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Application Type	BLA Supplement
STN	125814/428
CBER Received Date	August 18, 2025
PDUFA Goal Date	June 18, 2026
Committee Chair	Diana Oram
Clinical Reviewer	Nicholas Geagan
Project Manager	Hilda Grabczewski, Leda Lotspeich-Cole, Emily Smith
Priority Review	No
Reviewer Name	Trinetri Ghosh, Mathematical Statistician, VEB/DB/OBPV
Review Completion Date / Stamped Date	June 10, 2026
Supervisory Concurrence	Sang Ahnn, Concurring Reviewer, VEB/DB/OBPV Tsai-Lien Lin, Branch Chief, VEB/DB/OBPV
Applicant	Merck Sharp & Dohme LLC
Established Name	Pneumococcal 21-valent Conjugate Vaccine
(Proposed) Trade Name	CAPVAXIVE®
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	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
Dosage Form(s) and Route(s) of Administration	A single 0.5 mL solution intramuscularly
Dosing Regimen	Single dose
Purpose of Supplement	To extend the prescribing information (PI) 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 children and adolescents 2 to less than 18 years of age with increased risk of pneumococcal disease.

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GLOSSARY

AE	Adverse event
AESI	Adverse event of special interest
APaT	All participants as treated
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CRF	Case report form
CSR	Clinical study report
deOAc	De-O-acetylated
eVRC	Electronic vaccination report card
FAS	Full analysis set
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IPD	Invasive pneumococcal disease
LB	Lower bound
LLOQ	Lower limit of quantitation
M&N	Miettinen and Nurminen
MedDRA	Medical dictionary for regulatory activities
NI	Noninferiority
OPA	Opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
PnPs	Pneumococcal polysaccharide
POCBP	Participant/participants of childbearing potential
PP	Per-protocol
PPSV23	Pneumococcal vaccine, 23-valent (PNEUMOVAX™23)
PREA	Pediatric Research Equity Act
PT	Preferred term
RCDC	Reverse cumulative distribution curve
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SDTM	Study data tabulation model
SOC	System organ class
ULOQ	Upper limit of quantitation
US	United States
V116	Pneumococcal 21-valent conjugate vaccine
YOA	Years of age

1. Executive Summary

The Merck Sharp & Dohme LLC Pneumococcal 21-valent Conjugate Vaccine (V116), registered under the trade name CAPVAXIVE®, has been approved in the United States (US) since June 17, 2024 for active immunization to prevent 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, and to prevent 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 (YOA) and older as a single dose (0.5 mL) vaccine administered intramuscularly. The applicant submitted a Biologics License Application (BLA) supplement (sBLA; STN 125814/428) on August 18, 2025 to extend the invasive disease indication to children and adolescents 2 to <18 YOA with increased risk of pneumococcal disease under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), as a part of post-marketing requirements.

This sBLA is supported by data from one pivotal Phase III active comparator-controlled study, V116-013, in the proposed age expansion group. This statistical review focuses on the safety and immunogenicity data from participants 2 to <18 YOA with increased risk of pneumococcal disease.

V116-013 was a Phase III, randomized, double-blind, multisite, parallel-group, active-comparator controlled study to evaluate the safety, tolerability and immunogenicity of V116 in children and adolescents aged 2 to <18 years who have completed a primary pneumococcal vaccination regimen and are at increased risk for pneumococcal disease due to chronic heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, and/or chronic kidney disease. A total of 882 participants were randomized in a 3:2 ratio to receive a single dose of either V116 or PPSV23. Randomization was stratified by the number of increased-risk conditions for pneumococcal disease (1 increased-risk condition, or ≥2 increased-risk conditions), by prior pneumococcal vaccination (prior PCV7 alone, prior PCV7 and 1 prior PPSV23 dose, prior PCV10 alone, prior PCV10 and 1 prior PPSV23 dose, prior PCV13 alone, or prior PCV13 and 1 prior PPSV23 dose), and age (2 to <6 years or ≥6 to <18 years).

The pre-specified noninferiority (NI) criterion for opsonophagocytic activity (OPA) geometric mean titer (GMT) at 30 days post-vaccination of V116 compared to PPSV23 were met (via lower bound [LB] of the 2-sided 95% confidence interval [CI] of OPA GMT ratio [V116/PPSV23] > 0.5) for each of the 12 common serotypes (3, 7F, 8, 9N, 10A, 11A, 12F, 17F, 19A, 20A, 22F and 33F). The pre-specified superiority criterion for OPA GMT at 30 days post vaccination of V116 compared to PPSV23 were met (via LB of the 2-sided 95% CI of OPA GMT ratio [V116/PPSV23] > 2.0) for each of the 9 serotypes unique to V116 (6A, 15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B).

The overall proportions of participants with one or more adverse events (AEs) were generally comparable between two intervention groups. The most frequently reported AEs (≥5%) in both intervention groups were the solicited AEs, with the exception of urticaria (<5% in both groups) and arthralgia (<5% in the V116 group). The proportions of participants with solicited systemic AEs were generally comparable between intervention

groups (45.7% in the V116 group and 40.3% in the PPSV23 group). The proportion of participants with solicited injection-site AEs was higher in the V116 group (72.3%) compared to the PPSV23 group (58.2%). Specially, the proportion of participants with injection site erythema and injection site pain was higher in the V116 group (24.3% and 67.7%, respectively) compared with the PPSV23 group (16.4% and 54.5%, respectively). Among the participants with solicited AEs, the majority had events that were of short duration (≤3 days) and most of them had intensity of mild or moderate in both intervention groups. The proportions of participants reporting serious adverse events (SAEs) occurring Day 1 through the duration of study participation (approximately 6 months) were 5.5% in the V116 group and 7.2% in the PPSV23 group. Three SAEs were assessed as related to the study vaccine by the investigator: a case of syncope in the V116 group and two cases of anaphylactic reactions in the PPSV23 group. These three cases were reported on Day 1 of vaccination. There were no deaths in the V116 group. Two deaths (0.6%) (1 due to septic shock and 1 due to cardiopulmonary failure) were reported in the PPSV23 group and neither were considered to be vaccine related by the investigator.

Overall, from a statistical perspective, I consider the immunogenicity data presented in this application supportive of approving the pneumococcal 21-valent conjugate vaccine, V116, in children and adolescents aged 2 to <18 YOA who have completed a primary pneumococcal vaccination regimen and are at increased risk for pneumococcal disease. I defer to the clinical reviewer on the safety conclusions.

2. Clinical and Regulatory Background

V116 (CAPVAXIVE®) was approved in the US on June 17, 2024, for active immunization to prevent 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, and active immunization to prevent 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 YOA and older. Further, the applicant submitted a BLA supplement on September 30, 2024, under section 351(a) of the Public Health Service Act for Pneumococcal 21-valent Conjugate Vaccine (CAPVAXIVE) to update Section 8 "Use in Specific Populations", Section 6 “Clinical Trials Experience”, and Section 14 “Clinical Studies” of the package insert (PI) for the inclusion of individuals living with Human immunodeficiency virus (HIV) and individuals at increased risk of pneumococcal disease. On August 18, 2025, the applicant submitted a BLA supplement (STB 125814/428) to fulfill PREA pediatric study requirement and to extend current indication for the prevention of invasive disease caused by Streptococcus pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 2 to less than 18 YOA who are at increased risk for pneumococcal disease.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is complete and organized to facilitate a thorough review.

3.2 Compliance With Good Clinical Practices And Data Integrity

During the review, discrepancies between the occurrence of solicited adverse reactions reported in SDTM.CE and SDTM.FACE datasets for some subjects were found. An information request (IR) was sent to the applicant regarding this issue on October 16, 2025. In their response on October 29, 2025, the applicant clarifies that SDTM.CE reflects the occurrence of the event per the investigator's assessment, whereas records in SDTM.FACE reflect the daily solicited complaint data entered by the participant on electronic vaccination report card (eVRC). Further, if the investigator's assessment differs from the data entered by the participants, the applicant recorded the reason for the difference in SDTM.SUPPCE with QNAM = "CEDIFFRS".

Overall, no data integrity issue was found. Please refer to reviews of other review disciplines.

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

Please refer to reviews of other review disciplines.

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

5.1 Review Strategy

This statistical review focuses on the immunogenicity and safety data in children and adolescents aged ≥2 to <18 years with increased risk of pneumococcal disease from a Phase III study V116-013 up to database lock at March 18, 2025.

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

The following documents submitted to the BLA supplement are reviewed.

STN 125814/428.0:

- Section 2.7.3 Summary of Clinical Efficacy
- Section 2.7.4 Summary of Clinical Safety
- Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    - P013V116 (Study V116-013)
        - Clinical Study Report (P013V116)
        - 16.1.1 Protocol and Protocol Amendments
        - 16.1.9 Documentation of Statistical Methods
        - Analysis Datasets
        - Tabulation Datasets

STN 125814/428.6:

- Section 1.11.3 Clinical Information Amendment

STN 125814/428.8:

- Section 1.11.3 Clinical Information Amendment

- Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    - P013V116 (Study V116-013)
        - Datasets

5.3 Table of Studies/Clinical Trials

Data from one completed Phase III study was submitted to support the proposed indication in children and adolescents (Table **1**).

Table 1: Study Submitted to STN 125814/428

Study (Country)	**Study Design**	**Study Population**	**Treatment Groups / No. of Participants**	**Study Primary Endpoints**
V116-013 (Canada, Chile, Colombia, Finland, France, Israel, Japan, Poland, Spain, Sweden, Turkiye, Thailand, United States)	Randomized, double-blinded, active comparator-control, parallel-group, and multisite study. Randomization was stratified by the number of increased-risk conditions for pneumococcal disease, by prior pneumococcal vaccination, and age.	Children and adolescents aged ≥2 to <18 years, who were at increased risk for pneumococcal disease and had completed a primary PCV regimen	Randomization Ratio: V116:PPSV23 = 3:2 V116 Group: • Randomized: 531 • Vaccinated: 528 • Completed: 522 PPSV23 Group: • Randomized: 351 • Vaccinated: 348 • Completed: 345	• Solicited injection-site and systemic AEs Day 1 through Day 5 post-vaccination • Vaccine-related SAEs Day 1 through the duration of participation in the study • Serotype-specific OPA responses

Source: Adapted from Table 2.7.3-AdultPCVpeds: 1 in Section 2.7.3 Summary of Clinical Efficacy from sBLA 125814/428.0.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study V116-013 (Phase III)

Title: A Phase III, randomized, double-blind study to evaluate the safety, tolerability, and immunogenicity of V116 in children and adolescents with increased risk of pneumococcal disease.

Study initiation date: January 19, 2024 (First participant first visit).
Study completion date: February 26, 2025 (Last participant last visit).

6.1.1 Objectives and Endpoints

The study objectives and endpoints are given in Table **2**.

Table 2: Study Objectives and Endpoints

Study Objectives	**Study Endpoints**
Primary Safety Objective	**Primary Safety Endpoints**
To evaluate the safety and tolerability of V116 with respect to the proportion of participants with AEs.	• Solicited injection-site and systemic AEs Day 1 through Day 5 post-vaccination. • Vaccine-related SAEs Day 1 through the duration of participation in the study.
Primary Immunogenicity Objective	**Primary Immunogenicity Endpoint**
To compare the serotype-specific OPA GMTs at 30 days post-vaccination with V116 versus PPSV23.	• Serotype-specific OPA responses.
Secondary Immunogenicity Objectives	**Secondary Immunogenicity Endpoints**
To evaluate the serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) at 30 days post-vaccination with V116 compared with PPSV23.	• Serotype-specific IgG responses.
To evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥4-fold rise in serotype-specific OPA responses and IgG responses from baseline to 30 days post-vaccination within each vaccination group.	• Serotype-specific OPA and IgG responses.
Tertiary/Exploratory Objective	**Tertiary/Exploratory Endpoints**
To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days post-vaccination.	• Serotype specific OPA and IgG responses.

Source: Adapted from Table in Section 8 in Clinical Study Report (CSR) for study V116-013, p.30.

The 4-fold rise for a specific serotype was defined as achieving either 4×pre-vaccination responses among participants whose pre-vaccination responses were ≥lower limit of quantitation (LLOQ) or 4×LLOQ among participants whose pre-vaccination titers were <LLOQ.

6.1.2 Design Overview

This was a Phase III, randomized, double-blind, active comparator-controlled clinical study to evaluate the safety, tolerability, and immunogenicity of V116 in children and adolescents aged ≥2 to <18 years who have completed a primary pneumococcal vaccination regimen and who are at increased risk of pneumococcal disease (i.e., chronic

heart disease, chronic lung disease, diabetes mellitus, chronic liver disease, or chronic kidney disease). Approximately 820 participants were planned to be randomized in a 3:2 ratio to receive a single dose of either V116 or PPSV23 on Day 1. Randomization were stratified by the number of increased-risk conditions for pneumococcal disease (1 increased-risk condition, or ≥2 increased-risk conditions) and by prior pneumococcal vaccination and age:

- Prior PCV7 alone,
- Prior PCV7 and one prior PPSV23 dose,
- Prior PCV10 alone and ≥2 to <6 years old,
- Prior PCV10 alone and ≥6 to <18 years old,
- Prior PCV10 and one prior PPSV23 dose,
- Prior PCV13 alone and ≥2 to <6 years old,
- Prior PCV13 alone and ≥6 to <18 years old,
- Prior PCV13 and one prior PPSV23 dose.

The applicant excluded participants who received a combination of PCV7, PCV10, and/or PCV13 or any doses of PCV15 or PCV20 from study V116-013.

The participant/participant's legally authorized representative used an electronic vaccination report card (eVRC) to record solicited injection-site AEs, solicited systemic AEs, and daily body temperatures from Day 1 through Day 5 after vaccination, and unsolicited AEs from Day 1 through Day 30 after vaccination. Information for SAEs and deaths were collected through Day 180. Blood samples for immunogenicity assays were drawn on Day 1 (Visit 1) pre-vaccination and Day 30 (Visit 3) post-vaccination.

This trial was a double-blind study under in-house blinding procedures, with the participant, participant's representative, the investigator, the sponsor, and other study personnel blinded to the treatment assignment. The study vaccines were prepared and administered by an unblinded pharmacist or qualified study-site personnel. Blinded site personnel were responsible for all other study procedures/assessments.

6.1.3 Population

The study population included children and adolescents aged ≥2 to <18 years at the time of informed consent, completed primary PCV regimen with PCV7, PCV10 or PCV13 with either a 2+1 or 3+1 regimen at least 8 weeks prior to enrollment, and had documented diagnosis of ≥1 of the following risk conditions for pneumococcal disease:

- Diabetes mellitus receiving treatment with antidiabetic medication,
- Chronic compensated liver disease,
- Chronic lung disease, including but not limited to asthma (a diagnosis of asthma requires current medical therapy),
- Chronic heart disease due to heart failure, congenital heart disease, cardiomyopathy, and/or valvular heart disease,
- Chronic kidney disease, with chronic kidney insufficiency/impairment.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The test product V116 is a 21-valent conjugate pneumococcal vaccine which was injected as a single dose of 0.5 mL solution intramuscularly. Each unit dose consists of 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). The comparator product PPSV23 is a 23-valent conjugate pneumococcal vaccine which was injected as a single dose of 0.5 mL solution intramuscularly. Each unit dose consists of 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, 33F).

6.1.6 Sites and Centers

The study was conducted at 5 sites in Canada, 5 sites in Chile, 4 sites in Colombia, 7 sites in Finland, 3 sites in France, 3 sites in Israel, 8 sites in Japan, 4 sites in Poland, 8 sites in Spain, 1 site in Sweden, 4 sites in Thailand, 7 sites in Türkiye, and 23 sites in United States.

6.1.7 Surveillance/Monitoring

Please refer to this section in the clinical reviewer's review memo.

6.1.8 Hypotheses and Criteria for Study Success

For the primary immunogenicity objective, V116 was compared to PPSV23 based on the following two primary hypotheses:

- *H1 (Noninferiority testing for 12 common serotypes)*: For each of the 12 common serotypes, the primary noninferiority hypothesis regarding OPA GMT levels between recipients of V116 and PPSV23, i.e., H_0: $GMT_1/GMT_2 \leq 0.5$ versus H_a: $GMT_1/GMT_2 > 0.5$, was conducted at 1-sided type-I error of 0.025.
- *H2 (Superiority testing for 9 serotypes unique to V116)*: For each of the 9 serotypes that are unique to V116, the primary superiority hypothesis regarding OPA GMT levels between recipients of V116 and PPSV23, i.e., H_0: $GMT_1/GMT_2 \leq 2.0$ versus H_a: $GMT_1/GMT_2 > 2.0$, was conducted at 1-sided type-I error of 0.025.

GMT_1 is the serotype-specific OPA GMT for the V116 group and GMT_2 is the serotype-specific OPA GMT for the PPSV23 group. If the lower bound of 2-sided 95% confidence interval (CI) on the GMT ratio (V116/PPSV23) was > 0.5, the null hypothesis for H1 was rejected. If the lower bound of 2-sided 95% CI on the GMT ratio (V116/PPSV23) was > 2.0, the null hypothesis for H2 was rejected.

The study would meet its primary immunogenicity objective if noninferiority was demonstrated with respect to the OPA GMTs for the 12 common serotypes (via H1), and superiority was demonstrated with respect to OPA GMTs for the 9 unique serotypes (via H2).

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Sets: The following analysis sets were defined.

- *Full Analysis Set (FAS)*: The FAS population consisted of all randomized participants who received at least 1 study vaccination and have at least 1 serology

result. Participants were included in the vaccination group to which they were randomized for the analysis of the immunogenicity data using the FAS population. FAS was used as analysis population for supportive analyses for primary immunogenicity endpoint.

- *Per Protocol Analysis Set (PP)*: The PP population was served as the primary population for the analysis of immunogenicity data in this study. The PP population consisted of all randomized participants without deviations from the protocol. Potential deviations that might result in the exclusion of a participant from the PP population for all immunogenicity analyses included:
    - Failure to receive study vaccine at Day 1,
    - Failure to receive correct clinical material as per randomization schedule at Day 1,
    - Receipt of prohibited medication or prohibited vaccine prior to study vaccination,
    - Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection,
    - Collection of blood samples outside the prespecified window. As an exception, participants who returned to postvaccination blood sample collection 1 day before or 1 day after the prespecified window were included in the PP population for immunogenicity analyses.
- *All Participants as Treated (APaT) population*: Safety analyses were conducted on APaT population, which consisted of all randomized participants who received one dose of study intervention. Participants were included in the vaccination group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population.

Primary Safety Analyses:
Safety analyses were based on the APaT set. Safety analyses included a summary by vaccination group of descriptive statistics such as the number and percentage of participants with any AEs, any unsolicited AEs, any vaccine-related AEs, any SAEs, any vaccine-related SAEs, and any AEs resulting in death after vaccination. CIs for between-group differences were provided using the Miettinen and Nurminen method (1985).

Primary Immunogenicity Analyses:
Primary immunogenicity analyses were conducted for each serotype separately on the PP set and supportive analyses were carried out on FAS. For hypotheses H1 and H2, the GMT ratio estimation, 95% CI, and the hypothesis test (i.e., 1-sided p-value) were calculated using a cLDA method proposed by Liang and Zeger (2000) based on data from both vaccination groups. In this model, the response vector consisted of the log transformed antibody titers at baseline and 30 days postvaccination. The repeated measures model included terms for time, vaccination group, the interaction of time-by-vaccination group, prior pneumococcal vaccination stratum (prior PCV7 alone, prior PCV7 and one prior PPSV23, prior PCV10 alone (combined age stratum), prior PCV10 and one prior PPSV23, prior PCV13 alone (combined age stratum), prior PCV13 and one prior PPSV23), the time-by-prior pneumococcal vaccination stratum, number of increased-risk conditions stratum (1 increased-risk condition only, ≥2 increased-risk conditions), and the time-by-number of

increased-risk conditions stratum. This model allowed for different baseline means for each stratum level within the stratification factors but restrict the baseline mean within each stratum level to be the same for both vaccination groups. The term for time was treated as a categorical variable. An unstructured covariance matrix was used to model the correlation among repeated measurements. The Kenward-Roger adjustment was used with REML to make proper statistical inference. This model allowed the inclusion of participants who were missing either the baseline or postbaseline measurements, thereby increasing efficiency.

Secondary Immunogenicity Analyses:
Descriptive statistics were provided for secondary immunogenicity endpoints. A similar statistical model as used for the first primary objective was used to obtain the point estimate and 95% CI to address the secondary objective that compared the serotype-specific IgG GMCs at 30 days post-vaccination with V116 compared with PPSV23. GMFR and proportions of participants with a ≥4-fold rise for both serotype-specific OPA and IgG responses from baseline to 30 days postvaccination included descriptive summaries and within-group 95% CIs at 30 days postvaccination.

Missing Data:
For estimating primary endpoints, model-based imputation approach was used for missing data. Model-based imputation was also used for estimating secondary endpoints where serotype-specific IgG GMCs at 30 days post-vaccination was compared between V116 and PPSV23. For other analyses, missing data was not imputed.

Further, for responses smaller than LLOQ, half of the LLOQ was used for analysis when calculating the OPA GMTs and IgG GMCs. For responses that were larger than the upper limit of quantitation (ULOQ), a value equal to ULOQ + 1 was used for all OPA and IgG analyses.

Sample Size and Power:
Using a simulation-based approach, the applicant mentioned that this study had >90% power to demonstrate the noninferiority of V116 to PPSV23 for 12 common serotypes (H1) and superiority of V116 to PPSv23 for the 9 serotypes unique to V116 (H2). The sample size and power calculations were based on the following assumptions:

- 1-sided type-I error = 0.025,
- 90% evaluability (443 participants in the V116 group and 295 participants in the PPSV23 group),
- For the 12 common serotypes, the underlying serotype-specific OPA GMT ratios (V116/PPSV23) and the standard deviations of natural log-transformed OPA results were assumed to be the same as those observed in the V116-004 Phase 3 study. The OPA GMT ratios ranged from 0.84 to 1.74. The standard deviations ranged from 0.93 to 1.43 for V116 and ranged from 0.96 to 1.43 for PPSV23,
- For the 9 unique serotypes, the underlying serotype-specific OPA GMT ratios (V116/PPSV23) and the standard deviations of natural log-transformed OPA results were assumed to be the same as those observed in the V116-004 Phase 3

study. The OPA GMT ratios ranged from 2.90 to 23.72. The standard deviations ranged from 1.03 to 1.52 for V116 and ranged from 1.05 to 2.54 for PPSV23.

Subgroup Analyses:
Subgroup analyses were performed separately for select safety endpoints as well as primary immunogenicity endpoints based on following subgroups:

- Prior pneumococcal vaccination (prior PCV7 alone, prior PCV7 and one prior PPSV23 dose, prior PCV10 alone, prior PCV10 and one prior PPSV23 dose, prior PCV13 alone, prior PCV13 and one prior PPSV23 dose),
- Prior PCV primary regimen (3+1 regimen, 2+1 regimen),
- Age (2 to <6, 6 to <12, 12 to 17),
- Type of increased-risk condition (diabetes mellitus only, chronic liver disease only, chronic lung disease only, chronic heart disease only, chronic kidney disease only),
- Number of increased-risk conditions (1 increased-risk condition only, ≥2 increased-risk conditions),
- Sex (Female, Male),
- Race (American Indian or Alaska Native, Asian, Black or African American, Multiple, Native Hawaiian or Other Pacific Islander, White),
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino).

If the number of participants in any one subgroup category was ≤5% of the total randomized and vaccinated participants, the applicant might have combined subgroup category with other subgroup category(ies) or excluded it from the subgroup analysis.

Reviewer's Comment:

- *Multiple hypotheses were prespecified for the primary objective. All hypotheses were tested individually for each serotype at a 1-sided α = 0.025. As study success depended on demonstrating noninferiority of each of the 12 common serotypes and superiority of each of the 9 serotypes unique to V116, no multiplicity adjustment was required.*
- *To address the exploratory immunogenicity objective for evaluating the cross-reactive immune responses to serotypes within a serogroup, descriptive summaries were provided for serotype-specific OPA GMTs and IgG GMCs at Day 1 and at Day 30 post-vaccination. Descriptive summaries were also provided for GMFR and proportions of participants with a ≥4-fold rise from both serotype-specific OPA and IgG responses from baseline to 30 days post-vaccination.*
- *The applicant conducted a post hoc analysis of the OPA GMTs for serotype 15B using the same statistical methods that were used for the primary immunogenicity analyses.*
- *To avoid convergence issues during primary immunogenicity analyses due to small numbers of participants in strata, the applicant combined two strata – prior PCV10 alone and ≥2 to <6 years old and prior PCV10 alone and ≥6 to <18 years old – to prior PCV10 alone, and combined two strata – prior PCV13 alone and ≥2 to <6 years old and prior PCV13 alone and ≥6 to <18 years old – to prior PCV13 alone before the study unblinding. This is acceptable.*
- *The applicant considered excluding the intercept from the cLDA model in some scenarios where a specific pneumococcal serotype did not converge. During my*

review, I found that this happened for the supportive analyses of the primary immunogenicity objective on FAS.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

In this study, a total of 882 participants were randomized, and 876 received study intervention. The majority (98.3%) of participants in both groups completed the study. Overall, the disposition of participants was generally comparable between intervention groups (Table 3). Two participants were vaccinated without documented initial consent and/or assent, and they were excluded from the All Vaccinated Participants, PP, APaT, and FAS populations.

Table 3: Disposition of Participants (All Randomized Participants)

Disposition	**V116 (N = 531) n (%)**	**PPSV (N = 351) n (%)**	**Total (N = 882) n (%)**
Vaccinated at Visit 1			
V116	528 (99.4)	0 (0.0)	528 (59.9)
PPSV23	0 (0.0)	348 (99.1)	348 (39.5)
Trial Disposition			
Completed	522 (98.3)	345 (98.3)	867 (98.3)
Discontinued	9 (1.7)	6 (1.7)	15 (1.7)
Death	0 (0.0)	2 (0.6)	2 (0.2)
Lost to follow-up	2 (0.4)	0 (0.0)	2 (0.2)
Randomized by mistake without study treatment	1 (0.2)	1 (0.3)	2 (0.2)
Withdrawal by parent / guardian	5 (0.9)	3 (0.9)	8 (0.9)
Other	1 (0.2)	0 (0.0)	1 (0.1)

Percentages are calculated based on the number (N) of participants randomized.
Source: Table 10-1 in CSR P013V116 for study V116-013, p.40.

Important protocol deviations were reported for 144 participants. Of these, 122 participants (68 in V116 and 54 in PPSV23) had important protocol deviations that were considered to be clinically important. The most frequently reported clinically important protocol deviations were due to a participant being pneumococcal vaccine naive or receiving a prior pneumococcal vaccine regimen prohibited by the protocol study vaccination (n=45), immunogenicity blood sample was not drawn or a sample could not be tested due to an error by the site in processing and/or handling of the sample (n=31), and immunogenicity blood sample being drawn outside the protocol-defined window (n=27).

Most randomized participants were included in the PP population for the OPA analyses for at least 1 timepoint (91.0%), and for both Day 1 and Day 30 timepoints (81.0%) (Table **4**). Most randomized participants were included in the PP population for the IgG analyses for at least 1 timepoint (86.3%). A total of 66.8% of participants were included in the IgG analyses for both Day 1 and Day 30 timepoints (Table **4**). APaT population included all

874 participants (527 in V116 and 347 in PPSV23) who received study intervention and had documented initial consent.

Table 4: Participant Accounting for OPA and IgG Analyses for the Per-Protocol Population (All Randomized Participants)

PP Analysis Set	**V116 (N = 531) n (%)**	**PPSV23 (N = 351) n (%)**	**Total (N = 882) n (%)**
OPA			
Day 1	468 (88.1)	307 (87.5)	775 (87.9)
Day 30	451 (84.9)	291 (82.9)	742 (84.1)
At least one timepoint	488 (91.9)	315 (89.7)	803 (91.0)
Both Day 1 and Day 30	431 (81.2)	283 (80.6)	714 (81.0)
IgG			
Day 1	413 (77.8)	276 (78.6)	689 (78.1)
Day 30	408 (76.8)	253 (72.1)	661 (74.9)
At least one timepoint	462 (87.0)	299 (85.2)	761 (86.3)
Both Day 1 and Day 30	359 (67.6)	230 (65.5)	589 (66.8)

Percentages are calculated based on the number (N) of participants randomized.
Source: Adapted from Table 14.1-5 and Table 14.1-6 in CSR P013V116 for study V116-013, p.76 and p.77, respectively.

6.1.10.1.1 Demographics
Participant demographic and baseline characteristics were generally comparable between intervention groups (Table **5**) for all vaccinated population.

Table 5: Participant Characteristics (All Vaccinated Participants)

Characteristic	**V116 (N = 527) n (%)**	**PPSV23 (N = 347) n (%)**	**Total (N = 874) n (%)**
Sex			
Male	308 (58.4)	207 (59.7)	515 (58.9)
Female	219 (41.6)	140 (40.3)	359 (41.1)
Age (years)[a]			
>=2 to <6	165 (31.3)	107 (30.8)	272 (31.1)
>= 6 to <18	361 (68.5)	240 (69.2)	601 (68.8)
>=18	1 (0.2)	0 (0.0)	1 (0.1)
Mean	8.2	7.8	8.0
SD	4.1	3.8	4.0

Characteristic	**V116 (N = 527) n (%)**	**PPSV23 (N = 347) n (%)**	**Total (N = 874) n (%)**
Median	8.0	7.0	8.0
Range	2 to 18	2 to 17	2 to 18
Race			
American Indian or Alaska Native	48 (9.1)	43 (12.4)	91 (10.4)
Asian	47 (8.9)	37 (10.7)	84 (9.6)
Black or African American	31 (5.9)	19 (5.5)	50 (5.7)
Multiple	80 (15.2)	48 (13.8)	128 (14.6)
White	321 (60.9)	200 (57.6)	521 (59.6)
Ethnicity			
Not Hispanic or Latino	296 (56.2)	189 (54.5)	485 (55.5)
Hispanic or Latino	231 (43.8)	157 (45.2)	388 (44.4)
Unknown	0 (0.0)	1 (0.3)	1 (0.1)
Country			
Canada	36 (6.8)	21 (6.1)	57 (6.5)
Chile	72 (13.7)	53 (15.3)	125 (14.3)
Colombia	120 (22.8)	83 (23.9)	203 (23.2)
Finland	37 (7.0)	18 (5.2)	55 (6.3)
France	9 (1.7)	7 (2.0)	16 (1.8)
Israel	13 (2.5)	7 (2.0)	20 (2.3)
Japan	23 (4.4)	25 (7.2)	48 (5.5)
Poland	22 (4.2)	19 (5.5)	41 (4.7)
Spain	37 (7.0)	25 (7.2)	62 (7.1)
Sweden	0 (0.0)	2 (0.6)	2 (0.2)
Türkiye	43 (8.2)	29 (8.4)	72 (8.2)
Thailand	21 (4.0)	10 (2.9)	31 (3.5)
United States	94 (17.8)	48 (13.8)	142 (16.2)
Prior Pneumococcal Vaccination[a]			
Prior PCV7 alone	31 (5.9)	24 (6.9)	55 (6.3)
Prior PCV7 and one prior PPSV23 dose	2 (0.4)	2 (0.6)	4 (0.5)
Prior PCV10 alone	176 (33.4)	111 (32.0)	287 (32.8)
Prior PCV10 and one prior PPSV23 dose	4 (0.8)	2 (0.6)	6 (0.7)
Prior PCV13 alone	302 (57.3)	195 (56.2)	497 (56.9)
Prior PCV13 and one prior PPSV23 dose	5 (0.9)	4 (1.2)	9 (1.0)

Characteristic	**V116 (N = 527) n (%)**	**PPSV23 (N = 347) n (%)**	**Total (N = 874) n (%)**
Others[b]	6 (1.1)	9 (2.6)	15 (1.7)
Missing	1 (0.2)	0 (0.0)	1 (0.1)
Number of increased-risk conditions for pneumococcal disease at randomization[a]			
1 increased-risk condition	508 (96.4)	330 (95.1)	838 (95.9)
≥2 increased-risk conditions	19 (3.6)	17 (4.9)	36 (4.1)
Prior PCV primary regimen[c]			
3+1 regimen	201 (38.1)	140 (40.3)	341 (39.0)
2+1 regimen	303 (57.5)	189 (54.5)	492 (56.3)
Others	22 (4.2)	18 (5.2)	40 (4.6)
Missing	1 (0.2)	0 (0.0)	1 (0.1)

Percentages are calculated based on the number (N) of participants vaccinated.
a: Randomization was stratified based on the participant's prior pneumococcal vaccination and age, and by the number of increased-risk conditions for pneumococcal disease at the time of randomization.
b: Includes any combinations of prior pneumococcal vaccines, other than the 2+1 or 3+1 primary regimens, in which all doses of the primary regimen consist of the same pneumococcal vaccine (PCV7, PCV10, or PCV13), followed by one dose of the PPSV23 vaccine.
c: 2+1 regimen refers to the administration of 2 priming doses followed by 1 booster dose prior to 2 years of age according to local recommendations. 3+1 regimen refers to the administration of 3 priming doses followed by 1 booster dose prior to 2 years of age according to local recommendations. Others include any regimen other than the 3+1 or 2+1 regimen.
Source: Adapted from Table 10-2 in CSR P013V116 for study V116-013, p.43.

Reviewer's Comment:

- *There was one vaccinated participant (V116-013(b) (6)) whose age was 18 years and 3 months. This participant was included in the immunogenicity and safety analyses.*
- *Participant V116-013(b) (6) received the fourth PCV13 dose at age of 2 years and <1 month. This should have been considered an important protocol deviation because the fourth PCV13 dose was administered after 24 months of age, and the participant's prior PCV primary regimen should have been considered as 'Others'. An IR was sent to the Applicant. In reply, the applicant assessed this deviation as not clinically important because a dose delay of less than one month was not expected to have a substantial effect on the primary immunogenicity and safety endpoints. Therefore, this participant was retained in the '3+1' regimen group for analysis.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The pre-specified increased-risk conditions for pneumococcal disease in all vaccinated participants were generally comparable between intervention groups. The 6 most common prespecified single increased-risk conditions were asthma (52.0% in V116 vs 48.1% in

PPSV23), diabetes mellitus (14.8% in V116 vs 16.4% in PPSV23), heart disease congenital (10.1% in V116 vs 10.7% in PPSV23), chronic kidney disease (8.7% in V116 vs 8.6% in PPSV23), chronic lung disease (7.4% in V116 vs 9.2% in PPSV23), and cardiac valve disease (5.5% in V116 vs 7.5% in PPSV23).

Proportions of participants with prior (88.2% in V116 vs 86.2% in PPSV23) and concomitant medications (91.8% in V116 vs 90.5% in PPSV23) and concomitant non-study vaccines (6.1% in V116 vs 4.9% in PPSV23) were generally comparable between intervention groups.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Table **6** provides the post-vaccination OPA GMTs on PP population and shows that for each of 12 common serotypes V116 met the predefined criterion for noninferiority compared to PPSV23 at 30 days post-vaccination, i.e., lower bound of 95% CI of OPA GMT ratio [V116/PPSV23]>0.5.

Table 6: Analysis of Post-Vaccination OPA GMTs for Common Serotypes (Per-Protocol Population)

Serotype	**V116* n[a]**	**V116 GMT[b]**	**PPSV23* n[a]**	**PPSV23 GMT[b]**	**GMT Ratio[b] (V116/PPSV23) (95% CI[b])**	**P-value[b]**
3	488	526.6	314	517.0	1.02 (0.89, 1.17)	<0.001
7F	486	20618.1	315	14207.2	1.45 (1.24, 1.70)	<0.001
8	485	12294.5	313	8966.9	1.37 (1.20, 1.56)	<0.001
9N	485	35556.8	315	18587.8	1.91 (1.64, 2.23)	<0.001
10A	485	13719.7	311	5363.8	2.56 (2.18, 3.00)	<0.001
11A	486	10396.3	312	3129.8	3.32 (2.80, 3.95)	<0.001
12F	486	14752.0	314	4820.1	3.06 (2.62, 3.58)	<0.001
17F	481	40011.8	312	11267.4	3.55 (3.02, 4.17)	<0.001
19A	486	9009.8	314	9797.6	0.92 (0.78, 1.08)	<0.001
20A	480	37532.2	311	14787.0	2.54 (2.13, 3.02)	<0.001
22F	487	20162.7	313	7770.3	2.59 (2.21, 3.04)	<0.001
33F	488	73201.8	314	40609.0	1.80 (1.54, 2.11)	<0.001

**: N = 527 for V116 and N= 347 for PPSV23, where N = Number of participants who were vaccinated.*
a: n = Number of participants contributing to the analysis.
b:GMTs, GMT ratios, 95% CIs and p-values are estimated using cLDA model.
Source: Table 14.2-1 in CSR P013V116 for study V116-013, p.193.

Table **7** provides the post-vaccination OPA GMTs on PP population and shows that for each of 9 unique serotypes in V116 met the predefined criterion for superiority compared to PPSV23 at 30 days post-vaccination, i.e., lower bound of 95% CI of OPA GMT ratio [V116/PPSV23]>2.0.

Table 7: Analysis of Post-Vaccination OPA GMTs for Unique Serotypes (Per-Protocol Population)

Serotype	**V116* n[a]**	**V116 GMT[b]**	**PPSV23* n[a]**	**PPSV23 GMT[b]**	**GMT Ratio[b] (V116/PPSV23) (95% CI[b])**	**P-value[b]**
6A	480	16910.9	311	5653.8	2.99 (2.46, 3.64)	<0.001
15A	485	69527.8	315	5332.2	13.04 (11.13, 15.27)	<0.001
15C	480	34539.1	308	4398.4	7.85 (6.29, 9.81)	<0.001
16F	485	31544.9	313	5449.7	5.79 (5.01, 6.69)	<0.001
23A	474	28591.7	296	4882.0	5.86 (4.88, 7.03)	<0.001
23B	485	5988.2	312	370.5	16.16 (12.03, 21.72)	<0.001
24F	478	11102.2	297	2771.8	4.01 (3.40, 4.72)	<0.001
31	484	46163.7	311	2563.0	18.01 (15.09, 21.50)	<0.001
35B	482	40102.8	311	7812.5	5.13 (4.45, 5.93)	<0.001

**: N = 527 for V116 and N= 347 for PPSV23, where N = Number of participants who were vaccinated.*
a: n = Number of participants contributing to the analysis.
b: GMTs, GMT ratios, 95% CIs and p-values are estimated using cLDA model.
Source: Table 14.2-3 in CSR P013V116 for study V116-013, p.200.

Reviewer's Comment:

1. *Primary immunogenicity analyses based on two primary hypotheses, H1 and H2, were also conducted using FAS as a supportive analysis. The results in FAS were consistent with those observed in the PP population.*
2. *Noninferiority criteria for all 12 common serotypes and superiority criteria for all 9 unique serotypes in V116 were met.*

6.1.11.2 Analyses of Secondary Endpoints

Table **8** shows that results from between-group comparisons of IgG GMCs for all serotypes at 30 days post-vaccination were, in general, consistent with results observed in primary analysis on OPA GMTs. Point estimates for GMC ratios and corresponding 95% CI are given in Table 8.

Table 8: Analysis of Post-Vaccination IgG GMCs (Per-Protocol Population)

Serotype	**V116* n[a]**	**V116 GMC[b]**	**PPSV23* n[a]**	**PPSV23 GMC[b]**	**GMC Ratio[b] (V116/PPSV23) (95% CI[b])**
Common Serotype					
3	462	1.56	299	1.88	0.83 (0.72, 0.95)
7F	462	7.33	299	7.37	0.99 (0.86, 1.15)
8	462	13.68	299	17.86	0.77 (0.67, 0.87)
9N	462	7.11	299	9.41	0.76 (0.65, 0.88)
10A	462	8.47	299	4.69	1.81 (1.50, 2.17)
11A	462	7.47	299	4.32	1.73 (1.49, 2.01)
12F	462	1.78	299	1.38	1.28 (1.07, 1.54)
17F	462	14.75	298	6.13	2.41 (2.06, 2.81)
19A	462	13.50	299	15.97	0.85 (0.71, 1.00)

Serotype	V116* n[a]	V116 GMC[b]	PPSV23* n[a]	PPSV23 GMC[b]	GMC Ratio[b] (V116/PPSV23) (95% CI[b])
20A	462	9.09	299	5.75	1.58 (1.34, 1.87)
22F	462	14.20	299	10.23	1.39 (1.17, 1.64)
33F	462	6.75	299	9.34	0.72 (0.61, 0.85)
Unique Serotype					
6A	462	11.98	299	6.25	1.92 (1.59, 2.31)
15A	462	12.00	299	1.24	9.67 (8.07, 11.60)
15C	462	13.54	299	2.55	5.32 (4.35, 6.50)
16F	462	2.35	299	0.18	12.97 (11.04, 15.24)
23A	462	7.17	299	1.05	6.84 (5.56, 8.43)
23B	462	6.47	299	1.29	5.03 (4.18, 6.04)
24F	462	2.39	299	0.22	10.72 (8.83, 13.01)
31	462	4.67	299	0.27	17.38 (14.92, 20.24)
35B	462	8.96	299	0.89	10.10 (8.72, 11.70)

**: N = 527 for V116 and N= 347 for PPSV23, where N = Number of participants who were vaccinated.*
a: n = Number of participants contributing to the analysis.
b: GMCs, GMC ratios and 95% CIs are estimated using cLDA model.
Source: Table 14.2-5 and Table 14.2-6 in CSR P013V116 for study V116-013, p.206 and p.207, respectively.

Reviewer's Comment:

- *Please note that for serotype 6A, unique to V116, the lower bound and the point estimate for the GMC ratio (V116/PPSV23) were less than 2.0 (Table 8). This is different from what was observed in primary analyses using OPA GMT ratio (Table 7).*
- *For both OPA and IgG responses in the PP set, serotype-specific GMFRs from baseline to 30 days postvaccination were generally comparable in both intervention groups for the 12 common serotypes. In particular, the point estimates of serotype-specific OPA GMFRs from baseline to 30 days postvaccination were higher in V116 group for serotypes 7F, 9N, 10A, 11A, 12F, 17F, 20A, 22F and 33F.*
- *Based on the PP set, while the proportions of participants with a ≥4-fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination were generally comparable in both intervention groups for the 12 common serotypes, proportions of participants with ≥4-fold rise in OPA responses seemed to be higher in V116 than PPSV23 for serotypes 10A, 11A, 17F, 20A, 22F, and 33F.*
- *For both OPA and IgG responses in the PP set, the serotype-specific GMFRs and the proportions of participants with a ≥4-fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination were higher in the V116 group for the 9 serotypes unique to V116, compared to the PPSV23 group.*

6.1.11.3 Subpopulation Analyses

Subgroup analyses were carried out based on following subgroups where more than 5% of the total vaccinated participants were in each intervention group within that subgroup.

- Age (2 to <6 YOA, 6 to <12 YOA and 12 to 17 YOA),
- Sex (Female and Male),

- Race (American Indian or Alaska Native Participants, Asian, Black or African American, Multiple and White),
- Ethnicity (Hispanic or Latino and Not Hispanic or Latino),
- Number of increased risk-conditions (single increased-risk condition),
- Type of increased risk-conditions (chronic heart disease only, chronic kidney disease only, chronic liver disease only, chronic lung disease only, and diabetes mellitus only),
- Prior pneumococcal vaccination status (prior PCV7 alone, prior PCV10 only, and prior PCV13 only), and
- Primary PCV regimen (3+1 regimen and 2+1 regimen).

There were no notable differences within each of the subgroup categories analyzed as assessed by OPA GMTs at 30 days postvaccination for all 21 serotypes contained in V116. No notable trends were observed.

Reviewer's Comment: Results from the subgroup analyses, in general, were consistent with those observed in the overall PP population for OPA responses with the following exceptions –

- *The lower bounds of 95% CIs for GMT ratio for serotype 6A unique to V116 were less than 2 for most of the subgroups – 12 to 17 YOA (95% CI: [1.45, 3.53]), Asian (95% CI: [1.27, 4.52]), Black or African American (95% CI: [1.27, 6.33]), Not Hispanic or Latino (95% CI: [1.79, 3.00]), chronic kidney disease only (95% CI: [1.38, 5.99]), chronic liver disease only (95% CI: [1.05, 6.99]), diabetes mellitus only (95% CI: [1.79, 5.15]), prior PCV7 alone (95% CI: [0.50, 3.31]), prior PCV13 alone (95% CI: [1.79, 3.02]), and 3+1 primary PCV regimen (95% CI: [1.71, 3.31]).*
- *Besides serotype 6A, serotypes 15C, 23A, 23B, 24F, and 35B unique to V116 had lower bounds of 95% CI for GMT ratios as less than 2 for subgroups – Black or African American (95% CI for 23B: [1.11, 10.19]), chronic kidney disease only (95% CI for 24F: [1.51, 6.67]), and prior PCV7 alone (95% CI for 15C: [1.90, 10.52], for 23A: [1.87, 13.67], for 24F: [1.06, 2.28], and for 35B: [1.90, 5.85]).*
- *Further, the lower bounds of 95% CI of GMT ratios were ≤0.5 in few subgroups for serotype 19A. For serotype 19A, the 95% CI of GMT ratio was [0.46, 2.59] in Black or African American, [0.50, 1.80] in chronic liver disease only, and [0.34, 1.25] in prior PCV7 alone. Also, for prior PCV7 alone subgroup, 95% CI of GMT ratio was [0.47, 1.62] for serotype 8.*

6.1.11.4 Dropouts and/or Discontinuations

Table 3 shows the study discontinuation rates and their reasons. The rates were similar between the two groups (1.7% in both groups). The proportion of participants included in the Per-Protocol analysis set by timepoints was similar between the two groups (Table 4).

6.1.11.5 Exploratory and Post Hoc Analyses

V116 elicited immune responses to serotype 6C (cross-reactive to serotype 6A) and serotype 15B (cross-reactive to serotype 15C), as assessed by OPA titers and IgG

concentrations for serotypes within a serogroup in V116 at 30 days postvaccination (Table 9).

Table 9: Summary of OPA and IgG Antibody Responses for Serotypes 6C and 15B (Per-Protocol Population)

Serotype / Endpoint	**V116 (N = 527) n***	**V116 Response (95% CI[a])**	**PPSV23 (N = 347) n***	**PPSV23 Response (95% CI[a])**
OPA response for 6C				
GMT (Day 1)	432	738.9 (624.2, 874.8)	283	763.3 (620.5, 938.8)
GMT (Day 30)	443	7129.9 (6247.7, 8136.5)	278	2549.6 (2216.4, 2932.8)
GMFR	389	9.1 (7.5, 10.9)	247	2.9 (2.4, 3.5)
%≥4-fold rise	389	60.2% (234/389) (55.1%, 65.1%)	247	30.0% (74/247) (24.3%, 36.1%)
OPA response for 15B				
GMT (Day 1)	401	370.7 (306.2, 448.9)	256	375.8 (295.7, 477.6)
GMT (Day 30)	435	18302.6 (16069.2, 20846.4)	272	4879.8 (4027.1, 5913.1)
GMFR	353	41.6 (33.2, 52.1)	221	10.7 (8.2, 13.9)
%≥4-fold rise	353	86.1% (304/353) (82.1%, 89.6%)	221	65.6% (145/221) (58.9%, 71.9%)
IgG response for 6C				
GMT (Day 1)	413	0.39 (0.35, 0.44)	276	0.46 (0.39, 0.54)
GMT (Day 30)	408	4.24 (3.69, 4.88)	253	1.28 (1.07, 1.54)
GMFR	359	7.4 (6.3, 8.6)	230	2.2 (1.9, 2.6)
%≥4-fold rise	359	61.0% (219/359) (55.7%, 66.1%)	230	22.6% (52/230) (17.4%, 28.6%)
IgG response for 15B				
GMT (Day 1)	413	0.59 (0.50, 0.70)	276	0.60 (0.49, 0.74)
GMT (Day 30)	408	10.84 (9.42, 12.47)	253	7.30 (6.09, 8.76)
GMFR	359	17.3 (15.0, 20.0)	230	10.8 (9.0, 13.1)
%≥4-fold rise	359	82.7% (297/359) (78.4%, 86.5%)	230	76.5% (176/230) (70.5%, 81.8%)

**: N=Number of participants randomized and vaccinated; n=Number of participants contributing to the analysis.*
a: For the continuous endpoints, the within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.

Source: Adapted from Table 14.2-9 and Table 14.2-10 in CSR P013V116 for study V116-013, p.230 and p.232, respectively.

The applicant analyzed the ratio of OPA GMTs for serotype 15B post hoc, using the same methodology conducted for the primary immunogenicity analyses. The results indicated that the estimated GMT ratio (V116/PPSV23) for serotype 15B was 3.78 with 95% CI of (3.03, 4.73). This post hoc analysis shows that V116 elicited an immune response to the cross-reactive serotype 15B that met the pre-specified noninferiority criterion for the set of common serotypes between V116 and PPSV23 (lower bound of 95% CI of GMT ratio [V116/PPSV23]>0.5).

Reviewer's Comment: This post-hoc analysis for the ratio of OPA GMTs for serotype 15B is acceptable as this analysis was used as an exploratory analysis only, and all the null hypothesis for primary endpoints were rejected.

6.1.12 Safety Analyses

This section summarizes the main safety analysis results. The safety analyses were descriptive, and no hypotheses were tested. The safety analyses were conducted on APaT population.

The proportions of participants with solicited systemic AEs were generally comparable between intervention groups. The proportion of participants with any solicited injection-site AEs was higher in the V116 group (72.3%) compared with the PPSV23 group (58.2%). The proportion of participants with solicited injection-site pain was higher in the V116 group (67.7%) compared with the PPSV23 group (54.5%). Solicited local and systemic AEs from Day 1 through Day 5 postvaccination, by maximum intensity, are summarized in Table 10. Most solicited AEs were mild or moderate in intensity. Overall, the proportions of participants with solicited AEs by maximum intensity grade were generally comparable between intervention groups. The most frequently reported injection site and systemic AEs were injection site pain (67.7% in V116 and 54.5% in PPSV23) and fatigue (20.1% in V116 and 21.0% in PPSV23). Of the participants with solicited AEs, the majority had events of short duration (≤3 days). One participant in each intervention group had an event (injection-site erythema in the V116 group and injection-site pain in the PPSV23 group) with duration >10 days.

Table 10: Participants with Solicited Adverse Events by Maximum Intensity Grade (All Participants as Treated Population)

Solicited AE / Intensity	**V116 (N = 527) n**	**V116 (N = 527) %**	**PPSV23 (N = 347) n**	**PPSV23 (N = 347) %**
Solicited injection site AE	381	72.3	202	58.2
Injection site erythema				
Any	128	24.3	57	16.4
Mild	79	15.0	45	13.0
Moderate	40	7.6	10	2.9
Severe	9	1.7	2	0.6

Solicited AE / Intensity	**V116 (N = 527) n**	**V116 (N = 527) %**	**PPSV23 (N = 347) n**	**PPSV23 (N = 347) %**
Injection site pain				
Any	357	67.7	189	54.5
Mild	243	46.1	127	36.6
Moderate	109	20.7	55	15.9
Severe	5	0.9	7	2.0
Injection site swelling				
Any	99	18.8	63	18.2
Mild	64	12.1	49	14.1
Moderate	26	4.9	13	3.7
Severe	9	1.7	1	0.3
Solicited Systemic AE	241	45.7	140	40.3
Arthralgia				
Any	23	4.4	19	5.5
Mild	20	3.8	11	3.2
Moderate	2	0.4	7	2.0
Severe	1	0.2	1	0.3
Fatigue				
Any	106	20.1	73	21.0
Mild	70	13.3	43	12.4
Moderate	32	6.1	28	8.1
Severe	4	0.8	2	0.6
Headache				
Any	90	17.1	53	15.3
Mild	66	12.5	40	11.5
Moderate	24	4.6	13	3.7
Irritability				
Any	61	11.6	38	11.0
Mild	37	7.0	25	7.2
Moderate	23	4.4	12	3.5
Severe	1	0.2	1	0.3
Malaise				
Any	70	13.3	32	9.2
Mild	43	8.2	16	4.6
Moderate	27	5.1	15	4.3
Severe	0	0.0	1	0.3
Myalgia				
Any	33	6.3	18	5.2
Mild	19	3.6	10	2.9
Moderate	14	2.7	8	2.3
Pyrexia				
Any	24	4.6	20	5.8
Mild	14	2.7	7	2.0

Solicited AE / Intensity	**V116 (N = 527) n**	**V116 (N = 527) %**	**PPSV23 (N = 347) n**	**PPSV23 (N = 347) %**
Moderate	8	1.5	12	3.5
Severe	2	0.4	1	0.3
Somnolence				
Any	50	9.5	32	9.2
Mild	38	7.2	18	5.2
Moderate	9	1.7	14	4.0
Severe	3	0.6	0	0.0
Urticaria				
Any	14	2.7	6	1.7
Mild	9	1.7	5	1.4
Moderate	5	0.9	1	0.3

Source: Adapted from Table 14.2-11 in CSR P013V116 for study V116-013, p.331.

The Proportions of participants with unsolicited AEs reported from Day 1 through Day 30 postvaccination were comparable between two intervention groups. A total of 162 (30.7%) in V116 and 97 (28.0%) in PPSV23 reported at least one unsolicited AEs. Of these, 5.7% (30/527) in V116 and 5.2% (18/347) in PPSV23 groups experienced vaccine-related unsolicited AEs.

The Proportions of participants with SAEs reported from Day 1 throughout the study were also comparable between two groups. These proportions were 5.5% (29/527) in V116 and 7.2% (25/347) in PPSV23. Of these, 3 participants were considered to be experiencing vaccine-related SAEs by the investigator – 1 participant with an SAE of syncope in V116, and 2 participants with an SAE of anaphylactic reaction in PPSV23.

No deaths were reported in the V116 group. One death due to septic shock and one death due to cardiopulmonary failure were reported in the PPSV23 group within 2-month postvaccination. None of these deaths were considered vaccine related by the investigator.

Reviewer's Comment:

- *An overall summary of safety and summary of solicited AEs were also performed based on subgroups, i.e., age, sex, race, ethnicity, number of increased-risk conditions, type of increased risk conditions, prior pneumococcal vaccination status and prior PCV primary regimen. The results were comparable between intervention groups across subgroups.*
- *All solicited AE results were verified using SDTM.CE dataset.*

7. Integrated Overview of Efficacy

No integrated analysis of efficacy is considered in this sBLA.

8. Integrated Overview of Safety

No integrated analysis of safety is considered in this sBLA.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The hypotheses testing for the primary immunogenicity endpoints showed that V116 met the predefined noninferiority criteria compared to PPSV23 for all 12 common serotypes and met the predefined superiority criteria compared to PPSV23 for all 9 serotypes unique to V116, based on OPA GMT ratios at 30 days postvaccination.

Overall, the proportions of participants with one or more AEs were generally comparable between two intervention groups. The proportions of participants with solicited systemic AEs were also comparable between intervention groups (45.7% in the V116 group and 40.3% in the PPSV23 group). The proportion of participants with solicited injection-site AEs was higher in the V116 group (72.3%) compared to the PPSV23 group (58.2%). Specially, the proportion of participants with injection site erythema and injection site pain was higher in the V116 group (24.3% and 67.7%, respectively) compared with the PPSV23 group (16.4% and 54.5%, respectively). Among the participants with solicited AEs, the majority had events that were of short duration (≤3 days) and most of them had intensity of mild or moderate in both intervention groups. The proportions of participants reporting any SAE during the study (approximately 6 months) were 5.5% in the V116 group and 7.2% in the PPSV23 group. Three SAEs were assessed as related to the study vaccine by the investigator: a case of syncope in the V116 group and two cases of anaphylactic reactions in the PPSV23 group. These three cases were reported on Day 1 of vaccination. There were no deaths in the V116 group. Two deaths (1 due to septic shock and 1 due to cardiopulmonary failure) were reported in the PPSV23 group and neither were considered to be vaccine related by the investigator.

Results presented in this review related to the primary safety and immunogenicity and secondary immunogenicity endpoints were verified using R 4.5.1.

10.2 Conclusions and Recommendations

Considering the totality of the evidence, based on my review of the statistical analyses and results presented in this BLA supplement, the data support that CAPVAXIVE elicited immune responses in children and adolescents aged 2 to less than 18 years with increased risk for pneumococcal disease due to chronic conditions who had completed a primary pneumococcal vaccination regimen. I defer to the clinical reviewer on the safety conclusions.