0.6)	2 (0.4)
Systemic adverse events [†]	--	--
Fatigue	--	--
Any	573 (35.5)	184 (34.0)
Mild	338 (20.9)	119 (22.0)
Moderate	201 (12.4)	60 (11.1)
Severe	34 (2.1)	5 (0.9)
Headache	--	--
Any	440 (27.2)	116 (21.4)
Mild	275 (17.0)	70 (12.9)
Moderate	151 (9.3)	43 (7.9)
Severe	14 (0.9)	3 (0.6)
Myalgia	--	--
Any	264 (16.3)	47 (8.7)
Mild	146 (9.0)	33 (6.1)
Moderate	103 (6.4)	12 (2.2)
Severe	15 (0.9)	2 (0.4)
Pyrexia [‡]	--	--

Adverse Events	CAPVAXIVE (Combined Lots) N=1616 n (%)	PPSV23 N=541 n (%)
≥38.0°C	48 (3.0)	12 (2.2)
≥38.0°C to <38.5°C	31 (1.9)	4 (0.7)
≥38.5°C to <39.0°C	11 (0.7)	2 (0.4)
≥39.0°C	6 (0.4)	6 (0.1)

Source: adapted from STN 125814.0 V116-004 Clinical Study Report: Table 14.3-12

All Participants as Treated (APaT): defined as all randomized participants who received the study intervention.

Abbreviations: N=number of participants in particular cohort; n (%)=number and percentage of participants with specified adverse event; YOA=years of age; PPSV23=23-valent pneumococcal polysaccharide vaccine

† Injection-site erythema, injection-site pain, injection-site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination.

a. 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.

‡ 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.

Notes: Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity

- **Unsolicited AEs (Day 1-30)**
27.4% of participants in the CAPVAXIVE group (3 lots combined) reported at least one unsolicited AE. The most commonly reported unsolicited AEs were fatigue (34.2%), headache (26.3%), myalgia (16.2%), and pyrexia (3.0%).

6.2.12.3 Deaths

One (1) participant in the PPSV23 group died from a road traffic accident. The death was not considered by the Applicant, study investigator or the FDA clinical reviewer to be related to study vaccination.

6.2.12.4 Nonfatal Serious Adverse Events

A total of 14 (0.9%) of participants in the CAPVAXIVE (3 lots combined) reported at least 1 SAE within 6 months after vaccination compared to 6 (1.1%) of participants in the PPSV23 group. None of the SAEs were assessed by the Applicant, study investigator or FDA clinical reviewer as related to study intervention.

The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) for cohort 1 included: *Infections and infestations* (CAPVAXIVE 0.1% vs PCV20 0.9%), and *Psychiatric disorders* (CAPVAXIVE 0.4% vs PCV20 0.0%).

Reviewer Comment: Case narratives were provided and reviewed. None of the nonfatal serious adverse events are considered by the Applicant, study investigator or this clinical reviewer as related to vaccination due to either timing of event, comorbid conditions/age of participants, or pathologic implausibility.

6.2.12.5 Dropouts and/or Discontinuations

See [section 6.2.10](#).

6.2.13 Study Summary and Conclusions

Study 004 was designed as a lot consistency, immunogenicity, and safety study in adults 18 through 49 years of age. Pneumococcal vaccine-naïve adults 18 through 49 years of age

received one of three CAPVAXIVE lots or PPSV23. The equivalence criteria were met for all 21 serotypes in CAPVAXIVE, demonstrating lot-to-lot equivalency.

The percentages of participants with AEs were generally comparable between the CAPVAXIVE and PPSV23 intervention groups. The percentage of participants with solicited AEs of moderate (Grade 2) intensity grade were $\leq 32\%$ in CAPVAXIVE recipients and $\leq 26\%$ in PPSV23 recipients. The percentage of participants with solicited AEs of severe (Grade 3) intensity grade were $\leq 6\%$ in CAPVAXIVE recipients and $\leq 4\%$ in PPSV23 recipients. The percentages of participants with SAEs were low (0.9% in CAPVAXIVE recipients vs 1.1% in PPSV23 recipients) with none assessed as related to vaccination.

6.3 Study V116-006

NCT 05420961

“A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of CAPVAXIVE in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older.”

6.3.1 Objectives

Primary Objectives, Endpoints, and Statistical Criteria

- To evaluate the safety and tolerability of CAPVAXIVE as assessed by the proportion of participants with AEs
 - Solicited injection site/systemic AEs from postvaccination Day 1 through Day 5
 - Vaccine-related SAEs from postvaccination Day 1 through the duration of participation in the study.
- To evaluate the serotype-specific OPA GMTs at 30 days postvaccination for all serotypes included in CAPVAXIVE.

Secondary Objectives, Endpoints, and Statistical Criteria

- To evaluate the percentage of participants who achieve a serotype-specific ≥ 4 -fold increase from baseline to 30 days postvaccination for OPA responses for all serotypes included in CAPVAXIVE.

Exploratory Objectives, Endpoints, and Statistical Criteria

- To evaluate the immune responses to serotypes within a serogroup not included in the vaccine (i.e., 15B and 6C) 30 days postvaccination.
 - Serotype-specific OPA and IgG responses

6.3.2 Design Overview

Study 006 was a multisite study to evaluate the safety, tolerability, and immunogenicity of CAPVAXIVE in participants ≥ 50 years of age who are pneumococcal vaccine-experienced. Participants were considered to be pneumococcal vaccine-experienced and eligible for enrollment in this study if they received any of PCV13, PCV15, PCV20, PPSV23, PCV13+PPSV23, PCV15+PPSV23, or PPSV23+PCV13 ≥ 1 year before enrollment. The study was conducted in 51 centers in 9 countries. A total of 717 participants were enrolled into one of three cohorts based on prior pneumococcal vaccination history.

- Cohort 1: 350 participants who were vaccinated with PPSV23 ≥ 1 year prior to enrollment were randomized in a 2:1 ratio to receive either CAPVAXIVE or PCV15 on Day 1.
- Cohort 2: 261 participants who were vaccinated with PCV13 ≥ 1 year prior to enrollment were randomized in a 2:1 ratio to receive either CAPVAXIVE or PPSV23 on Day 1.

- Cohort 3: 106 participants who were vaccinated with PCV13+PPSV23, PCV15+PPSV23, PCV15, PCV20, or PPSV23+PCV13 ≥ 1 year prior to enrollment received CAPVAXIVE on Day 1.

Cohort 1 and 2 were double-blind, parallel group, and active comparator-controlled while Cohort 3 was open-label and single group.

Safety monitoring and data collection methods were the same as for study 003 (see [section 6.1.7](#)). Blood samples were collected at 30 days after vaccination.

6.3.3 Population

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

- The participant may have underlying chronic conditions if they are assessed to be stable as per the investigator's judgment.
- Is pneumococcal vaccine-experienced, defined as prior receipt (≥ 1 year before enrollment) of PCV13, PCV15, PCV20, PPSV23, PCV13+PPSV23, PPSV23+PCV13, or PCV15+PPSV23.
- Is male or female, ≥ 50 years of age, at the time of informed consent.
- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
 - Not a woman of childbearing potential, OR
 - A woman of childbearing potential who uses an acceptable contraceptive method; has a negative highly sensitive pregnancy test within 24hrs before the first dose of study intervention; medical history, menstrual history, and recent sexual activity has been reviewed by the investigator.
- The participant has provided documented informed consent for the study.
- The participant has the ability to complete eVRC data collection without assistance.

Except for the exclusion criteria of having received PPSV23 followed by either PCV15 or PCV20 and not excluding participants who received prior administration of any pneumococcal vaccine, the exclusion criteria are the same as Study 003 (See [section 6.1.3](#)).

6.3.4 Study Treatments or Agents Mandated by the Protocol

All study interventions were administered IM as a single dose (0.5mL).

CAPVAXIVE: see [section 6.1.4](#). Lot #: 0001471935

PCV15 (comparator)

- Composition: 2 μ g of each PnPs antigen (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F)
- Presentation: Pre-filled syringe for injection
- Lot#: 0001401588

PPSV23 (comparator)

- Composition: 25 μ g 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)
- Presentation: Pre-filled syringe for injection
- Lot #: 0001432932

6.3.5 Directions for Use

Same as for Study 003 (see [section 6.1.5](#))

6.3.6 Sites and Centers

37 sites in 9 countries: Canada, France, Israel, Italy, Japan, South Korea, Spain, Taiwan, and the U.S.

6.3.7 Surveillance/Monitoring

Safety Monitoring

Same as Study 003 (see [section 6.1.7](#))

Immunogenicity

Same as Study 004 (see [section 6.2.7](#))

6.3.8 Endpoints and Criteria for Study Success

See [section 6.3.1](#).

6.3.9 Statistical Considerations & Statistical Analysis Plan

All immunogenicity endpoints are descriptive.

Immunogenicity endpoints was assessed for all serotypes included in CAPVAXIVE and for serotypes within a serogroup not included in the vaccine (i.e., 15B and 6C) using OPA GMT, IgG GMC, GMFR, and percentage of participants with 4-fold rise from baseline to 30 days postvaccination for OPA and IgG responses.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

Same as Study 004 (see [section 6.2.10.1](#)).

6.3.10.1.1 Demographics

The demographics of participants in the APaT set are shown in Table 12.

The median age of participants was 68.0 years among all groups and cohorts with 71% of participants ≥65 years of age. Approximately 54% of participants were female, 85.4% were non-Hispanic or Latino ethnicity, 64% were White, 33% were Asians, and 3% were Black or African American. Demographics and baseline characteristics were similar between the intervention groups.

Table 12. Demographic Characteristics, All-Participants-as-Treated Set, Study 006

Characteristic	Cohort 1 CAPVAXIVE N=229	Cohort 1 PCV15 N=119	Cohort 2 CAPVAXIVE N=174	Cohort 2 PPSV23 N=85	Cohort 3 CAPVAXIVE N=105
Sex, n (%)	--	--	--	--	--
Male	112 (48.9)	59 (49.6)	74 (42.5)	36 (42.4)	50 (47.6)
Female	117 (51.1)	60 (50.4)	100 (57.5)	49 (57.6)	55 (52.4)

Characteristic	Cohort 1 CAPVAXIVE N=229	Cohort 1 PCV15 N=119	Cohort 2 CAPVAXIVE N=174	Cohort 2 PPSV23 N=85	Cohort 3 CAPVAXIVE N=105
Age (Years)	--	--	--	--	--
Mean age (SD)	68.7 (7.5)	69.0 (7.1)	65.5 (7.8)	65.4 (6.6)	71.0 (7.6)
Median age	69.0	69.0	66.0	65.0	71.0
50 through 64, n (%)	48 (21.0)	25 (21.0)	80 (46.0)	39 (45.9)	17 (16.2)
≥65, n (%)	181 (79.0)	94 (79.0)	94 (54.0)	46 (54.1)	88 (83.8)
Race, n (%)	--	--	--	--	--
Asian	96 (41.9)	47 (39.5)	55 (31.6)	25 (29.4)	13 (12.4)
Black or African American	6 (2.6)	3 (2.5)	3 (2.5)	1 (1.2)	6 (5.7)
Multiple	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
White	125 (54.6)	69 (58.0)	116 (66.7)	59 (69.4)	85 (81.0)
Ethnicity, n (%)	--	--	--	--	--
Hispanic or Latino	21 (9.2)	17 (14.3)	34 (19.5)	16 (18.8)	14 (13.3)
Not Hispanic or Latino	206 (90.0)	102 (85.7)	140 (80.5)	69 (81.2)	91 (86.7)
Not Reported	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Country, n (%)	--	--	--	--	--
Canada	23 (10.0)	10 (8.4)	21 (12.1)	14 (16.5)	7 (6.7)
France	1 (0.4)	1 (0.8)	0 (0.0)	2 (2.4)	0 (0.0)
Israel	46 (20.1)	25 (21.0)	3 (1.7)	3 (3.5)	22 (21.0)
Italy	0 (0.0)	0 (0.0)	24 (13.8)	7 (8.2)	0 (0.0)
Japan	31 (13.5)	19 (16.0)	11 (6.3)	2 (2.4)	0 (0.0)
South Korea	51 (22.3)	22 (18.5)	17 (9.8)	10 (11.8)	0 (0.0)
Spain	17 (7.4)	12 (10.1)	15 (8.6)	6 (7.1)	0 (0.0)
Taiwan	13 (5.7)	5 (4.2)	25 (14.4)	13 (15.3)	11 (10.5)
United States	47 (20.5)	25 (21.0)	58 (33.3)	28 (32.9)	65 (61.9)
Time since last pneumococcal vaccination, n (%)	--	--	--	--	--
1 to 4 years	108 (47.2)	54 (45.4)	135 (77.6)	66 (77.6)	78 (74.3)
5 to 9 years	85 (37.1)	45 (37.8)	33 (19.0)	18 (21.2)	27 (25.7)
≥ 10 years	36 (15.7)	20 (16.8)	6 (3.4)	1 (1.2)	0 (0.0)

Source: Adapted from STN 125814.0, V116-006 Clinical Study Report: Table 10-2

All Participants as Treated: defined as all randomized participants who received the study intervention.

Abbreviations: N=number of participants; n (%)=number and percentage of participants in a given category; PCV15=Pneumococcal 15-valent conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine; SD=standard deviation; CAPVAXIVE=Pneumococcal 21-valent conjugate vaccine

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In the Cohort 1, 28.4% of participants had diabetes mellitus. In Cohort 2, 22.0% of participants had diabetes mellitus. In Cohort 3, 26.7% of participants had diabetes mellitus.

6.3.10.1.3 Participant Disposition

There were 717 participants randomized into three cohorts and 712 received study interventions. There were 350 participants randomized in Cohort 1 with 231 in the CAPVAXIVE group and 119 in the PCV15 group. In Cohort 2, there were 261 participants with 176 in the CAPVAXIVE group and 85 in the PPSV23 group. In Cohort 3, there were 106 participants in the CAPVAXIVE group. The APaT set included 711 of 712 randomized participants who received at least one dose of study intervention. One participant randomized to receive PCV15 in Cohort 1 inadvertently received PPSV23 and thus was excluded from the APaT population since the intervention received was not one of the designated interventions.

Important protocol deviations were reported for 33 participants (4.6%), 27 of which were considered clinically important. The most frequently reported clinically important protocol deviations were due to:

- Participant was administered improperly stored study intervention that was deemed unacceptable for use (n=9)
- Participant's immunogenicity blood sample was drawn outside the protocol-defined window (n=6)
- Participant was assigned to the incorrect cohort based on prior pneumococcal vaccine history as required per-protocol (n=5)

Of the participants randomized in cohort 1, 327 (93.4%) of participants were included in the Per Protocol population (n=212 CAPVAXIVE, n=115 PCV15). Of the participants randomized in cohort 2, 240 (92.0%) of participants were included in the Per Protocol population (n=164 CAPVAXIVE, n=76 PCV15). Of the participants randomized in cohort 3, 98 (92.5%) of participants were included in the Per Protocol population.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

In Cohort 1, CAPVAXIVE elicited immune responses that were generally comparable to PCV15 for the 6 common serotypes and higher than PCV15 for the 15 serotypes unique to CAPVAXIVE, as assessed by OPA GMTs at 30 days postvaccination (Table 13).

Table 13. Serotype-specific OPA GMTs (Cohort 1), Per Protocol Set

Pneumococcal Serotype	CAPVAXIVE N=229 GMT^a (n)	PCV15 N=119 GMT^a (n)
6 common serotypes	--	--
3	262.1 (197)	226.3 (103)
6A	1653.5 (191)	9076.1 (94)
7F	2184.4 (209)	1750.3 (110)
19A	1513.8 (204)	2022.9 (109)
22F	1983.8 (206)	1595.6 (108)
33F	4311.9 (188)	3397.2 (99)
15 serotypes unique to CAPVAXIVE	--	--
8	1273.0 (208)	345.8 (113)
9N	3805.1 (191)	2176.5 (111)
10A	1986.2 (209)	467.5 (112)
11A	1998.5 (197)	335.6 (100)
12F	981.8 (212)	80.5 (114)
15A	4184.9 (175)	877.2 (93)
15C	2307.8 (206)	539.6 (110)
16F	3060.5 (187)	392.3 (107)
17F	3599.8 (194)	939.6 (108)
20A	2847.4 (195)	1058.9 (110)
23A	2363.9 (202)	310.2 (91)
23B	673.2 (197)	153.0 (110)
24F	1822.6 (201)	106.6 (97)

Pneumococcal Serotype	CAPVAXIVE N=229 GMT^a (n)	PCV15 N=119 GMT^a (n)
31	3018.4 (194)	113.2 (108)
35B	6703.1 (194)	1019.1 (107)

Source: Adapted from STN 125814.0 V116-006 Clinical Study Report: Table 14.2-1 – 14.2-2

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.

Abbreviations: GMT=geometric mean titer; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis

Notes: a: GMTs were estimated from a constrained Longitudinal Data Analysis model.

In Cohort 2, CAPVAXIVE elicited immune responses that were generally comparable to PPSV23 for the 12 common serotypes and higher than PPSV23 for the 9 serotypes unique to CAPVAXIVE, as assessed by OPA GMT at 30 days postvaccination (Table 14).

Table 14. Serotype-specific OPA GMTs (Cohort 2), Per Protocol Set

Pneumococcal Serotype	CAPVAXIVE N=174 GMT^a (n)	PPSV23 N=85 GMT^a (n)
12 common serotypes	--	--
3	391.1 (149)	583.1 (75)
7F	3129.8 (150)	4057.0 (70)
8	2320.1 (161)	2723.2 (75)
9N	7214.4 (143)	6482.5 (58)
10A	3976.8 (155)	1797.6 (73)
11A	2846.6 (142)	1736.6 (71)
12F	2552.6 (160)	1402.5 (73)
17F	5963.8 (125)	4367.3 (67)
19A	2528.9 (158)	3241.5 (74)
20A	6005.5 (138)	3393.9 (72)
22F	4389.2 (143)	2524.0 (71)
33F	8162.9 (131)	8761.9 (59)
9 serotypes unique to CAPVAXIVE	--	--
6A	3624.0 (152)	1812.3 (74)
15A	6185.2 (134)	1668.2 (63)
15C	4334.4 (152)	1470.4 (72)
16F	4626.5 (146)	832.8 (74)
23A	4253.4 (156)	433.6 (60)
23B	1530.7 (160)	203.9 (75)
24F	2746.1 (151)	48.5 (63)
31	4413.5 (146)	171.8 (68)
35B	8143.5 (148)	1527.7 (76)

Source: Adapted from STN 125814.0 V116-006 Clinical Study Report: Table 14.2-3 – 14.2-4

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.

Abbreviations: GMT=geometric mean titer; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis

Notes: a: GMTs were estimated from a constrained Longitudinal Data Analysis model.

In Cohort 3, CAPVAXIVE elicited immune responses that were generally comparable to that of Cohorts 1 and 2 as assessed by OPA GMT at 30 days postvaccination (Table 15).

Table 15. Serotype-specific OPA GMTs (Cohort 3), Per Protocol Set

Pneumococcal Serotype	CAPVAXIVE N=105 GMT^a (n)
3	318.3 (85)
6A	2097.3 (93)
7F	2051.3 (96)
8	1486.8 (98)
9N	4054.5 (90)
10A	2564.0 (96)
11A	2373.0 (87)
12F	1235.3 (99)
15A	4328.6 (86)
15C	2191.9 (89)
16F	2477.0 (89)
17F	3836.7 (82)
19A	1533.8 (93)
20A	2433.4 (88)
22F	1913.5 (99)
23A	3967.2 (86)
23B	844.0 (97)
24F	2041.5 (90)
31	3285.5 (90)
33F	4654.3 (88)
35B	5836.8 (90)

Source: Adapted from STN 125814.0 V116-006 Clinical Study Report: Table 14.2-5

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.

Abbreviations: GMT=geometric mean titer; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis

Notes: a: GMTs were estimated from a constrained Longitudinal Data Analysis model.

6.3.11.2 Analyses of Secondary Endpoints

≥4-fold Increase in Serotype-specific OPA Responses

Across all 3 cohorts, CAPVAXIVE was immunogenic as assessed by percentages of participants with a ≥4-fold increase in serotype-specific OPA responses from pre-vaccination to 30 days postvaccination for all 21 serotypes contained in the vaccine [range: Cohort 1 (19.8%-80.2%), Cohort 2 (33.6%-93.0%), Cohort 3 (29.4%-89.0%)].

In Cohorts 1 and 2, CAPVAXIVE elicited immune responses that were generally comparable to the active comparator for the common serotypes and higher than the active comparator for the unique serotypes, as assessed by ≥4-fold increases in OPA responses.

6.3.11.3 Subpopulation Analyses

No significant differences in immunogenicity were noted with regards to age, sex, race, or ethnicity.

6.3.11.4 Dropouts and/or Discontinuations

The number of participants with at least 1 important protocol deviation was 33 (4.6%). Most of the protocol deviations were related to missed/out of window assessment (5 participants in CAPVAXIVE group, 1 participant in PCV15 group, and 5 participants in PPSV23 group).

6.3.11.5 Exploratory Analyses

Across all 3 cohorts CAPVAXIVE elicited OPA responses to serotype 6C and serotype 15B at 30 days postvaccination in a descriptive analysis. The distribution of serotype-specific OPA titers with CAPVAXIVE were generally 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 except in Cohort 3 where they were generally similar.

6.3.12 Safety Analyses

6.3.12.1 Methods

See [section 6.3.7](#).

6.3.12.2 Overview of Adverse Events

A total of 711 participants were included in the ES (509 participants who received CAPVAXIVE, 117 participants who received PCV15, and 85 participants who received PPSV23). Table 16 provides an overview of the rates of adverse events in CAPVAXIVE groups compared with the active comparator groups during the study period. The rates of solicited adverse reactions and unsolicited adverse events were comparable between the groups. Non-fatal SAEs were reported by 0.9%-1.9% of participants in the CAPVAXIVE groups, 3.4% of participants in the PCV15 group, and 3.5% of participants in the PPSV23 group. There were no AEs that led to death in any of the study groups.

Table 16. Overview of Adverse Events, Study 006, All Participants as Treated

Event	Cohort 1 CAPVAXIVE N=230 n (%)	Cohort 1 PCV15 N=117 n (%)	Cohort 2 CAPVAXIVE N=174 n (%)	Cohort 2 PPSV23 N=85 n (%)	Cohort 3 CAPVAXIVE N=105 n (%)
Solicited injection site reaction within 5 days	93 (40.4)	56 (47.9)	75 (43.1)	46 (54.1)	46 (43.8)
Solicited systemic adverse reaction within 5 days	69 (30.0)	44 (37.6)	56 (32.2)	33 (38.8)	33 (31.4)
Unsolicited non-serious AE within 30 days	32 (13.9)	21 (17.9)	22 (12.6)	14 (16.5)	11 (10.5)
SAEs	--	--	--	--	--
Up to 6 months	2 (0.9)	4 (3.4)	2 (1.1)	3 (3.5)	2 (1.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: adapted from STN125814.0 study V116-006 CSR table 12-1

All Participants as Treated: defined as all randomized participants who received the study intervention.

Abbreviations: AE=adverse event; SAE=serious adverse event; N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis

Solicited Adverse Reactions

Across all 3 cohorts, >46% of participants in each intervention group experienced ≥1 solicited injection-site or systemic AE. The most common solicited injection site adverse reaction was pain (Cohort 1: CAPVAXIVE 35.7% vs PCV15 43.6%; Cohort 2: CAPVAXIVE 41.4% vs

PPSV23 47.1%; Cohort 3: CAPVAXIVE 43.8%). The most common solicited systemic adverse reaction was fatigue (Cohort 1: CAPVAXIVE 14.3% vs PCV15 17.1%; Cohort 2: CAPVAXIVE 19.0% vs PPSV23 12.9%; Cohort 3: CAPVAXIVE 21.9%). The percentage of Grade 3 solicited adverse reactions were <3% across all intervention groups (Cohort 1: CAPVAXIVE 1.7% vs PCV15 1.7%; Cohort 2: CAPVAXIVE 2.9% vs PPSV23 0.0%; Cohort 3: 1.9% CAPVAXIVE).

Unsolicited Adverse Events

Across all 3 cohorts, <18% of participants in each intervention group reported unsolicited AEs from Day 1 through Day 30 postvaccination (Cohort 1: CAPVAXIVE 13.9%, PCV15 17.9%; Cohort 2: CAPVAXIVE 12.6%, PPSV23 16.5%; Cohort 3: CAPVAXIVE 10.5%).

The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) for included: *General disorders and administration site conditions* (Cohort 1: CAPVAXIVE 14.8% vs PCV15 17.9%; Cohort 2: CAPVAXIVE 19.5% vs PPSV23 15.3%; Cohort 3: CAPVAXIVE 21.9%; most commonly *fatigue*), *Nervous system disorders* (Cohort 1: CAPVAXIVE 7.4% vs PCV15 9.4%; Cohort 2: CAPVAXIVE 10.3% vs PPSV23 11.8%; Cohort 3: CAPVAXIVE 8.6%; most commonly *headache*), and *Musculoskeletal and connective tissue disorders* (Cohort 1: CAPVAXIVE 7.8% vs PCV15 3.4%; Cohort 2: CAPVAXIVE 9.8% vs PPSV23 9.4%; Cohort 3: CAPVAXIVE 9.5% most commonly *myalgia*).

6.3.12.3 Deaths

There were no deaths due to AEs reported in the study.

6.3.12.4 Nonfatal Serious Adverse Events

Across all 3 cohorts, <4% of participants in each intervention group reported SAEs (Cohort 1: CAPVAXIVE 0.9%, PCV15 3.4%; Cohort 2: CAPVAXIVE 1.1%, PPSV23 3.5%; Cohort 3: CAPVAXIVE 1.9%) In Cohort 1, two CAPVAXIVE recipients developed SAEs (cardiac failure congestive and injection site cellulitis) and four PCV15 recipients developed one or more SAEs (cardiac failure, myocardial ischemia, aortoenteric fistula, Mallory-Weiss syndrome, small intestinal perforation, pneumonia, hypotension). In cohort 2, two CAPVAXIVE recipients developed SAEs (anal fissure, chronic obstructive pulmonary disease) and three PPSV23 developed SAEs (cholangitis, ischemic stroke, chronic obstructive pulmonary disease). In cohort 3, two CAPVAXIVE recipients developed SAEs (cholelithiasis, urinary tract infection).

One participant in the CAPVAXIVE group in Cohort 1 reported an SAE of injection-site cellulitis. Onset was Day 5 postvaccination and required hospitalization on Day 8 due to worsening of symptoms. During their hospital course they were treated with cefazolin with discharge from the hospital on Day 11 with resolution on Day 16.

Reviewer Comment: Case narratives were provided and reviewed. Except for the case of injection site cellulitis described above, none of the nonfatal serious adverse events are considered by the Applicant, study investigator or this clinical reviewer as related to vaccination due to either timing of event, comorbid conditions/age of participants, or pathologic implausibility. We recommend inclusion of case of severe injection site cellulitis in the package insert.

6.3.12.5 Dropouts and/or Discontinuations

See [section 6.3.11.4](#).

6.3.13 Study Summary and Conclusions

Study 006 was designed to descriptively evaluate the safety and immunogenicity of CAPVAXIVE in pneumococcal vaccine-experienced adults ≥ 50 years of age compared with an active control (PCV15 or PPSV23) for 2 of the 3 cohorts. In Cohort 1, participants who were vaccinated with PPSV23 ≥ 1 year prior to enrollment were randomized to receive either CAPVAXIVE or PCV15. In Cohort 2, participants who were vaccinated with PCV13 ≥ 1 year prior to enrollment were randomized to receive either CAPVAXIVE or PPSV23. In Cohort 3, participants who were vaccinated with PCV13+PPSV23, PCV15+PPSV23, PCV15, PCV20, or PPSV23+PCV13 ≥ 1 year prior to enrollment received CAPVAXIVE. For cohorts 1 and 2, CAPVAXIVE is generally similar to the active comparators for the shared serotypes contained in the vaccine and statistically superior for the unique serotypes as assessed by serotype-specific OPA GMTs at 30 days postvaccination. For cohort 3, CAPVAXIVE was immunogenic for 21 serotypes contained in the vaccine, as assessed by OPA GMTs at 30 days following CAPVAXIVE vaccination.

The percentage of participants with AEs were generally comparable between the CAPVAXIVE and active comparator intervention groups. In Cohort 1, the percentage of participants with solicited AEs of moderate (Grade 2) intensity grade were $\leq 13\%$ in CAPVAXIVE recipients and $\leq 16\%$ in PCV15 recipients and the percentage of participants with solicited AEs of severe (Grade 3) intensity grade were $\leq 2\%$ in both groups. In Cohort 2, the percentage of participants with solicited AEs of moderate (Grade 2) intensity grade were $\leq 17\%$ in CAPVAXIVE recipients and $\leq 23\%$ in PPSV23 recipients and the percentage of participants with solicited AEs of severe (Grade 3) intensity grade were $\leq 3\%$ in CAPVAXIVE recipients and 0% in PPSV23 recipients. In Cohort 3, the percentage of participants with solicited AEs of moderate (Grade 2) intensity grade was $\leq 11\%$ in CAPVAXIVE recipients and the percentage of participants with solicited AEs of severe (Grade 3) intensity grade was $\leq 2\%$ in CAPVAXIVE recipients. Across all 3 cohorts, the percentage of participants with SAEs was $< 4\%$. One SAE of injection-site cellulitis was considered as related to study intervention by the Applicant, investigator, and FDA clinical reviewer and was recommended for inclusion in the package insert.

The descriptive data from Study 006, in pneumococcal vaccine-experience participants, provides additional support for the safety and effectiveness of CAPVAXIVE.

6.4 Study V116-005

NCT 05526716

“A Phase 3 randomized, double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, and immunogenicity of CAPVAXIVE when administered concomitantly with influenza vaccine in adults 50 years of age or older.”

6.4.1 Objectives

Primary Objectives, Endpoints and Statistical Criteria

- To evaluate the safety and tolerability of CAPVAXIVE when administered concomitantly with Quadrivalent Influenza vaccine (QIV) compared with CAPVAXIVE administered sequentially with QIV as assessed by the proportion of participants with AEs
 - Endpoints:
 - Solicited injection site AEs from postvaccination Day 1-Day 5
 - Solicited systemic AEs from postvaccination Day 1-Day 5
 - Vaccine-related SAEs from Day 1 through the duration of participation in the study

- To compare the serotype-specific OPA GMTs at 30 days postvaccination of concomitantly administered CAPVAXIVE and QIV with sequentially administered CAPVAXIVE and QIV.
 - Endpoints: Serotype-specific OPA responses
 - Statistical criterion: The LB of 95% CI of the OPA GMT ratio (concomitant group/sequential group) is above 0.5
- To compare the strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination of concomitantly administered QIV and CAPVAXIVE with sequentially administered QIV and CAPVAXIVE.
 - Endpoint: Strain-specific HAI responses
 - Statistical criterion: The LB of 95% CI of the HAI GMT ratio (concomitant group/sequential group) is above 0.67

Secondary Objectives, Endpoints and Statistical Criteria

Secondary objectives to evaluate serotype-specific IgG GMCs and GMFRs are not presented in this memo for the following reasons: measurement of IgG antibody responses in the adult population studied includes non-functional IgG antibodies, and GMFRs, after adjusting for baseline titer, provide similar information as GMT ratios.

Tertiary/Exploratory Objective and Endpoint

Evaluation of serotypes 6C and 15B were the same as the objective and endpoint described in Study 003. Please see sections [6.1.1](#) and [6.1.11](#).

6.4.2 Design Overview

Study 005 was a Phase 3 randomized, double-blind, placebo-controlled, study designed to evaluate the safety, tolerability, and immunogenicity CAPVAXIVE, when administered concomitantly with a quadrivalent influenza vaccine (QIV) in US adults 50 years of age or older. A total of 1080 enrolled participants were randomized in a 1:1 ratio to the concomitant or sequential study groups. Enrollment was stratified based on age at enrollment and by pneumococcal vaccination status (vaccine-naïve or vaccine experienced with PCV13 only, PPSV23 only, or both vaccines). At least 50% of participants were ≥65 years of age and at least 50% of participants were naïve to PCV13 and PPSV23. The concomitant group received CAPVAXIVE and QIV at the first visit and then 1 month later received placebo. The sequential group received QIV and placebo at the first visit and 1 month later received CAPVAXIVE.

After each vaccination visit, the following safety information was collected: solicited injection site and systemic adverse reactions (ARs) and body temperature reported daily for 4 days and recorded in an eVRC, unsolicited, non-serious AEs occurring within 30 days, and SAEs through six months after the last vaccination visit (Day 210). An independent, unblinded, external DMC conducted periodic review of safety data.

A blood sample was obtained 1 month after each vaccination visit. Pneumococcal OPA antibody responses to 21 vaccine serotypes and to serotypes 6C and 15B were measured by MOPA. HAI responses were assessed for the 4 influenza types and subtypes contained in QIV.

6.4.3 Population

Adults ≥50 years of age with or without a history of previous vaccination with PCV13 and/or PPSV23 were eligible to participate in the study. Adults ≥50 years of age who received a PCV vaccine 12 months or more prior to enrollment or any influenza vaccine greater than 6 months prior to enrollment were also eligible to participate in the study. Other criteria were as follows:

Inclusion criteria

- Stable underlying chronic conditions.
- Male or female, ≥ 50 years of age, at the time of informed consent.
- A female participant was eligible to participate if she was not of child-bearing age, pregnant or breastfeeding, and she was using an acceptable contraceptive method, was abstinent or had a negative pregnancy test before the first dose of the study intervention was administered.
- The participant (or legally acceptable representative) provided documented informed consent.
- The participant had the ability to complete eVRC data collection without assistance based on the judgment of the investigator.

Exclusion criteria

- History of IPD (positive blood culture, positive CSF culture, or positive culture at another sterile site) or known history of other culture-positive pneumococcal disease within 3 years of Visit 1 (Day 1).
- Known hypersensitivity to any component of CAPVAXIVE or any influenza vaccine, including diphtheria toxoid.
- Known or suspected impairment of immunological function including, but not limited to, a history of congenital or acquired immunodeficiency, documented HIV infection, functional or anatomic asplenia, or history of autoimmune disease (including, but not limited to the autoimmune conditions outlined in the Investigator Trial File Binder for this study).
- Coagulation disorder contraindicating intramuscular vaccination.
- Known malignancy that was progressing or required active treatment < 3 years before enrollment. Note: participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
- Expected to receive any pneumococcal vaccine during the study outside of the protocol.
- Received any pneumococcal vaccine < 12 months prior to enrollment (including PCV13 followed by PPSV23 and PPSV23 followed by PCV13).
- Prior administration of PCV15 or PCV20.
- Received or expected to receive an influenza vaccine < 6 months prior to enrollment.
- Receiving immunosuppressive therapy during the time of the study, including chemotherapeutic agents or other immunotherapies/immunomodulators used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease.
- Received a blood transfusion or blood products, including immunoglobulin ≤ 6 months before receipt of study vaccine or is scheduled to receive a blood transfusion or blood product before the Day 30 postvaccination blood draw is complete. Autologous blood transfusions are not considered an exclusion criterion.
- Participating in or had participated in an interventional clinical study with an investigational compound or device within 2 months of participating in this current study.
- In the opinion of the investigator, had a history of clinically relevant drug or alcohol use that would interfere with participation in protocol-specified activities.
- History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might expose the participant to risk by participating in the study, confound the results of the study, or interfere with the participant's participation for the full duration of the study.

- Was or had an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who was investigational site or Sponsor staff directly involved with this study.

Temporary exclusion criteria. Visit 1 was rescheduled if one of the following criteria were met:

- Febrile illness (defined as oral or tympanic temperature $\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$] or axillary or temporal temperature $\geq 99.4^{\circ}\text{F}$ [$\geq 37.4^{\circ}\text{C}$]) or received antibiotic therapy for any acute illness occurring < 72 hours before receipt of study vaccine.
- Received systemic corticosteroids (prednisone equivalent of ≥ 20 mg/day) for ≥ 14 consecutive days and has not completed intervention ≥ 14 days before receipt of study vaccine. Note: physiologic replacement doses (prednisone equivalent of approximately 5 mg/day), topical, ophthalmic, intra-articular or soft-tissue (e.g., bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.
- Received any nonlive vaccine ≤ 14 days before receipt of study vaccine or scheduled to receive any nonlive vaccine ≤ 30 days after receipt of study vaccine. Exception: SARS-CoV-2 mRNA or SARS-CoV-2 protein subunit vaccines may be administered but must be given ≥ 7 days before or ≥ 15 days after receipt of study vaccine.
- Received any live virus vaccine ≤ 30 days before receipt of study vaccine or scheduled to receive any live virus vaccine ≤ 30 days after receipt of study vaccine.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Study personnel who prepared and administered the study interventions were not blinded to the vaccine assignment, and did not participate in data collection, evaluation or review of any study endpoint. QIV was administered open label. All study interventions were administered as a single dose (0.5mL) intramuscularly.

Table 17. Study Interventions, Study 005

Study Intervention	Formulation	Lot or Batch #	Presentation
CAPVAXIVE	4 μg of each PnPs antigen (Serotypes 3, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B, and deOAc15B	0001471935	Pre-filled syringe for injection
Fluzone Quadrivalent (Sanofi Pasteur Inc.) (QIV)	60 μg HA total (15 μg of each strain A/H1N1, A/H3N2, B/Victorian lineage, B/Yamagata lineage)	UT7681JA	Pre-filled syringe for injection
Placebo	Sterile saline solution 0.9%	0001187512	Sterile solution for injection

Source: Adapted from STN 125814.0, V116-005 Clinical Study Report: Table 9-1; 16.1.6 Clinical Supplies Dispensed to Participants; Fluzone Package Insert
Abbreviations: HA=hemagglutinin; PnPs=pneumococcal polysaccharide; QIV=quadrivalent influenza vaccine; CAPVAXIVE=Pneumococcal 21-valent conjugate vaccine

6.4.5 Directions for Use

CAPVAXIVE (concomitant group) or placebo (sequential group) was administered intramuscularly in the deltoid region of the participant's left arm. QIV was administered in the deltoid region of the participant's right arm. At visit 1 month later, a single dose of placebo (concomitant group) or CAPVAXIVE (sequential group) was administered.

6.4.6 Sites and Centers

This study was conducted at 56 centers in the U.S.

6.4.7 Surveillance/Monitoring

Safety Monitoring

- Clinical Assessments: medical history (prior to vaccination; Day 1) and physical exam (Days 1 and 30)
- Adverse Event Monitoring:
 - Solicited reactions: postvaccination Days 1-5
 - injection site: pain, erythema, swelling
 - Systemic: fever (oral or axillary), headache, fatigue, myalgia
 - Unsolicited (non-serious) AEs: postvaccination Days 1-30
 - SAEs through 6 months after the last vaccination

All participants recorded solicited and unsolicited AEs on an eVRC diary. Participants lost to follow-up were attempted to be contacted.

An independent external data monitoring committee (eDMC) reviewed unblinded safety data and made recommendations to the Executive Oversight Committee (EOC) about study continuation. The EOC consisted of members of Applicant's senior management, who then made the final decisions regarding study continuation.

Immunogenicity Monitoring

Same as Study 003 (see [section 6.1.7](#)). HAI assay testing was performed at Q2 Solutions (Collegeville, Pennsylvania and Valencia, California).

6.4.8 Endpoints and Criteria for Study Success

See [section 6.4.1](#).

6.4.9 Statistical Analysis Plan

Primary Hypothesis 1 (H1)

Hypothesis: One month after CAPVAXIVE vaccination, pneumococcal OPA GMTs following CAPVAXIVE administered concomitantly with QIV were noninferior to OPA GMTs when CAPVAXIVE was administered sequentially (i.e., CAPVAXIVE then QIV), for each pneumococcal vaccine serotype

- NI criterion: the LB of 95% CI of the OPA GMT ratio ($\text{GMT}_{\text{concomitant}} / \text{GMT}_{\text{sequential}}$) was >0.50

Primary Hypothesis 2 (H2)

Hypothesis: One month after QIV vaccination, HAI GMTs following QIV administered concomitantly with CAPVAXIVE were noninferior to HAI GMTs when QIV was administered sequentially (i.e., CAPVAXIVE then QIV), for each influenza vaccine subtype

- NI criterion: the LB of 95% CI of the HAI GMT ratio ($\text{GMT}_{\text{concomitant}} / \text{GMT}_{\text{sequential}}$) was >0.67

The 2 hypotheses were assumed to be independent. Subgroup analyses were provided according to age stratum (i.e., 50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥ 85 years) and prior pneumococcal vaccination status (i.e., PCV13- and PPSV23-naïve, prior receipt of PCV13 only, prior receipt of PPSV23 only, and prior receipt of PCV13 and PPSV23).

Planned enrollment of 1000 participants (500 concomitant group, 500 sequential group) was anticipated to result in a total of 900 evaluable participants (450 concomitant group, 450 sequential group). The sample size would provide approximately 90% power overall to demonstrate noninferiority for the primary endpoints, with an overall 1-sided 2.5% alpha-level. Assumptions: (a) The true OPA GMT ratio was 0.80 (concomitant group/sequential group) for the 21 pneumococcal serotypes, based on results of studies evaluating the administration of PCVs with concomitant influenza vaccines. The variabilities for OPA titers in both concomitant and sequential groups were the same as those observed in V116-001 Phase 2; (b) The true HAI GMT ratio was 1.0 (concomitant group/sequential group) for the 4 influenza subtypes. The variabilities for HAI titers in both concomitant and sequential groups were the same as that observed in V114-021; (c) Overall, 10% non-evaluable participants for immunogenicity analyses.

Analyses of OPA responses to serotypes 6C and 15B (exploratory immunogenicity endpoint) safety parameters were summarized via descriptive statistics.

6.4.10 Study Population and Disposition

Of 1080 enrolled participants, 1072 were included in the All-Participants-as-Treated set (APaT). A total of 1017 (94.2%) participants (n=510 Concomitant, n=507 Sequential) completed the study. The main reasons for discontinuation from the study were lost to follow-up and withdrawal by participants.

A total of 939 participants were included in the PP for the OPA analysis at the postvaccination timepoint. The number of participants excluded from the PPS for the OPA analyses at the postvaccination timepoint was higher in the sequential group (n=449) than the concomitant group (n=490), mainly due to missing serology results (12.1% Sequential, 6.5% Concomitant) and blood sample collected outside the pre-specified window (5.6% Sequential, 3.1% Concomitant).

The PP for the HAI analyses at the postvaccination timepoint included 985 (n=495 Concomitant, n=490 Sequential) participants, mainly for the reasons described above for the OPA per-protocol population.

6.4.10.1 Populations Enrolled/Analyzed

Same as Study 004 (see [section 6.2.10.1](#)).

6.4.10.1.1 Demographics

The demographics of participants in the APaT set are shown in Table 18.

The median age of participants was 64.5 years for both the concomitant group and sequential group. Overall, 54% of participants were female, 76.7% of participants were White, 19.4% were Black or African American, 1.2% were Asian, and 75.7% were of non-Hispanic or Latino ethnicity. Approximately 30% of the participants had previously received a pneumococcal vaccine (either PCV13 and/or PPSV23).

Table 18. Demographic Characteristics, All-Participants-as-Treated Set, Study 005

Characteristic	Concomitant Group N=536	Sequential Group N=536
Sex, n (%)	--	--
Male	239 (44.6)	249 (46.5)
Female	297 (55.4)	287 (53.5)
Age (Years)	--	--
Mean age (SD)	64.2 (8.4)	64.2 (8.4)
Median age	64.5	64.5
50 through 64, n (%)	268 (50.0)	268 (50.0)
65 through 74, n (%)	207 (38.6)	209 (39.0)
75 through 84, n (%)	54 (10.1)	53 (9.9)
≥85, n (%)	7 (1.3)	6 (1.1)
Race, n (%)	--	--
American Indian or Alaska Native	1 (0.2)	4 (0.7)
Asian	3 (0.6)	10 (1.9)
Black or African American	107 (20.0)	101 (18.8)
Multiple	13 (2.4)	8 (1.5)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.2)
White	410 (76.5)	412 (76.9)
Missing	1 (0.2)	0 (0.0)
Ethnicity, n (%)	--	--
Hispanic or Latino	127 (23.7)	125 (23.3)
Not Hispanic or Latino	403 (75.2)	409 (76.3)
Not Reported	4 (0.7)	2 (0.4)
Unknown	2 (0.4)	0 (0.0)
Country, n (%)	--	--
United States	536 (100.0)	536 (100.0)
Prior pneumococcal vaccination status	--	--
PCV13- and PPSV23-naïve	376 (70.1)	381 (71.1)
Prior receipt of PCV13 only	29 (5.4)	29 (5.4)
Prior receipt of PPSV23 only	72 (13.4)	68 (12.7)
Prior receipt of PCV13 and PPSV23	59 (11.0)	58 (10.8)

Source: Adapted from STN 125814.0, V116-005 Clinical Study Report: Table 10-2

Abbreviations: All Participants as Treated (APaT): defined as all randomized participants who received at least 1 dose of study intervention.

N=number of participants; n (%)=number and percentage of participants in a given category; PCV13=13-valent pneumococcal conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine=SD=standard deviation

Notes: PCV13- and PPSV23-naïve participants are those who did not receive either PCV13 or PPSV23 prior to study entry

Prior receipt of PCV13 only are participants who received PCV13 only (including participants who received one or more PCV13) prior to study entry.

Prior receipt of PPSV23 only are participants who received PPSV23 only (including participants who received one or more PPSV23) prior to study entry.

Prior receipt of PCV13 and PPSV23 are participants who received both PCV13 and PPSV23 (including one or more doses of PCV13 and one or more doses of PPSV23) prior to study entry.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Reported medical history conditions were similar between the concomitant and sequential study groups. In both study groups, approximately 40% of the vaccinated participants had ≥1 prespecified medical history condition (alcoholism, chronic heart disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, or smoking) associated with an increased risk of pneumococcal disease.

6.4.10.1.3 Participant Disposition

See [section 6.4.10](#).

6.4.11 Immunogenicity Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

The noninferiority criterion (LB of 95% CI of the OPA GMT ratio ($(\text{GMT}_{\text{concomitant}} / \text{GMT}_{\text{sequential}}) > 0.5$) for 20 of the 21 serotypes at 30 days postvaccination. For serotype 23B, the LB of 95% CI of the OPA GMT ratio was 0.44. OPA GMT analyses based on the FAS were consistent with results based on the PPS.

Reviewer Comment: In general, pneumococcal OPA GMTs to all vaccine types trended lower in the concomitant group compared to corresponding GMTs in the sequential group. The PP Pn23B OPA GMT postvaccination was 934.3 in the concomitant group, compared to 1664.5 in the sequential group. However, the percentage of participants in the concomitant and sequential groups with ≥ 4 -fold in OPA GMT (postvaccination/pre-vaccination) to Pn23B were similar (83.0% [95% CI 79.3, 86.4] and 84.7% [95% CI 80.8, 88.0], respectively). With consideration of all data, it is acceptable.

Table 19. Serotype-Specific OPA GMTs for Concomitant and Sequential Groups, Per-Protocol Set

Pneumococcal Serotype	Concomitant Group N=536 GMT ^a (n)	Sequential Group N=536 GMT ^a (n)	GMT Ratio ^a (Concomitant/Sequential) (95% CI) ^{ab}
3	209.2 (519)	250.1 (497)	0.84 (0.72, 0.97)
6A	2056.4 (521)	2608.2 (496)	0.79 (0.66, 0.94)
7F	2399.2 (521)	3275.4 (496)	0.73 (0.63, 0.85)
8	1508.9 (519)	2135.7 (497)	0.71 (0.61, 0.82)
9N	5075.6 (522)	7566.6 (499)	0.67 (0.57, 0.79)
10A	3033.6 (524)	3966.2 (499)	0.76 (0.65, 0.91)
11A	2576.3 (519)	4051.1 (499)	0.64 (0.54, 0.75)
12F	1869.9 (525)	2499.5 (499)	0.76 (0.62, 0.94)
15A	4670.6 (511)	6559.7 (458)	0.71 (0.60, 0.85)
15C	3426.0 (522)	4832.6 (493)	0.71 (0.58, 0.87)
16F	5371.5 (522)	7757.2 (498)	0.69 (0.59, 0.81)
17F	5783.8 (520)	7924.3 (497)	0.73 (0.62, 0.86)
19A	1830.1 (524)	2453.3 (498)	0.75 (0.65, 0.85)
20A	5172.8 (522)	6986.9 (498)	0.74 (0.63, 0.87)
22F	3194.9 (517)	4158.2 (490)	0.77 (0.65, 0.91)
23A	3358.2 (511)	4319.9 (486)	0.78 (0.63, 0.96)
23B	934.3 (522)	1664.5 (498)	0.56 (0.44, 0.72)
24F	2996.5 (517)	4143.1 (494)	0.72 (0.61, 0.86)
31	2997.4 (522)	4390.6 (499)	0.68 (0.56, 0.83)
33F	9032.5 (520)	10765.1 (492)	0.84 (0.70, 1.01)
35B	7701.4 (522)	9940.2 (495)	0.77 (0.67, 0.89)

Source: Adapted from STN 125814.0 V116-005 Clinical Study Report: Figure 11-1; Abbreviations: GMT=geometric mean titer; N=Per-Protocol Set: defined as all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s); n=number of individuals contributing to the analysis

Notes: a: GMTs, GMT ratio, and 95% CI were estimated from a constrained Longitudinal Data Analysis model.

b: Non-inferiority criteria: lower bound of the 95% CI for the estimated GMT ratio (Concomitant Group/Sequential Group) is > 0.5 .

The noninferiority criterion (LB of 95% CI of the HAI GMT ratio ($\text{GMT}_{\text{concomitant}} / \text{GMT}_{\text{sequential}}) > 0.67$) was met for 3 of the 4 influenza subtypes at 30 days postvaccination. For influenza subtype A/H3N2, the LB of 95% CI of the HAI GMT ratio was 0.67.

Reviewer Comment: For influenza subtype A/H3N2, the difference between the pre-defined statistical success criteria (LB>0.67) and a lower bound of 0.67 (rounded from 0.6659) is minimal. Also, among participants in the concomitant and sequential groups, the percentage of participants with a postvaccination HAI titer $\geq 1:40$ (84.2% and 85.5%, respectively) and seroconversion rates were similar (63.8% and 68.3%, respectively). Seroconversion was defined as at least a 4-fold rise from baseline to 30 days postvaccination among participants who are seropositive at baseline (HAI titer $\geq 1:10$) or a titer of $\geq 1:40$ at postvaccination among participants who are seronegative at baseline (HAI titer $< 1:10$).

Table 20. Strain-Specific HAI GMTs for Concomitant and Sequential Groups, Per-Protocol Set

Influenza Strain	Concomitant Group N=536 GMT ^a (n)	Sequential Group N=536 GMT ^a (n)	GMT Ratio ^a (Concomitant/Sequential) (95% CI) ^{ab}
A/H1N1	268.23 (526)	325.06 (526)	0.83 (0.70, 0.97)
A/H3N2	128.07 (526)	163.06 (526)	0.79 (0.67, 0.93)
B/Victoria	70.02 (526)	85.66 (526)	0.82 (0.70, 0.95)
B/Yamagata	31.80 (526)	35.86 (526)	0.89 (0.78, 1.00)

Source: Adapted from STN 125814.0 V116-005 Clinical Study Report: Figure 11-2

Abbreviations: GMT=geometric mean titer; N= Per-Protocol Set: defined as all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint(s); n=number of individuals contributing to the analysis; HAI=hemagglutination inhibition

Notes: a: GMTs, GMT ratio, and 95% CI were estimated from a constrained Longitudinal Data Analysis model.

b: Noninferiority criteria: lower bound of the 95% CI for the estimated GMT ratio (Concomitant Group/Sequential Group) is >0.67

6.4.11.3 Subpopulation Analyses

In general, pneumococcal serotype-specific OPA GMT were lower in the older age groups (65 to 74 and ≥ 75 years of age) compared with the younger age group (50 to 64 years of age) in both the concomitant group and the sequential group. Pneumococcal serotype-specific OPA GMTs from the sequential group were higher in all age groups compared to the OPA GMTs from the concomitant group. This was also the case for influenza-strain specific HAIs. Influenza strain-specific HAI GMT ratios (concomitant/sequential) in adults 50 to 64 years of age compared to ≥ 65 years of age were similar to the overall population. The number of participants in each age stratum (50 to 64, 65 to 74, ≥ 75 year of age) were too small to make definitive conclusions.

Pneumococcal serotype-specific OPA GMTs were lower in male participants compared to female participants in both the concomitant and sequential groups. Influenza-strain specific HAIs were comparable between female and male participants. The pneumococcal serotype-specific OPA GMTs and influenza-strain specific HAIs were also lower in the concomitant group compared to the sequential group.

Approximately 70%-75% of participants were White, non-Hispanic/non-Latino, or PCV13- and PPSV23-naïve, depending on the baseline characteristic. The number of participants were too small to make definitive conclusions about differences pneumococcal or influenza antibody responses among the concomitant and sequential groups based on ethnicity, race, or participant with a history of pneumococcal vaccination.

6.4.11.4 Dropouts and/or Discontinuations

See [section 6.4.10](#).

6.4.11.5 Exploratory and Post Hoc Analyses

CAPVAXIVE elicited OPA responses to serotype 6C and serotype 15B at 30 days postvaccination. The distribution of serotype-specific OPA titers with CAPVAXIVE were generally consistent 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.

6.4.12 Safety Analyses

6.4.12.1 Methods

See [section 6.4.2](#).

6.4.12.2 Overview of Adverse Events

Table 21 provides an overview of the rates of solicited adverse reactions, adverse events, and participants who withdrew from the study due to an AE.

Table 21. Overview of Adverse Events, Study 005, All Participants as Treated

Event	Concomitant Group N=534 n (%)	Sequential Group N=535 n (%)
Solicited injection site reaction within 5 days	317 (59.4)	314 (58.7)
Solicited systemic adverse reaction within 5 days	219 (41.0)	224 (41.9)
Unsolicited non-serious AE within 30 days	144 (27.0)	168(31.4)
SAEs	10 (1.9)	17 (3.2)
Deaths	1 (0.2)	2 (0.4)
Withdrawal due to AE	2 (0.4)	1 (0.2)

Source: Adapted from STN 125814.0 V116-005 Clinical Study Report: Figure 12-1, 12-2, 14.3-11; Abbreviations: N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis

Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination.

All Participants as Treated (APaT): defined as all randomized participants who received the study intervention.

Reported unsolicited events include nonserious and serious adverse events within 30 days of vaccination, excluding adverse event terms injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia solicited from Day 1 through Day 5 postvaccination and pyrexia defined as maximum temperature $\geq 38.0^{\circ}\text{C}$ solicited from Day 1 through Day 5 postvaccination.

Solicited Adverse Reactions:

Overall proportions of participants with AEs were generally similar between intervention groups. The most commonly reported ARs were solicited injection-site pain, swelling, erythema, fatigue and headache. Except for injection site pain (1.1%), the frequencies of severe ARs and fever $\geq 39.0^{\circ}\text{C}$ were $<1.0\%$. Solicited ARs lasted ≤ 3 days.

Table 22. Solicited Local and Systemic Adverse Events Within 5 Days Postvaccination, Concomitant and Sequential Groups, Study 005, All Participants as Treated

Adverse Events	Concomitant N=534 n (%)	Sequential Group N=535 n (%)
One or more solicited adverse events	361 (67.6)	348 (65.0)
No solicited adverse events	173 (32.4)	187 (35.0)
Local adverse events ^a (injection site): Severity	--	--

Adverse Events	Concomitant N=534 n (%)	Sequential Group N=535 n (%)
Pain	--	--
Any	309 (57.9)	303 (56.6)
Mild	230 (43.1)	206 (38.5)
Moderate	77 (14.4)	91 (17.0)
Severe	2 (0.4)	6 (1.1)
Erythema^b	--	--
Any	61 (11.4)	59 (11.0)
Mild	47 (8.8)	47 (8.8)
Moderate	11 (2.1)	11 (2.1)
Severe	3 (0.6)	1 (0.2)
Swelling^b	--	--
Any	67 (12.5)	63 (11.8)
Mild	50 (9.4)	55 (10.3)
Moderate	14 (2.6)	7 (1.3)
Severe	3 (0.6)	1 (0.2)
Systemic adverse events: Severity	--	--
Fatigue	--	--
Any	160 (30.0)	175 (32.7)
Mild	106 (19.9)	95 (17.8)
Moderate	49 (9.2)	77 (14.4)
Severe	5 (0.9)	3 (0.6)
Headache	--	--
Any	107 (20.0)	118 (22.1)
Mild	79 (14.8)	85 (15.9)
Moderate	26 (4.9)	30 (5.6)
Severe	2 (0.4)	3 (0.6)
Myalgia	--	--
Any	74 (13.9)	80 (15.0)
Mild	39 (7.3)	39 (7.3)
Moderate	34 (6.4)	39 (7.3)
Severe	1 (0.2)	2 (0.4)
Pyrexia^b	--	--
≥38.0°C	10 (1.9)	3 (2.4)
≥38.0°C to <38.5°C	5 (0.9)	7 (1.3)
≥38.5°C to <39.0°C	2 (0.4)	4 (0.7)
≥39.0°C	3 (0.6)	2 (0.4)

Source: Adapted from STN 125814.0 V116-005 Clinical Study Report: Figure 14.3-9, 14.3-19; Abbreviations: N=number of individuals randomized and vaccinated; n=number of individuals contributing to the analysis

All Participants as Treated (APaT): defined as all randomized participants who received the study intervention.

Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination. Pyrexia was defined as maximum temperature ≥ 38.0 °C solicited from Day 1 through Day 5 postvaccination.

Notes: Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity

a: Injection-site pain, injection-site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination.

b. 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.

c: 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.

Unsolicited AEs (Non-serious) 30 days postvaccination:

Rates on non-serious unsolicited AEs within 30 days postvaccination were similar between the concomitant group and the sequential group (27.0% versus 31.4%). The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT terms included: *General disorders and administration site conditions, including injection site pruritis, bruising, erythema and swelling* (Concomitant 2.8% vs Sequential 3.7%), *Gastrointestinal disorders, including diarrhea and nausea* (Concomitant 1.7% vs Sequential 1.7%) and *Respiratory, thoracic, and mediastinal disorders, including cough and rhinorrhea* (Concomitant 1.1% vs Sequential 1.3%).

Reviewer Comment: Case narratives were included and reviewed. The AEs reported by participants represented signs, symptoms or medical conditions that commonly occur in the adult population. None of the non-serious unsolicited AEs were considered by the Applicant, investigator, or this clinical reviewer to be related to study intervention.

6.4.12.3 Deaths

Three deaths were reported during the study. Deaths were assessed by the Applicant, study investigator and this clinical reviewer as unrelated to study intervention.

6.4.12.4 Nonfatal Serious Adverse Events

At least 1 SAE occurred in 10 (1.9%) participants in concomitant group and 17 (3.2%) in sequential group. One participant (sequential group) with a history of seasonal and penicillin allergy experienced bronchospasm approximately 10 minutes after CAPVAXIVE vaccination, and resolved after treatment with diphenhydramine, salbutamol, and paracetamol. Bronchospasm recurred later the same day and resolved after treatment with diphenhydramine and albuterol. All episodes resolved within 23 hours after vaccination, were not life-threatening, and did not require hospitalization. The study investigator assessed the event as related to CAPVAXIVE vaccination.

Reviewer Comment: This clinical reviewer agrees with the Applicant and study investigator's assessment that the SAE is related to CAPVAXIVE vaccination and recommends its inclusion in the package insert.

6.4.12.7 Dropouts and/or Discontinuations

Three participants discontinued study intervention due to an AE. One participant in the concomitant group discontinued from the study following vaccination 1 (CAPVAXIVE+QIV) due to anemia. The participant had a history of malignant melanoma and pulmonary hypertension and presented to the Emergency Department on Day 18 with tarry stools, fatigue, weakness and nausea and was diagnosed with a gastric ulcer hemorrhage and *Helicobacter* infection, which the study investigator concluded as the likely cause of the anemia.

One participant in the concomitant group discontinued from the study following vaccination 1 (CAPVAXIVE+QIV) due to injection-site pain (Day 6), malaise (Day 6), injection-site swelling (Day 7), and injection-site erythema (Day 8), and all the events resolved; the study investigator assessed these events as related to study intervention.

One participant in the sequential group discontinued study intervention following Vaccination 1 (Placebo+QIV) due to dizziness (Day 6), which resolved by the following day. No treatment was reported. On review of the participant's medical history (seasonal allergy, drug hypersensitivity,

myopia, menopause, arthralgia, arthritis) and medications (naproxen sodium, vitamins, codeine phosphate, paracetamol), a potential cause of the dizziness is not apparent. The study investigator assessed this event as not related to study vaccination.

Reviewer Comment: Following review of the safety analyses and case narratives, this clinical reviewer agrees with the Applicant and study investigator's assessment for the events described for the concomitant group participants. Based on the narrative provided for the AE of dizziness, this clinical reviewer concludes that the event could be at least possibly related to the placebo or QIV and agrees that the event was not related to CAPVAXIVE since the event occurred prior to CAPVAXIVE vaccination.

6.4.13 Study Summary and Conclusions

Except for pneumococcal serotype 23B and influenza subtype A/H3N2, the primary objectives to demonstrate noninferiority of concomitant administration of CAPVAXIVE and QIV were met (LB of the 95% CI of the GMT ratio >0.5 and >0.67 , respectively) compared with pneumococcal and influenza antibody responses following sequential administration. For pneumococcal serotype 23B the LB of the 95% CI of the group GMT ratio was 0.44. For influenza subtype A/H3N2, the LB of the 95% CI of the group GMT ratio was 0.67.

The results of solicited reactions and unsolicited AEs analyses from this study were similar to the safety of CAPVAXIVE in Study 003. There were three deaths assessed by the Applicant, study investigator and this clinical reviewer as unrelated to study intervention. An SAE of bronchospasm that occurred within 30 minutes of administration of CAPVAXIVE, determined by the Applicant, study investigator and this clinical reviewer to be related to the vaccine which was recommended for inclusion in the package insert.

The safety and immunogenicity data generated from this study did not raise concern regarding concomitant administration of CAPVAXIVE with an inactivated standard dose influenza vaccine (Fluzone Quadrivalent).

6.5 Study V116-001

NCT04168190

"A Phase 1/Phase 2, Randomized, Double-blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Adults."

Reviewer Comment: Study V116-001 was a Phase 1/2, randomized, double-blind, active-controlled study designed to evaluate the safety and immunogenicity of CAPVAXIVE in pneumococcal vaccine-naïve adults. Adults 18 through 49 years of age were enrolled in phase 1, and adults ≥ 50 years of age were enrolled in phase 2. The report for phase 2 of study V116-001 was provided in the BLA.

Phase 2 design: Participants received a single dose of CAPVAXIVE or PPSV23. The primary objectives and endpoints were to evaluate the safety CAPVAXIVE with respect to the percentage of participants with solicited ARs and SAEs, and to evaluate vaccine serotype-specific OPA GMTs at 30 days postvaccination. Noninferiority criteria: LB of the 95% CI of the GMT ratio (CAPVAXIVE/PPSV23) was >0.33 for the 12 CAPVAXIVE serotypes in common with PPSV23 and >1.0 for the 9 CAPVAXIVE serotypes not shared with PPSV23. Serotype 15B is contained in PPSV23 but not CAPVAXIVE.

Phase 2 results

A total of 510 (n=245 CAPVAXIVE, n=256 PPSV23) participants ≥50 years of age were randomized in Phase 2, 508 were vaccinated, and 491 (n=244 CAPVAXIVE, n=247 PPSV23) completed the study. A total of 479 participants (n=240 CAPVAXIVE, n=239 PPSV23) were included in the PP at the 1-month postvaccination timepoint.

The percentage of participants reporting at least 1 solicited injection site ARs was higher in the CAPVAXIVE group (52.1%) compared with the PPSV23 group (40.9%), mainly due to injection site pain. The frequency of solicited systemic ARs was similar between study groups (34.6% CAPVAXIVE, 29.5% PPSV23).

The rate of SAEs was 1.6% in the CAPVAXIVE group and 1.2% in the PPSV23 group.

One CAPVAXIVE participant in the CAPVAXIVE group died due to COVID-19. None of the SAEs were assessed by the study investigator or this clinical reviewer to be related to study vaccine. The noninferiority criteria for the 21 serotypes contained in CAPVAXIVE were met.

Conclusions

The safety and immunogenicity data support selection of CAPVAXIVE (4 µg of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) for further evaluation in Phase 3 studies.

7. INTEGRATED OVERVIEW OF EFFICACY

An integrated summary of immunogenicity was not presented in this section because the populations enrolled in the 5 studies vary by age (≥50 years of age, 18 through 49 year of age) and pneumococcal vaccination history (vaccine-naïve, vaccine experienced). Pneumococcal antibody responses in CAPVAXIVE recipients ≥50 years of age who previously had not received a pneumococcal vaccine are presented in Phase 3 study 003 (n=1179) and phase 2 study 001 (n=254). Pneumococcal antibody responses in individuals 18 through 49 years of age, all who were previously pneumococcal vaccine-naïve, are presented in study 004 (n=1616) and study 003 (n=200). Study 006 enrolled pneumococcal vaccine-experienced individuals ≥50 years of age. Study 007 was a concomitant vaccine study that included both. Please see [section 6](#) for results presented by individual study.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data were integrated across the 4 Phase 3 studies in adults ≥18 years of age (V116-003, V116-004, V116-006, and V116-005); SAEs were assessed from day of vaccination (Day 1) through 6 months postvaccination. The solicited ARs and unsolicited AEs are not presented in this integrated summary since participants ≥50 years of age who are pneumococcal vaccine-naïve (study 003) and pneumococcal vaccine-experienced (study 006, study 005), and participants 18 through 49 years of age (study 004, study 003) were based largely on single study.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

A total of 4020 CAPVAXIVE recipients and 2018 Control (PCV20, PPSV23, or PCV15) recipients from the 4 Phase 3 studies were included in the APaT Set (Table 23). Of the 4020

CAPVAXIVE recipients, 54.8% were ≥50 years of age (n=1541 [38.3%] pneumococcal vaccine-naïve, n=663 [16.5%] pneumococcal vaccine-experienced), and the remaining CAPVAXIVE recipients were 18 through 49 years of age who were pneumococcal vaccine-naïve. Of the 2018 participants in the comparator group, 68.5% were ≥50 years of age (n=1541 [38.3%] pneumococcal vaccine-naïve, n=663 [16.5%] pneumococcal vaccine-experienced), and the remaining CAPVAXIVE recipients were 18 through 49 years of age who were pneumococcal vaccine-naïve.

Table 23. Number of Participants in Integrated Safety Summary, APaT

Study	CAPVAXIVE N	Comparator^a N
V116-003	1377	1275
V116-004	1616	541
V116-005	518 ^b	--
V116-006	509	202

Source: Adapted from iss.pdf, Table 5.3.5.3.3:1

Abbreviations: N=Number of participants in the APaT set.

APaT: All Participants as Treated; defined as all participants who received at least the first dose of the study intervention.

^aControl included participants in V116-003 who received PCV20, participants in V116-004 who received PPSV23, and participants in V116-006 who received PPSV23 or PCV15.

^bOnly sequential group participants who received CAPVAXIVE were included in the integrated analysis. Participants in the concomitant group were not included in the analysis.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Demographics for the 4 Phase 3 studies are presented in Table 24. The median age at the time of enrollment was 56.0 years for the CAPVAXIVE group and 58.0 for the comparator group. The age and sex distribution in the CAPVAXIVE groups and Comparator groups are similar. Participants were primarily White (CAPVAXIVE 77.1% and Comparator 73.6%) and Not Hispanic or Latino (CAPVAXIVE 78.4% and Comparator 79.1%).

Table 24. Participant Demographics, All Participants as Treated

	CAPVAXIVE^a N=4556 n (%)	Comparator^b N=2021 n (%)
Sex	--	--
Male	1949 (42.8)	868 (42.9)
Female	2607 (57.2)	1153 (57.1)
Age (Years)	--	--
18 through 49	1817 (39.9)	640 (31.7)
50 to 64	1252 (27.5)	651 (32.2)
65 to 74	1148 (25.2)	573 (28.4)
75 to 84	303 (6.7)	141 (7.0)
≥85	36 (0.8)	16 (0.8)
Race	--	--
American Indian or Alaska Native	21 (0.5)	9 (0.4)
Asian	390 (8.6)	263 (13.0)
Black or African American	492 (10.8)	181 (9.0)
Multiple	114 (2.5)	62 (3.1)
Native Hawaiian or Other Pacific Islander	23 (0.5)	19 (0.9)
White	3511 (77.1)	1487 (73.6)
Missing	5 (0.1)	0 (0.0)
Ethnicity	--	--
Hispanic or Latino	948 (20.8)	406 (20.1)

	CAPVAXIVE^a N=4556 n (%)	Comparator^b N=2021 n (%)
Not Hispanic or Latino	3573 (78.4)	1599 (79.1)
Not Reported	26 (0.6)	13 (0.6)
Unknown	9 (0.2)	3 (0.1)
Prior Pneumococcal Vaccination Status	--	--
Vaccine-Naïve	3734 (82.0)	1817 (89.9)
Vaccine-Experienced	822 (18.0)	204 (10.1)

Source: Adapted from iss.pdf, Table 5.3.5.3.3:4

Abbreviations: N=Number of participants in the APaT set; n=number of individuals contributing to the analysis

APaT Set: All Participants as Treated; defined as all participants who received at least the first dose of the study intervention.

^aIncludes CAPVAXIVE recipients from Studies V116-003, -004, -006, and -005

^bPCV20, PPSV23 or PCV15, depending on the study.

8.2.3 Categorization of Adverse Events

See [section 8.1](#).

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

See [section 8.1](#). SAEs analyses were based on the APaT set, defined as all randomized participants who received at least 1 dose of study vaccination.

8.4 Safety Results

Overall safety characteristics are shown in Table 25. Overall, the SAE rates at each timepoint among CAPVAXIVE and comparator recipients were similar.

Table 25. Safety Overview, All Participants as Treated

	CAPVAXIVE N=4020 n (%)	Comparator^a N=2018 n (%)
SAEs from Day 1 through Day 30 postvaccination	14 (0.3)	7 (0.3)
SAEs from Day 1 through Month 6 postvaccination	56 (1.4)	40 (2.0)
Deaths from Day 1 through 6 months postvaccination	6 (0.1)	3 (0.1)

Source: Adapted from iss.pdf, Table 5.3.5.3.3:10

Abbreviations: N=Number of participants in the APaT set; n=number of individuals contributing to the analysis; SAE=serious adverse event

APaT Set: All Participants as Treated; defined as all participants who received at least the first dose of the study intervention.

^aComparator included participants in V116-003 who received PCV20, participants in V116-004 who received PPSV23, and participants in V116-006 who received PPSV23 or PCV15

8.4.1 Deaths

Deaths were reported for 6 CAPVAXIVE recipients and 3 comparator recipients. Fatal outcomes for CAPVAXIVE were categorized as the following MedDRA terms: myocardial infarction, hepatic cirrhosis, sepsis, septic shock, cerebrovascular accident, hepatic encephalopathy, and victim of homicide. Fatal outcomes for comparator group participants were categorized as: cardiac arrest, abdominal abscess, and road traffic accident. Based on independent review of event narratives, this clinical reviewer considers the deaths to be either attributable to the participants underlying medical conditions, risk factors, concurrent medical conditions, or events that are not physiologically plausible to be attributed to vaccination.

8.4.2 Nonfatal Serious Adverse Events

SAEs occurring within 6 months after study intervention were reported in 1.4% of CAPVAXIVE recipients and 2.0% of comparator recipients. SAEs were most commonly reported in the SOC of *Infections and Infestations* (CAPVAXIVE 0.4%; Comparator 0.5%).

Two SAEs were considered by the Applicant, investigator and this clinical reviewer to be related to the study vaccination:

- One participant in study 005 (sequential group) reported bronchospasm approximately 10 minutes after CAPVAXIVE vaccination, which resolved with medical intervention, but was neither life-threatening nor required hospitalization. The event resolved after approximately 24 hours. See [section 6.4.12.4](#) for additional details.
- One participant in the CAPVAXIVE group in study 006 (Cohort 1) reported an SAE of injection-site cellulitis. Onset was Day 5 postvaccination and required hospitalization on Day 8 due to worsening of symptoms. During their hospital course they were treated with cefazolin with discharge from the hospital on Day 11 with resolution on Day 16.

8.4.3 Study Dropouts/Discontinuations

Overall, 2.2% of participants discontinued from the 4 Phase 3 studies (CAPVAXIVE 2.2%; Comparator 2.2%). The most common cause for discontinuation was lost to follow-up (CAPVAXIVE 1.5%; Comparator 1.5%).

8.6 Safety Conclusions

In 4 Phase 3 clinical trials included in the integrated analysis, 4020 participants received one dose of CAPVAXIVE and 2018 received a comparator vaccine. The SAE rates among CAPVAXIVE and comparator (PCV20, PPSV23, or PCV15) were similar. Two SAEs (bronchospasm, injection site cellulitis) were assessed by the Applicant, study investigator and FDA to be related to CAPVAXIVE vaccination which were recommended to be included in the package insert. No additional safety concerns were identified when a single dose of CAPVAXIVE was administered to adults ≥ 18 years of age, with or without prior pneumococcal vaccine exposure.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Currently, no studies have been conducted to evaluate in pregnant individuals.

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

Pneumonia indication

The Applicant's request for partial waiver and partial deferral of the required pediatric assessment was presented to FDA's Pediatric Review Committee on April 30, 2024. The committee agreed with the Applicant's requests and the proposed timelines for the deferred study in individuals 2 to <18 years of age.

A full waiver was granted for 0 to <18 years of age because the necessary studies are impossible or highly impracticable. Demonstration of CAPVAXIVE effectiveness to prevent vaccine serotype pneumonia in children would require a clinical endpoint efficacy study. An active-controlled clinical efficacy trial would require a sample size considered prohibitively large. Also, there are currently no reliable methods for detecting vaccine-type nonbacteremic pneumonia in children (the most common type of pneumonia). Urine antigen detection assays to detect pneumonia for certain pneumococcal serotypes have been used in PCV pneumonia studies in adults. However, urine antigen detection assays have not been validated for use in children due to high pneumococcal carriage rates in children.

IPD indication

A partial waiver was granted for 0 to <2 years of age because the drug or biological product (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (II) is not likely to be used by a substantial number of pediatric patients in that age group. CAPVAXIVE is being developed primarily to prevent IPD due to serotypes that cause disease in adults and is not intended to replace the PCVs currently used in the routine infant immunization schedule. A complementary approach in which CAPVAXIVE would be provided to infants and children in addition to one or more doses of licensed Vaxneuvance (Pneumococcal 15-valent Conjugate Vaccine) or Prevnar 20 would be difficult to implement in an already crowded immunization schedule and may not provide a meaningful benefit as the incidence of disease due to serotypes in CAPVAXIVE accounts for ~3.9 cases/100,000 in children <5 years of age. In addition, due to limitations of the neonatal immune response, initiating vaccination at 0 to <6 weeks of age with CAPVAXIVE would not provide a meaningful therapeutic benefit over initiating vaccination with other licensed PCVs at 6 weeks of age.

While CAPVAXIVE is not intended for any of the existing doses in the current routine PCV schedule for infants and children, some individuals 2 to <18 years of age who are at increased risk for PD potentially may benefit from vaccination with CAPVAXIVE after completion of the four-dose series of Vaxneuvance or Prevnar 20. A deferral to conduct a study in individuals 2 to <18 years of age was granted because the drug or biological product is ready for approval for use in adults before pediatric studies are complete.

9.1.4 Immunocompromised Patients

At present, safety and immunogenicity data on CAPVAXIVE are not available for immunocompromised individuals.

9.1.5 Geriatric Use

Across studies 1-4, approximately 34% of individuals were 65 years of age and older. Of the 4,556 individuals who received CAPVAXIVE, 1,487 (32.6%) were 65 years of age and older, and 339 (7.4%) were 75 years of age and older. In Study 003, no clinically meaningful differences in safety were observed between these individuals and individuals less than 65 years of age. The OPA responses in individuals 65 years of age and older were generally lower than those observed in individuals less than 65 years of age.

10. SUMMARY AND CONCLUSIONS

This BLA contains clinical data from 4 main studies (003, 006, 004, and 005) to support the effectiveness and safety of vaccine candidate, CAPVAXIVE.

Immunogenicity

Immunogenicity of CAPVAXIVE to prevent invasive disease and pneumonia caused by *S. pneumoniae* was evaluated in study 003, a Phase 3, randomized, active comparator-controlled, double-blind, international clinical trial. A total of 2,663 participants (1382 CAPVAXIVE, 1281 PCV20) enrolled in the study, of which 1379 received CAPVAXIVE and 1281 received PCV20. The primary endpoint in adults 50 years of age was to compare the serotype-specific OPA GMTs at 30 days postvaccination with CAPVAXIVE versus PCV20. The predefined noninferiority criteria (lower bound of 95% CI of the OPA GMT ratio [CAPVAXIVE/PCV20] >0.5) were met for the 10 common serotypes. The predefined criteria for statistically significantly higher OPA responses (LB of the 95% CI of the OPA GMT ratio >2.0) compared with PCV20 were met for 10 of 11 serotypes unique to CAPVAXIVE. For serotype 15C, the LB of the 95% CI of the OPA GMT ratio was 1.77. The predefined criteria for immunobridging were met for CAPVAXIVE in participants 18 through 49 years of age compared with CAPVAXIVE in participants 50 through 64 years of age for all 21 serotypes as assessed by serotype-specific OPA GMTs (lower bound of the 95% CI of the OPA GMT >0.5) at 30 days postvaccination.

Analyses of secondary outcomes included immunogenicity against serotypes 15B and 6C. For serotype 15B, CAPVAXIVE met the predefined criterion for antibody response (lower bound of 95% CI of the proportion of participants with a ≥ 4 -fold rise in OPA responses >0.5) with the percentage of participants with a ≥ 4 -fold rise in OPA responses from baseline to 30 days postvaccination being 64.7% (95% CI: 61.4, 67.8). For serotype 6C, CAPVAXIVE did not meet the predefined criterion for antibody response with the percentage of participants with a ≥ 4 -fold rise in OPA responses from baseline to 30 days postvaccination being 49.3% (95% CI: 46.0, 52.6).

Study 006 was designed to descriptively evaluate the safety and immunogenicity of CAPVAXIVE in pneumococcal vaccine-experienced adults ≥ 50 years of age compared with an active control (PCV15 or PPSV23) for 2 of the 3 cohorts. Across all 3 cohorts, CAPVAXIVE was immunogenic for all 21 serotypes contained in the vaccine, as assessed by serotype-specific OPA GMTs at 30 days postvaccination.

Safety

The safety of CAPVAXIVE after a single dose was evaluated in 4 Phase 3 studies (4,018 CAPVAXIVE, 2018 active control). Solicited adverse reactions within 5 days of vaccination (Study 003) occurred at similar rates between CAPVAXIVE and PCV20 (51.0% CAPVAXIVE, 60.3% PCV20). In both groups there was a trend towards higher rates of events in the 18 through 49 years of age group. The most frequently reported local reaction in all groups was pain at the injection site (Cohort 1: 39.4% CAPVAXIVE, 51.7% PCV20; Cohort 2: 71.5% CAPVAXIVE, 74.0% PCV20) and the most frequently reported systemic reaction was fatigue (Cohort 1: 20.1% CAPVAXIVE, 19.6% PCV20; Cohort 2: 40.5% CAPVAXIVE, 34.0% PCV20). Severe (Grade 3) solicited local and systemic reactions were rare, reported in 0.5% of CAPVAXIVE recipients in Cohort 1, 1.0% of PCV20 recipients in Cohort 1, 4.5% of CAPVAXIVE recipients in Cohort 2, and 3.0% of PCV20 recipients in Cohort 2. The percentage of participants in the pooled analysis set reported at least 1 unsolicited, non-serious adverse event (AE) through 1-month postvaccination was 22.3% in CAPVAXIVE recipients and 22.2% in active control recipients.

The percentage of participants reporting at least 1 non-fatal serious adverse event (SAE) in the 4 Phase 3 studies was 1.4% among CAPVAXIVE recipients and 2.0% of comparator recipients. Two SAEs were considered by the investigator and the FDA to be related to the study vaccination: one participant in study 005 with reported bronchospasm and one participant in

study 006 who reported injection-site cellulitis (See individual studies in [section 6](#) for narrative details). Deaths were reported for 6 CAPVAXIVE recipients and 3 active comparator recipients. Based on independent review of event narratives, FDA considers the deaths to be either attributable to the participants underlying medical conditions, risk factors, concurrent medical conditions, or events that are not physiologically plausible to be attributed to vaccination.

Manufacturing lot consistency

The statistical criteria for lot consistency were met based on the results of Study 004.

Concomitant vaccination with Influenza QIV

Study 005 was a Phase 3, randomized, double-blind, placebo-controlled, study in which immunogenicity was assessed for CAPVAXIVE when administered concomitantly with QIV compared with when administered sequentially. Except for pneumococcal serotype 23B and influenza subtype A/H3N2, the primary objectives to demonstrate noninferiority of concomitant administration of CAPVAXIVE and QIV were met (LB of the 95% CI of the GMT ratio >0.5 and >0.67 , respectively) compared with pneumococcal and influenza antibody responses following sequential administration. For pneumococcal serotype 23B the LB of the 95% CI of the group GMT ratio was 0.44. For influenza subtype A/H3N2, the LB of the 95% CI of the group GMT ratio was 0.67.

Overall Conclusions

The clinical data submitted in the application support the safety and effectiveness of CAPVAXIVE in individuals 18 years of age and older in preventing IPD due to serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B and accelerated approval of CAPVAXIVE to prevent pneumonia due to serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 26. Risk-Benefit Assessment of CAPVAXIVE, Pneumococcal 21-valent Conjugate Vaccine for Use in Individuals 18 Years and Older

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> 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. <i>Streptococcus pneumoniae</i> is a common cause of pneumonia leading to approximately 150,000 hospitalizations annually in the US. It causes significant illness in older adults, ranging from invasive disease, such as meningitis, bacteremia, osteomyelitis, or septic joint, to non-invasive infections such as pneumonia (without bacteremia). 	<ul style="list-style-type: none"> Invasive pneumococcal disease and pneumococcal pneumonia are significant causes of morbidity and mortality in older adults Younger adults with certain medical conditions and those who are immunocompromised are at risk of serious pneumococcal disease.
Unmet Medical Need	<ul style="list-style-type: none"> Four pneumococcal vaccines have been approved by FDA and are available in the United States; Prevnar 13 (PCV13), Vaxneuvance (PCV15), Prevnar 20 (PCV20) are approved for 6 weeks of age and older, depending on the indication. Pneumovax 23 (PPVS23), is approved for use in individuals ≥50 years of age and individuals ≥2 years of age who are at increased risk for IPD. PPVS23 has not been shown to be effective in preventing non-bacteremic pneumococcal pneumonia. CAPVAXIVE has 11 serotypes in common with PCV20. There are 10 serotypes for which CAPVAXIVE is indicated that were not in PCV20. There are 7 serotypes for which CAPVAXIVE is indicated that were not in PPVS23. 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. 	<ul style="list-style-type: none"> There is unmet medical need for effective prevention of IPD and pneumonia caused by serotypes that are not included in PCV20 or PPVS23.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	<ul style="list-style-type: none"> Effectiveness of CAPVAXIVE was evaluated based on OPA which is the primary mechanism for prevention of pneumococcal disease. In study 003, CAPVAXIVE met the predefined criterion for noninferiority to PCV20 for each of the 10 common serotypes and 15B. CAPVAXIVE met the predefined criterion for statistical superiority for 10 of the 11 serotypes not included in PCV20 at 30 days postvaccination in adults ≥50 years of age. CAPVAXIVE did not meet the predefined criterion for superiority to PCV20 for serotype 15C 	<ul style="list-style-type: none"> The studies provided in the BLA support CAPVAXIVE effectiveness to prevent IPD due to serotypes contained in the vaccine and due to serotype 15B. Accelerated approval of CAPVAXIVE for prevention of pneumonia due to CAPVAXIVE vaccine serotypes in individuals ≥18 years of age, based on an immunological surrogate endpoint (OPA GMT). The Applicant will conduct a postmarketing real-world effectiveness study as a confirmatory study to verify and describe clinical benefit of CAPVAXIVE for the prevention of pneumonia caused by 21 serotypes.
Risk & Risk Management	<ul style="list-style-type: none"> The most commonly reported (>10%) solicited adverse reactions in individuals 18 through 49 years of age who received CAPVAXIVE were: injection site pain (73.1%), fatigue (36.0%), headache (27.5%), myalgia (16.4%), injection site erythema (13.8%), and injection site swelling (13.3%). Severe solicited adverse reactions occurred in <6%. The most commonly reported (>10%) solicited adverse reactions in individuals 50 years of age and older who received CAPVAXIVE were: injection site pain (41.2%), fatigue (19.7%), and headache (11.0%). Severe solicited adverse reactions occurred in <3%. The percentage of individuals reporting 1 or more SAEs within 6 months postvaccination was comparable between individuals vaccinated with CAPVAXIVE (1.4%) and individuals vaccinated with an active comparator (2.0%) 2 SAEs (bronchospasm, cellulitis) were assessed as related to CAPVAXIVE. 	<ul style="list-style-type: none"> The reactogenicity of CAPVAXIVE is described in the prescribing information. Routine pharmacovigilance is considered adequate to monitor safety in the postmarketing setting.

11.2 Risk-Benefit Summary and Assessment

The data submitted to this BLA demonstrate the effectiveness of CAPVAXIVE administered as single dose in individuals 18 years of age and older 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.

The safety of CAPVAXIVE is adequately described in the prescribing information, and the Applicant's proposal for routine pharmacovigilance is adequate for monitoring AEs postmarketing.

11.3 Discussion of Regulatory Options

It has been established that OPA titers similar to comparator vaccines support the prevention of invasive disease. No bridge to effectiveness for community-acquired, non-bacteremic pneumococcal pneumonia has been established. The Applicant proposed prevention of pneumococcal pneumonia as an additional indication using the accelerated approval regulations (21 CFR 601.41).

In the Applicant's proposal, vaccine effectiveness of CAPVAXIVE to prevent pneumococcal pneumonia in individuals ≥ 18 years of age relies on an immunological surrogate endpoint reasonably likely to predict clinical benefit in preventing serotype-specific pneumococcal pneumonia. There is regulatory precedent (PCV13, PCV20) for the use of OPA as a surrogate marker for pneumococcal pneumonia under accelerated approval.

As a condition of accelerated approval, the Applicant must conduct a postmarketing confirmatory study to verify and describe clinical benefit of CAPVAXIVE for the prevention of serotype-specific pneumococcal pneumonia. The Applicant has proposed to conduct an observational real-world evidence study to confirm effectiveness of CAPVAXIVE in preventing serotype-specific pneumococcal pneumonia.

In individuals 18 years and older, licensure of CAPVAXIVE would provide additional vaccine coverage for prevention of IPD due to serotypes not contained in currently available pneumococcal vaccines.

11.4 Recommendations on Regulatory Actions

The clinical review team recommends licensure of CAPVAXIVE for the indications of:

- 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 18 years of age and older
- 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 under the accelerated approval regulations (21 CFR 601.41)

11.5 Labeling Review and Recommendations

The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved.

11.6 Required Postmarketing Actions

The Applicant is required to conduct the following studies:

Deferred pediatric study under PREA to evaluate the safety and immunogenicity of CAPVAXIVE in individuals 2 to <18 years of age

Final Protocol Submission: July 31, 2024
Study Completion Date: June 30, 2026
Final Report Submission: December 31, 2026

RWE Study to evaluate pneumococcal pneumonia indication as part of accelerated approval requirement

Final Protocol Submission: May 30, 2025
Study Completion Date: June 29, 2029
Final Report Submission: December 31, 2029