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Statistical Review and Evaluation	
Application Type	BLA (Original Application)
STN	125814/0
CBER Received Date	Oct 18, 2023
PDUFA Goal Date	June 17, 2024
Division / Office	DVRPA /OVR
Committee Chair	Tatiana ClarodaSilva
Clinical Reviewer(s)	Sarah Benke, Nicholas Geagan
Project Manager	Margaret Dayhoff-Brannigan, Hilda Grabczewski, Diana Oram, Debra Vause
Priority Review	Yes
Reviewer Name(s)	Trinetri Ghosh, Mathematical Statistician, VEB/DB/OBPV
Supervisory Concurrence	Sang Ahnn, Concurring Reviewer, VEB/DB/OBPV Tsai-Lien Lin, Brach Chief, VEB/DB/OBPV Shiowjen Lee, Deputy Division Director, 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 Forms and Routes of Administration	A single 0.5mL solution intramuscularly
Dosing Regimen	Single dose
Indication(s) and Intended Populations	For the prevention of invasive disease and pneumonia 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) in adults 18 years of age and older

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GLOSSARY

ABCs	Active Bacterial Core surveillance
AE	Adverse event
APaT	All participants as treated
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome
	Coronavirus 2
CRF	Case report form
CSR	Clinical study report
deOAc	de-O-acetylated
EMA	European Medicines Agency
ERC	Ethics Review Committee
EU	European Union
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GPvP	Good Pharmacovigilance Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IPD	Invasive pneumococcal disease
IRT	Interactive response technology
iSAP	Integrated Statistical Analysis Plan
IRB	Institutional Review Board
M&N	Miettinen and Nurminen
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Merck Sharp & Dohme LLC, Rahway, NJ, USA
OPA	Opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
PCV7	Pneumococcal 7-valent conjugate vaccine (Prevnar™)
PCV10	Pneumococcal 10-valent conjugate vaccine (Synflorix™)
PCV13	Pneumococcal 13-valent conjugate vaccine (Prevnar 13™)
PCV15	Pneumococcal 15-valent conjugate vaccine (VAXNEUVANCE™)
PCV20	Pneumococcal 20-valent conjugate vaccine (PREVNAR 20™)
PnPs	Pneumococcal polysaccharide
PPSV	Pneumococcal polysaccharide vaccine
PPSV	Pneumococcal polysaccharide, polyvalent (23-valent)

	(PNEUMOVAX™23)
PP	Per-protocol
PT	Preferred term
QA	Quality assurance
QIV	Quadrivalent influenza vaccine
QTL	Quality tolerance limits
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan
SDR	Source data review
SDV	Source document verification
SOC	System organ class
SOP	Standard operating procedure
sSAP	Supplemental statistical analysis plan
US	United States
V116	Pneumococcal 21-valent conjugate vaccine
WOCBP	Woman/women of childbearing potential
YOA	Years of Age

1. Executive Summary

Merck Sharp & Dohme LLC submitted an original Biologics License Application (BLA; STN 125814/0) on October 18, 2023 to seek licensure of V116 for an active immunization for the prevention of invasive disease and pneumonia 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 adults 18 years of age and older. This application is supported by the data from four completed Phase 3 studies (V116-003, V116-004, V116-005, and V116-006). This statistical review focuses on the immunogenicity and safety data from adults 18 years of age and older. Brief overviews for these four studies are given below.

V116-003:

V116-003 was a double-blind, randomized, active comparator-controlled, multisite study to evaluate the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-naïve adults ≥ 18 years of age, conducted in Australia, Belgium, Chile, Germany, Republic of Korea, New Zealand, Puerto Rico, Sweden, Taiwan, Turkey and US. In Cohort 1, 2362 pneumococcal vaccine-naïve adults ≥ 50 years of age were randomized in a 1:1 ratio, and in Cohort 2, 301 pneumococcal vaccine-naïve adults 18 to 49 YOA were randomized in a 2:1 ratio to receive a single dose of V116 or PCV20, respectively. Individuals 18 to 49 YOA were included to support immunobridging analyses.

Prespecified noninferiority criteria for V116 to PCV20 (lower bound (LB) of the 2-sided 95% confidence interval of the OPA GMT ratio [V116/PCV20] >0.5) in Cohort 1 were met for each of the 10 common serotypes at 30 days postvaccination. Prespecified superiority criteria for V116 to PCV20 (LB of the 2-sided 95% confidence interval of the OPA GMT ratio [V116/PCV20] >2) in Cohort 1 were met for 10 of 11 serotypes unique to V116 at 30

days postvaccination. LB of the 2-sided 95% CI of the OPA GMT ratio for 15C was 1.77. Similarly in Cohort 1, except serotype 15C, V116 met the predefined criteria for superiority to PCV20 (LB of the 2-sided 95% CI of $[V116 - PCV] > 0.1$) for the remaining 10 unique serotypes in V116 based on the proportion of participant with a ≥ 4 -fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination. Prespecified immunobridging success criteria comparing GMTs based on participants 18 to 49 YOA who received V116 in Cohort 2 to GMTs based on participants 50 to 64 YOA who received V116 in Cohort 1 were met for all 21 serotypes (LB of the 2-sided 95% CI of the OPA GMT ratio $[V116_{18 \text{ to } 49 \text{ YOA}}/V116_{50 \text{ to } 64 \text{ YOA}}] > 0.5$) at 30 days postvaccination. Higher GMT values were observed in 18 to 49 YOA participants than 50 to 64 YOA participants who received V116.

The proportions of participants with AEs were generally comparable between the V116 and PCV20 groups. The most frequently reported AEs in both intervention groups were injection-site pain, fatigue, headache, injection-site erythema, injection-site swelling, and myalgia. The proportions of participants with solicited AEs were generally comparable between the V116 and PCV20 intervention groups, except for injection-site pain, which is lower in the V116 intervention group compared with the PCV20 intervention group in Cohort 1. 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. The proportions of participants with SAEs were low ($\leq 3\%$) and generally comparable between the V116 and PCV20 intervention groups. No vaccine-related SAEs were reported. There were 6 deaths reported in Cohort 1 (4 in the V116 intervention group and 2 in the PCV20 intervention group) and none were considered related to study intervention. There were no deaths reported in Cohort 2.

V116-004:

V116-004 was a randomized, active comparator-controlled, parallel-group, multisite, double-blind, lot-to-lot consistency study conducted in Austria, Canada, Denmark, Finland, Israel, Poland, Spain, and US to evaluate the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-naïve adults 18 to 49 YOA. A total of 2162 participants were randomized in a 1:1:1:1 ratio to receive a single dose of either V116 Lot 1, V116 Lot 2, V116 Lot 3 or PPSV23.

All 3 lots of V116 met equivalence criteria as assessed by serotype specific OPA GMTs at 30 days postvaccination for all serotypes included in V116. The 2-sided 95% CI of the serotype-specific OPA GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all serotypes included in V116.

The overall proportions of participants with AEs and solicited AEs were comparable across the 3 lots of V116. The overall proportions of participants with AEs were generally comparable between the V116 (combined lots) and the PPSV23 intervention groups (80.4 % vs 74.9%). The most frequently reported ($\geq 5\%$) AEs in all intervention groups were injection-site pain, fatigue, headache, myalgia, injection-site erythema, and injection-site swelling. The proportions of participants with solicited AEs were generally comparable between the V116 (combined lots) and the PPSV23 intervention groups, except for

injection-site pain, which was higher in the V116 (combined lots) compared with the PPSV23 group (73.3% vs. 60.6%). Of the participants with solicited AEs, the majority had events that were of short duration (≤ 3 days) and had a maximum intensity of mild or moderate. The proportion of participants with SAEs was low ($\leq 1\%$) and comparable between the V116 (combined lots) and the PPSV23 intervention groups. No vaccine-related SAEs were reported. There was 1 death reported in the PPSV23 intervention group. The event was considered not related to study vaccine.

V116-005:

V116-005, a randomized, parallel-group, multisite, double-blind study of V116, was conducted in 56 US sites to evaluate the safety, tolerability, and immunogenicity of V116 when administered concomitantly with QIV in adults ≥ 50 YOA. A total of 1080 participants were randomly assigned in a 1:1 ratio to receive either V116 administered concomitantly with QIV or V116 administered sequentially with QIV. Randomization was stratified by age at enrollment (50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥ 85 years) and by prior pneumococcal vaccination status (PCV13- and PPSV23-naïve, prior receipt of PCV13 only, prior receipt of PPSV23 only, and prior receipt of both PCV13 and PPSV23). Exactly 50% of participants were ≥ 65 years of age and approximately 70.6% of participants were naïve to PCV13 and PPSV23.

V116 administered concomitantly with QIV met the criterion for noninferiority to V116 administered sequentially with QIV (LB of the 2-sided 95% CI of the OPA GMT ratio [concomitant/sequential] >0.5) for 20 of 21 pneumococcal serotypes in V116 at 30 days postvaccination, except for Serotype 23B. QIV administered concomitantly with V116 met the criterion for noninferiority to QIV administered sequentially with V116 (LB of the 2-sided 95% CI of the GMT ratio [concomitant/sequential] >0.67) for 3 of 4 influenza strains in QIV at 30 days postvaccination, except for the strain A/H3N2.

The overall proportions of participants with AEs were generally comparable between the two groups. In both intervention groups, the most frequently reported AEs were the solicited AEs of injection-site pain, fatigue, headache, myalgia, injection-site swelling, and injection-site erythema. The proportions of participants with solicited AEs were generally comparable between intervention groups. Of the participants with solicited AEs, the majority had events that were mild or moderate in maximum intensity and of short duration (≤ 3 days) in both intervention groups. The proportions of participants with SAEs were low ($<4\%$) in both intervention groups. One vaccine-related SAE of bronchospasm was reported in the sequential group and occurred within 30 minutes following vaccination 2, i.e., vaccination with V116. There were 3 deaths, 1 in the concomitant intervention group, and 2 in the sequential intervention group. None were considered vaccine related.

V116-006:

V116-006 was conducted in Canada, France, Israel, Italy, Japan, Republic of Korea, Spain, Taiwan, and US to evaluate the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-experienced adults ≥ 50 YOA. In Cohort 1, 350 participants who had been vaccinated with PPSV23 ≥ 1 year prior to enrollment were randomized in a 2:1 ratio to receive either V116 or PCV15 on Day 1. In Cohort 2, 261 participants who had

been vaccinated with PCV13 ≥ 1 year prior to enrollment were randomized in a 2:1 ratio to receive either V116 or PPSV23 on Day 1. Cohort 1 and Cohort 2 were double-blind, parallel group, and active comparator-controlled. In Cohort 3, 106 Participants who had been vaccinated with PCV13+PPSV23, PCV15+PPSV23, PCV15, PCV20, or PPSV23+PCV13 ≥ 1 year prior to enrollment received V116 on Day 1. Cohort 3 was open-label and single group.

Across all 3 cohorts, descriptive summaries and within-group 95% CIs of serotype-specific OPA GMTs at 30 days postvaccination were provided. In Cohort 1, V116 elicited immune responses were generally comparable to PCV15 for the 6 common serotypes and higher than PCV15 for the 15 serotypes unique to V116, as assessed by OPA GMTs at 30 days postvaccination. In Cohort 2, V116 elicited immune responses were generally comparable to PPSV23 for the 12 common serotypes and higher than PPSV23 for the 9 serotypes unique to V116, as assessed by OPA GMTs at 30 days postvaccination.

The proportions of participants with AEs were generally comparable among participants who received V116, PCV15, or PPSV23, regardless of pneumococcal vaccination history. The proportions of participants with solicited injection-site and solicited systemic AEs were generally comparable among participants who received V116, PCV15, or PPSV23, regardless of pneumococcal vaccination history. Across all 3 cohorts, the majority of participants with solicited AEs in each intervention group had events that were of short duration (≤ 3 days) and had a maximum intensity of mild or moderate. The proportions of participants with SAEs were low ($< 4\%$) and generally comparable between intervention groups. One vaccine-related SAE of injection-site cellulitis was reported for a participant in Cohort 1 who received V116. There were no deaths reported.

Based on my review of the statistical analyses and results presented in the original BLA, I recommend approval of V116 for the proposed indication in adults ≥ 18 years of age.

2. Clinical and Regulatory Background

This submission was to seek licensure of pneumococcal 21-valent conjugate vaccine (V116) for an active immunization for the prevention of invasive disease and pneumonia 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 adults 18 years of age and older based on four Phase 3 studies.

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

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

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 from adults ≥ 18 years in four Phase 3 studies, V116-003, V116-004, V116-005 and V116-006.

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

The following documents submitted to the original BLA are reviewed.

STN 125814/0.0:

- Section 2.2 Introduction
- Section 5.3.5.1
 - P003V116 (Study V116-003)
 - Clinical Study Report
 - 16.1.1 Protocol and/or Amendment
 - 16.1.9 Documentation of statistical methods and interim analysis
 - Analysis Datasets
 - Tabulation Datasets
 - P004V116 (Study V116-004)
 - Clinical Study Report
 - 16.1.1 Protocol and/or Amendment
 - 16.1.9 Documentation of statistical methods and interim analysis
 - Analysis Datasets
 - Tabulation Datasets
 - P005V116 (Study V116-005)
 - Clinical Study Report
 - 16.1.1 Protocol and/or Amendment
 - 16.1.9 Documentation of statistical methods and interim analysis
 - Analysis Datasets
 - Tabulation Datasets
 - P006V116 (Study V116-006)
 - Clinical Study Report
 - 16.1.1 Protocol and/or Amendment
 - 16.1.9 Documentation of statistical methods and interim analysis
 - Analysis Datasets
 - Tabulation Datasets

STN 125814/0.16:

- Section 1.11.3 Clinical Information Amendment

5.3 Table of Studies/Clinical Trials

Table 1 contains a summary of V116-003, V116-004, V116-005 and V116-006.

Table 1: Studies submitted to STN 125814/0

Study Number (Status) Number of Study Sites (Location)	Design	Number of Participants by Intervention Group ^a	Study Population	Primary Endpoints
V116-003 (complete d) 112 sites (Australia, Belgium, Chile, Germany, Republic of Korea, New Zealand, Puerto Rico, Sweden, Taiwan, Turkey, US)	Double-blind, randomized, active-comparator study to evaluate the safety, tolerability and immunogenicity of V116	<p><u>Cohort 1:</u> Randomization ratio, V116:PCV20 = 1:1</p> <p>V116: Randomized 1181, Vaccinated 1179, Completed 1160</p> <p>PCV20: Randomized 1181, Vaccinated 1177, Completed 1152</p> <p><u>Cohort 2:</u> Randomization ratio V116:PCV20 = 2:1</p> <p>V116: Randomized 201, Vaccinated 200, Completed 195</p> <p>PCV20: Randomized 100,</p>	<p><u>Cohort 1:</u> Pneumococcal vaccine-naïve adults ≥50 YOA</p> <p>Sex: 999 M/1357 F</p> <p>Median age: 65 Years</p> <p>Age: 50 to 64 YOA 1176, 65 to 74 YOA 928, 75 to 84 YOA 225, ≥85 YOA 27</p> <p><u>Cohort 2:</u> Pneumococcal vaccine-naïve adults 18 to 49 YOA</p> <p>Sex: 99M/201 F</p> <p>Median age: 35 years</p>	<p>1. Solicited injection-site AEs, solicited systemic AEs, vaccine-related SAEs (Cohort 1 and Cohort 2)</p> <p>2. Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116 (Cohort 1)</p> <p>3. Proportion of participants who achieved ≥4-fold rise (baseline to 30 days postvaccination) in OPA responses for the serotypes unique to V116 (Cohort 1)</p>

Study Number (Status) Number of Study Sites (Location)	Design	Number of Participants by Intervention Group ^a	Study Population	Primary Endpoints
		Vaccinated 100, Completed 96		4. Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116 (Cohort 2)
V116-004 (completed) 72 sites (Austria, Canada, Denmark, Finland, Israel, Poland, Spain, US)	Double-blind, randomized, active-comparator study to evaluate the safety, tolerability, and immunogenicity of V116	<p>Randomization ratio, V116 Lot 1: V116 Lot 2: V116 Lot 3: PPSV23 = 1:1:1:1</p> <p><u>V116 Lot 1:</u> Randomized 541, Vaccinated 539, Completed 521</p> <p><u>V116 Lot 2:</u> Randomized 540, Vaccinated 538, Completed 520</p> <p><u>V116 Lot 3:</u> Randomized 541, Vaccinated 540, Completed 525</p> <p><u>PPSV23:</u> Randomized 540, Vaccinated 540,</p>	<p>Pneumococcal vaccine-naïve adults 18 to 49 YOA</p> <p>Sex: 914 M/1243 F</p> <p>Median age: 35 years</p>	<p>1. Solicited injection-site AEs, solicited systemic AEs, vaccine-related SAEs</p> <p>2. Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116.</p>

Study Number (Status) Number of Study Sites (Location)	Design	Number of Participants by Intervention Group ^a	Study Population	Primary Endpoints
		Completed 526		
V116-005 (complete d) 56 sites (US)	Double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of V116 when administered concomitantly with influenza vaccine	<p>Randomized ratio, Concomitant: Sequential = 1:1</p> <p><u>Concomitant group:</u> Randomized 540, Vaccinated with QIV 536, Vaccinated with V116: 534, Received placebo 552, Completed 510</p> <p><u>Sequential group:</u> Randomized 540, Vaccinated with QIV 536, Received placebo 535, Vaccinated with V116 518, Completed 507</p>	<p>Pneumococcal vaccine-naïve and vaccine-experienced (PCV13 and/or PPSV23) adults ≥50 YOA</p> <p>Sex: 488 M/ 584 F</p> <p>Median age: 64.5 years</p> <p>Age: 50 to 64 YOA 536, 65 to 74 YOA 416, 75 to 84 YOA 107, ≥85 YOA 13</p> <p><u>Prior pneumococcal vaccination status:</u> PCV13 and PPSV23 naïve 757, Prior receipt of PCV13 only 58,</p>	<p>1. Solicited injection-site AEs, solicited systemic AEs, Vaccine-related SAEs</p> <p>2. Serotype-specific OPA GMTs at 30 days postvaccination with V116</p> <p>3. Strain-specific HAI GMTs at 30 days postvaccination with QIV</p>

Study Number (Status) Number of Study Sites (Location)	Design	Number of Participants by Intervention Group ^a	Study Population	Primary Endpoints
			Prior receipt of PPSV23 only 140, Prior receipt of PCV13 and PPSV23 117	
V116-006 (complete d) 51 sites (Canada, France, Israel, Italy, Japan, Republic of Korea, Spain, Taiwan, US)	<p>Safety, tolerability and immunogenicity of V116 in pneumococcal vaccine-experienced adults</p> <p><u>Cohort 1</u> (prior PPSV23): Double-blind, randomized, active comparator</p> <p><u>Cohort 2</u> (prior PCV13): Double-blind, randomized, active comparator</p> <p><u>Cohort 3</u> (prior PCV13+PPSV23, PCV15+PPSV23+PCV15, PCV20, PPSV23+PCV13): Open-label, single arm</p>	<p><u>Cohort 1</u>: Randomization ratio, V116:PCV15=2:1</p> <p>V116: Randomization 231, Vaccinated 229, Completed 229</p> <p>PCV15: Randomized 119, Vaccinated 119, Completed 118</p> <p><u>Cohort 2</u>: Randomized ratio, V116:PPSV23=2:1</p> <p>V116: Randomized 176, Vaccinated 174, Completed 173</p> <p>PPSV23:</p>	<p>Pneumococcal vaccine-experienced adults ≥ 50 YOA</p> <p><u>Cohort 1</u>: Sex: 171 M / 177 F</p> <p>Median age: 69 years</p> <p>Age: 50 to 64 YOA 73, ≥ 65 YOA 275</p> <p>Time since last pneumococcal vaccination: 1 to 4 years 162, 5 to 9 years 130, ≥ 10 years 56</p>	<p>1. Solicited injection-site AEs, solicited systemic AEs, vaccine-related SAEs</p> <p>2. Serotype-specific OPA GMTs at 30 days postvaccination for all serotypes contained in V116</p>

Study Number (Status) Number of Study Sites (Location)	Design	Number of Participants by Intervention Group ^a	Study Population	Primary Endpoints
		<p>Randomized 85, Vaccinated 85, Completed 85</p> <p><u>Cohort 3:</u> V116: Randomized 106, Vaccinated 105, Completed 105</p>	<p><u>Cohort 2:</u> Sex: 110 M / 149 F</p> <p>Median age: 66 years</p> <p>Age: 50 to 64 YOA 119, ≥65 YOA 140</p> <p>Time since last pneumococcal vaccination: 1 to 4 years 210, 5 to 9 years 51, ≥10 years 7</p> <p>Cohort 3: Sex: 50 M / 55 F</p> <p>Median age: 71 years</p>	

Source: Adapted from Table 2.5-AdultPCV: 1 in Section 2.5 Clinical Overview.

^a : Number of participants vaccinated was based on assigned treatment group.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study V116-003 (Phase 3)

Title of the study: A Phase 3, randomized, double-blind, active comparator-controlled clinical study to evaluate the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-naïve adults

Study initiation date: July 13, 2022 (first participant first visit)

Study completion date: June 21, 2023 (last data available)

6.1.1 Objectives

Primary Objectives:

- To evaluate the safety and tolerability of V116 as assessed by the proportion of participants with AEs (Cohort 1 and Cohort 2 separately),
- To compare the serotype-specific OPA GMTs at 30 days postvaccination with V116 vs PCV 20 (Cohort 1),
- To compare the proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination with V116 vs PCV20 for unique serotypes in V116 (Cohort 1),
- To compare the serotype-specific OPA GMTs in adults 18 to 49 YOA from Cohort 2 to adults 50 to 64 YOA from Cohort 1 at 30 days postvaccination with V116 (Cohort 2).

Secondary Objectives:

- To evaluate serotype-specific cross-reactive OPA responses at 30 days postvaccination with V116 in adults ≥ 50 YOA from Cohort 1 and adults 18 to 49 YOA from Cohort 2 for serotypes within a serogroup (Cohort 1 and Cohort 2),
- To evaluate the serotype-specific IgG GMCs at 30 days postvaccination with V116 compared with PCV20 (Cohort 1),
- To evaluate the serotype-specific GMFR and proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination with V116 and separately for PCV20 (Cohort 1).

Tertiary/Exploratory Objectives:

- To evaluate the serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination with V116 and separately for PCV20 (Cohort 2),
- To evaluate the serotype-specific GMFR and proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination with V116 and separately for PCV20 (Cohort 2),
- To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination (Cohort 1 and Cohort 2, separately).

6.1.2 Design Overview

This was a randomized, active comparator-controlled, parallel-group, multisite, double-blind study of V116 in pneumococcal vaccine-naïve adults ≥ 18 years of age. Eligible participants were enrolled in 1 of 2 cohorts based on age at the time of enrollment. In Cohort 1, approximately 2300 individuals ≥ 50 years of age were randomly assigned in a 1:1 ratio to receive a single dose of V116 or PCV20 on Day 1. Randomization was stratified by participant age at enrollment (50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥ 85 years). At least 50% of participants in Cohort 1 were ≥ 65 years of age. In Cohort 2,

approximately 300 individuals 18 to 49 years of age were randomized in a 2:1 ratio to receive a single dose of V116 or PCV20 on Day 1.

Blood samples for immunogenicity assays were drawn on Day 1 and at 30 days postvaccination. An electronic Vaccination Report Card (eVRC) was used by all participants to record solicited injection-site AEs, solicited systemic AEs, and daily body temperature from Day 1 through Day 5 postvaccination. Unsolicited AEs were collected through Day 30 postvaccination. Information for SAEs and deaths, regardless of whether the events are considered to be vaccine-related by the investigator were collected until Day 180.

Because of the different appearance of V116 and PCV20, a double-blinded technique with in-house blinding was used. V116 and PCV20 were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. To avoid bias, contact between the unblinded study site personnel and study participants was strictly prohibited for any study-related procedures/assessments other than administration of study vaccines. Blinded site personnel were responsible for all other study procedures/assessments.

6.1.3 Population

Adult males or females, ≥ 18 YOA, at the time of informed consent were eligible for inclusion if they met the following criteria:

- The participant might have had underlying chronic conditions if they were assessed to be stable as per the investigator's judgment.
- 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 WOCBP, or
 - A WOCBP and
 - Used an acceptable contraceptive method or was abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), during the intervention period and for at least 6 weeks after the last dose of study intervention.
 - Had a negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention.
 - Medical history, menstrual history, and recent sexual activity had been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- The participant (or legally acceptable representative) provided documented informed consent for the study. The participant might have provided documented informed consent for FBR and/or assay development sample collection. However, the participant might be enrolled in the study without providing consent for FBR or assay development sample collection.
- The participant had the ability to complete eVRC data collection without assistance based on judgment of the investigator.

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, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B). The comparator product PCV20 is a 20-valent conjugate pneumococcal vaccine which was injected as a single dose of 0.5 mL suspension intramuscularly. Each unit dose consists of 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.

6.1.6 Sites and Centers

There were 5 sites in Australia, 2 sites in Belgium, 4 sites in Chile, 6 sites in Germany, 5 sites in New Zealand, 4 sites in Puerto Rico, 12 sites in South Korea, 5 sites in Sweden, 4 sites in Taiwan, 4 sites in Turkey, 58 sites in US for Cohort 1. There were 5 sites in Australia, 1 site in Belgium, 4 sites in Chile, 6 sites in Germany, 5 sites in New Zealand, 4 sites in Puerto Rico, 11 sites in South Korea, 4 sites in Sweden, 4 sites in Taiwan, 4 sites in Turkey, 54 sites in US for Cohort 2.

6.1.7 Surveillance/Monitoring

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

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoints:

- *Safety endpoints* (Cohort 1 and Cohort 2 separately)
 - Proportion of participants with solicited injection-site AEs from Day 1 through Day 5 postvaccination,
 - Proportion of participants with solicited systemic AEs from Day 1 through Day 5 postvaccination,
 - Proportion of participants with vaccine-related SAEs from Day 1 through the duration of participation in the study.
- *Immunogenicity endpoints* (Cohort 1)
 - V116 is noninferior to PCV20 as assessed by serotype specific OPA GMTs at 30 days postvaccination for the 10 common serotypes in V116 and PCV20. The statistical success criterion for noninferiority requires the lower bound of the 2 sided 95% CI of the OPA GMT ratio [V116/PCV20] to be >0.5 .
 - V116 is superior to PCV20 as assessed by serotype specific OPA GMTs at 30 days postvaccination for the 11 unique serotypes in V116. The statistical success criterion for superiority requires the lower bound of the 2 sided 95% CI of the OPA GMT ratio [V116/PCV20] to be >2.0 .
 - V116 is superior to PCV20 as assessed by the proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination for the 11 unique serotypes in V116. The statistical

success criterion for superiority requires the lower bound of the 2-sided 95% CI of the differences [V116 – PCV20] between the proportions of participants with a ≥ 4 -fold rise from baseline to 30 days postvaccination to be >0.1 .

- *Immunogenicity endpoints (Cohort 2)*
 - V116 in participants 18 to 49 years of age immunobridges to V116 in participants 50 to 64 years of age as assessed by serotype specific OPA GMTs at 30 days postvaccination for all 21 serotypes in V116. The statistical success criterion for immunobridging requires the lower bound of the 2 sided 95% CI of the OPA GMT ratio [V116 18 to 49 group/V116 50 to 64 group] to be >0.5 .

Secondary Endpoints:

- V116 induces an acceptable antibody response for adults ≥ 50 years of age as assessed by the proportions of participants with a ≥ 4 -fold rise in serotype-specific cross-reactive OPA responses from baseline to 30 days postvaccination for serotypes within a serogroup in V116. The statistical success criterion for an acceptable antibody response requires the lower bound of the 95% CI of proportions of participants with a ≥ 4 -fold rise from baseline to 30 days postvaccination for V116 to be >0.5 .
- V116 in participants 18 to 49 years of age immunobridges to V116 in participants 50 to 64 years of age as assessed by serotype specific cross-reactive OPA GMTs at 30 days postvaccination for serotypes within a serogroup in V116. The statistical success criterion for immunobridging requires the lower bound of the 2-sided 95% CI of the cross-reactive OPA GMT ratio [V116 18 to 49 group/V116 50 to 64 group] to be >0.5 .
- Serotype-specific IgG responses to evaluate serotype-specific IgG GMCs at 30 days postvaccination with V116 compared with PCV20 in Cohort 1.
- Serotype-specific OPA and IgG responses to evaluate serotype-specific GMFR and proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA and IgG responses, respectively, from baseline to 30 days postvaccination with V116 and separately for PCV20 in Cohort 1.

Tertiary/Exploratory Endpoints:

- Serotype-specific OPA and IgG responses to evaluate OPA GMTs and IgG GMCs, respectively, at 30 days postvaccination with V116 and separately for PCV20 in Cohort 2.
- Serotype-specific OPA and IgG responses to evaluate serotype-specific GMFR and proportions of participants with a ≥ 4 -fold rise in serotype specific OPA and IgG responses, respectively, from baseline to 30 days postvaccination with V116 and separately for PCV20 in Cohort 2.
- Serotype-specific OPA and IgG responses to evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination in Cohort 1 and Cohort 2, separately.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Intervention randomization occurred centrally using an IRT system. Participants were assigned randomly in a 1:1 ratio to receive either V116 or PCV20 in Cohort 1 and 2:1 ratio to receive either V116 or PCV20 in Cohort 2. Intervention randomization in Cohort 1 was stratified according to participant age at time of randomization (50 to 64 vs. 65 to 74 vs. 75 to 84 vs. ≥ 85 years of age) and at least 50% of participants in Cohort 1 would be ≥ 65 years of age. No stratification based on age or other characteristics was used in Cohort 2.

Analysis Sets:

- *Per-Protocol (PP) set:* The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. Potential deviations that might result in the exclusion of a participant from the PP population for all immunogenicity analyses included:
 - Failure to receive any study vaccine at Visit 1 (Day 1),
 - Failure to receive correct clinical material as per randomization schedule at Visit 1 (Day 1),
 - Receipt of prohibited medication or prohibited vaccine before study vaccination.

Additional potential deviations that might result in the exclusion of a participant's measurement from a specific time point assessment in the PP population for immunogenicity analyses included:

- Receipt of prohibited medication or prohibited vaccine before a blood sample collection,
 - Collection of blood sample outside the prespecified window.
- *Full analysis set (FAS):* The FAS population consists of all randomized participants who received 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 immunogenicity data using the FAS population.
- *All participants as treated (APaT) set:* APaT consists of all randomized participants who received study intervention. Participants were included in the group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This would be the group to which they were randomized except for participants who received incorrect study intervention; such participants were included in the intervention group corresponding to the study intervention actually received. At least 1 temperature measurement obtained subsequent to study intervention was required for inclusion in the analyses of temperature.

Primary Immunogenicity Analyses:

Primary immunogenicity analyses were conducted for each serotype separately on PP set and supportive analyses were carried out on FAS. The following primary hypotheses were tested. First, suppose GMT_{V116} is the serotype-specific OPA GMT for the V116 group and $\text{GMT}_{\text{PCV20}}$ is the serotype-specific OPA GMT for the PCV20 group. Also, suppose p_{V116} and p_{PCV20} are the proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination for the V116 group and PCV20 group, respectively. Further, let $\text{GMT}_{\text{Cohort 2, 18 to 49 years}}$ be the serotype-specific OPA GMT for the

V116 participants 18 to 49 years of age from Cohort 2 and GMT_{Cohort 1}, 50 to 64 years be the serotype-specific OPA GMT for the V116 participants 50 to 64 years of age from Cohort 1.

H1: Noninferiority testing for 10 common serotypes

For each of the 10 common serotypes, the primary noninferiority hypothesis (H1) regarding OPA GMT levels between recipients of V116 and PCV20, $H_0: \text{GMT}_{V116}/\text{GMT}_{PCV20} \leq 0.50$ versus $H_1: \text{GMT}_{V116}/\text{GMT}_{PCV20} > 0.50$ was conducted at 1-sided $\alpha=0.025$.

H2: Superiority testing for 11 unique serotypes to V116

For each of the 11 unique serotypes to V116, the primary superiority hypothesis (H2) regarding OPA GMT levels between recipients of V116 and PCV20, $H_0: \text{GMT}_{V116}/\text{GMT}_{PCV20} \leq 2.0$ versus $H_1: \text{GMT}_{V116}/\text{GMT}_{PCV20} > 2.0$ was conducted at 1-sided $\alpha=0.025$.

For hypotheses, H1 and H2, the GMT ratio estimation, 95% CI, and the hypothesis test (ie, 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, age stratum (ie, 50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥ 85 years of age) at baseline, and the interaction of time-by-age stratum. This model allowed for different baseline means for each age stratum, but restricted the baseline mean within each age stratum to be the same for all 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.

Reference: Liang K-Y, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankhya: The Indian Journal of Statistics 2000; 62(Series B, Part 1):134-48.

H3: Proportions of participants with a ≥ 4 -fold rise for 11 unique serotypes to V116

The superiority hypothesis for each of the 11 serotypes unique to V116 was tested via $H_0: p_{V116} - p_{PCV20} \leq 0.1$ versus $H_1: p_{V116} - p_{PCV20} > 0.1$ at 1-sided $\alpha=0.025$.

To address H3, the participants who were missing either baseline or 30 days postvaccination OPA responses was not included in the fold-rise calculation. Estimation of the proportion difference and 95% CI and the hypothesis test (ie, 1-sided value) were conducted using the stratified M&N method, an unconditional, asymptotic method. Sample size weighting scheme was used for this analysis using stratified M&N method.

H4: Immunobridging hypotheses for all 21 serotypes in V116

To compare the serotype-specific OPA GMTs in adults 18 to 49 years of age from Cohort 2 versus adults 50 to 64 years of age from Cohort 1 at 30 days, immunobridging hypotheses

for all 21 serotypes in V116 were tested via H_0 : $\text{GMT}_{\text{Cohort 2, 18 to 49 years}}/\text{GMT}_{\text{Cohort 1, 50 to 64 years}} \leq 0.50$ versus H_1 : $\text{GMT}_{\text{Cohort 2, 18 to 49 years}}/\text{GMT}_{\text{Cohort 1, 50 to 64 years}} > 0.50$ at 1-sided $\alpha=0.025$.

Similar to H_1 and H_2 , to address H_4 , the GMT ratio estimation, 95% CI, and the 1-sided p-value for the hypothesis testing were calculated using a cLDA method proposed by Liang and Zeger (2000) to allow for a different mean for each age group at each of the repeated time points in the analysis. For H_4 , the repeated measures model included terms for time, age group, and the interaction of time-by-age group.

All hypotheses were tested individually for each serotype at a 1-sided 0.025 alpha-level to control the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment was used.

Primary Safety Analyses:

Safety analyses were based on the APaT set. Safety analyses included 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 M&N method (1985).

Sample Size and Power for Primary Immunogenicity Analyses:

Primary Immunogenicity Hypotheses (H_1 , H_2 , H_3 ; Cohort 1)

Based on the following assumptions, the study had approximately 90% power to achieve the prespecified noninferiority and superiority statistical criteria for the 21 serotypes in V116.

- For 6 of the common serotypes, the underlying OPA GMT ratios (V116/PCV20) were assumed to be 1.0; the standard deviations of natural log-transformed OPA results for V116 (ranging from 1.06 to 1.64) and PCV20 (ranging from 1.31 to 2.22) were assumed to be the same as those observed in V116-001 Phase 2 and the PCV20 US label, respectively.
- For the other 4 common serotypes, the underlying OPA GMT ratios (V116/PCV20) were assumed to be 0.68; the standard deviations of natural log-transformed OPA results for V116 (ranging from 1.27 to 1.73) and PCV20 (ranging from 1.69 to 2.13) were assumed to be the same as those observed in V116-001 Phase 2 and the PCV20 US label, respectively. Four serotypes were selected based on conservative extrapolations of data from V116-001 and studies of other pneumococcal vaccines.
- For the 11 unique serotypes, the underlying OPA GMT ratios (V116/PCV20) were assumed to be 3.0 for serotype 15C, and 6.0 for the other 10 unique serotypes. The standard deviations of natural log-transformed OPA results for PCV20 are assumed to be the same as those of V116 observed in V116-001 Phase 2 for all 11 unique serotypes. The standard deviations of the natural log titers range from 1.25 to 1.95. The proportions of participants with a ≥ 4 -fold rise from baseline OPA responses were assumed to be 80% for V116 and at most 50% for PCV20 for all 11 unique serotypes.
- 90% evaluability rate (approximately 1035 evaluable participants per intervention group).

Primary Immunogenicity Hypothesis (H_4 ; Cohort 2)

Based on the following assumptions, the study had >95% power for demonstrating immunobridging for all 21 serotypes at an overall 1-sided 2.5% alpha-level.

- The underlying OPA GMT ratios (V116 18 to 49 group/V116 50 to 64 group) were assumed to be 1.0 for all 21 serotypes contained in V116.
- The standard deviations of natural log-transformed OPA results for V116 participants 18 to 49 years of age were assumed to be the same as those observed in V116-001 Phase 1. The standard deviations of the natural log titers ranged from 0.66 to 1.73.
- The standard deviations of natural log-transformed OPA results for V116 participants 50 to 64 years of age were assumed to be the same as those observed for V116 participants 50 to 64 years of age in V116-001 Phase 2. The standard deviations of the natural log titers ranged from 1.06 to 1.92.
- A 90% evaluability rate, with 50% of participants 50 to 64 years of age in Cohort 1 (approximately 180 evaluability participants in the V116 18 to 49 group and 518 evaluable participants in the V116 50 to 64 group).

Sample Size and Power for Safety Analyses:

Cohort 1: There is an 80% chance of observing at least 1 SAE among 1150 participants in the V116 group if the underlying incidence of an SAE is 0.14% (1 of every 715 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 1150 participants in the V116 group if the underlying incidence of an SAE is 0.06% (1 of every 1659 participants receiving the vaccine). If no SAEs are observed among 1150 participants, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.32% (1 in every 312 participants) in the V116 group.

Cohort 2: There is an 80% chance of observing at least 1 SAE among 200 participants in the V116 group if the underlying incidence of an SAE is 0.8% (1 of every 125 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 200 participants in the V116 group if the underlying incidence of an SAE is 0.35% (1 of every 289 participants receiving the vaccine). If no SAEs are observed among 200 participants, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <1.83% (1 in every 55 participants) in the V116 group.

Subgroup Analyses:

Subgroup analyses were performed within each cohort separately for selected safety endpoints as well as primary immunogenicity endpoints. Subgroup analyses were carried out based on sex, race, ethnicity, and number of chronic medical condition. In Cohort 1, subgroup analyses were also carried out based on age category.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Important protocol deviations were reported for 113 subjects in V116 arm and 109 subjects in PCV20 arm. Among them, there were 84 subjects in V116 arm and 93 subjects in PCV20 arm who had important protocol deviations that were considered to be clinically important.

Table 2 and Table 3 show the subject disposition in Cohort 1 and Cohort 2 in Study V116-003, respectively.

Table 2: Subject Disposition (Cohort 1)

	V116	PCV20	Total
Randomized participants	1181	1181	2362
Vaccinated at Visit 1			
V116	1179	0	1179
PCV20	0	1177	1177
Trial disposition			
Completed	1160	1152	2312
Discontinued	21	29	50
Death	4	2	6
Lost to follow-up	10	15	25
Physician decision	0	2	2
Randomized by mistake without study treatment	1	2	3
Withdrawal by subject	4	8	12
Other	2	0	2
Participants included in OPA analyses (PP set) by timepoints			
Day 1	1149	1151	2300
Day 30	1093	1077	2170
At least one timepoint	1162	1165	2327
Both Day 1 and Day 30 timepoint	1080	1063	2143

Source: Adapted from Table 14.1-4 and Table 14.1-10 in the CSR of Study V116-003 from the original BLA 125814/0.

Table 3: Subject Disposition (Cohort 2)

	V116	PCV20	Total
Randomized participants	201	100	301
Vaccinated at Visit 1			
V116	200	0	200
PCV20	0	100	100
Trial disposition			
Completed	195	96	291
Discontinued	6	4	10
Lost to follow-up	5	3	8
Withdrawal by subject	1	1	2
Participants included in OPA analyses (PP set) by timepoints			
Day 1	196	95	291
Day 30	182	90	272
At least one timepoint	198	96	294
Both Day 1 and Day 30 timepoint	180	89	269

Source: Adapted from Table 14.1-5 and Table 14.1-12 in the CSR of Study V116-003 from the original BLA 125814/0.

6.1.10.1.1 Demographics

Demographic characteristics of the enrolled participants were generally well-balanced across vaccine arms within each cohort.

Table 4: All vaccinated participants characteristics (Cohort 1)

	V116		PCV20		Total	
	n	Percent	n	Percent	n	Percent
Vaccinated Participants	1179	-	1177	-	2356	-
Sex						
Male	492	41.7	507	43.1	999	42.4
Female	687	58.3	670	56.9	1357	57.6
Age (Years)						
50 to 64	589	50.0	587	49.9	1176	49.9
65 to 74	464	39.4	464	39.4	928	39.4
75 to 84	112	9.5	113	9.6	225	9.6
≥85	14	1.2	13	1.1	27	1.1
Mean	63.9	-	63.9	-	63.9	-
SD	8.3	-	8.3	-	8.3	-
Median	65.0	-	65.0	-	65.0	-
Range	50-91	-	50-97	-	50-97	-
Race						
American Indian or Alaska Native	4	0.3	4	0.3	8	0.3
Asian	148	12.6	168	14.3	316	13.4
Black or African American	116	9.8	115	9.8	231	9.8
Multiple	26	2.2	30	2.5	56	2.4
Native Hawaiian or Other Pacific Islander	17	1.4	16	1.4	33	1.4
White	867	73.5	844	71.7	1711	72.6
Missing	1	0.1	0	0.0	1	0.0
Ethnicity						
Hispanic or Latino	259	22.0	242	20.6	501	21.3
Not Hispanic or Latino	909	77.1	922	78.3	1831	77.7
Not reported	8	0.7	10	0.8	10	0.8
Unknown	3	0.3	3	0.3	6	0.3
Country						
Australia	44	3.7	40	3.4	84	3.6
Belgium	73	6.2	68	5.8	141	6.0
Chile	53	4.5	47	4.0	100	4.2
Germany	36	3.1	27	2.3	63	2.7
New Zealand	119	10.1	144	12.2	263	11.2
Puerto Rico	64	5.4	76	6.5	140	5.9
South Korea	77	6.5	89	7.6	166	7.0
Sweden	51	4.3	47	4.0	98	4.2
Taiwan	57	4.8	55	4.7	112	4.8

	V116		PCV20		Total	
	n	Percent	n	Percent	n	Percent
Turkey	26	2.2	28	2.4	54	2.3
United States	579	49.1	556	47.2	1135	48.2

Source: Table 14.1-16 in the CSR of Study V116-003 from the original BLA 125814/0.

Table 5: All vaccinated participants characteristics (Cohort 2)

	V116		PCV20		Total	
	n	Percent	n	Percent	n	Percent
Vaccinated Participants	200	-	100	-	300	-
Sex						
Male	63	31.5	36	36.0	99	33.0
Female	137	68.5	64	64.0	201	67.0
Age (Years)						
18 to 49	200	100	100	100	300	100
Mean	35.2	-	34.6	-	35.0	-
SD	9.0	-	8.7	-	8.9	-
Median	36.0	-	34.0	-	35.0	-
Range	18-49	-	18-49	-	18-49	-
Race						
American Indian or Alaska Native	0	0.0	1	1.0	1	0.3
Asian	38	19.0	15	15.0	53	17.7
Black or African American	13	6.5	14	14.0	27	9.0
Multiple	9	4.5	6	6.0	15	5.0
Native Hawaiian or Other Pacific Islander	1	0.5	2	2.0	3	1.0
White	139	69.5	62	62.0	201	67.0
Ethnicity						
Hispanic or Latino	58	29.0	24	24.0	82	27.3
Not Hispanic or Latino	141	70.5	76	76.0	217	72.3
Unknown	1	0.5	0	0.0	1	0.3
Country						
Australia	5	2.5	6	6.0	11	3.7
Belgium	11	5.5	3	3.0	14	4.7
Chile	23	11.5	12	12.0	35	11.7
Germany	12	6.0	4	4.0	16	5.3
New Zealand	15	7.5	12	12.0	27	9.0
Puerto Rico	11	5.5	4	4.0	15	5.0
South Korea	24	12.0	10	10.0	34	11.3
Sweden	9	4.5	3	3.0	12	4.0
Taiwan	8	4.0	3	3.0	11	3.7
United States	82	41.0	43	43.0	125	41.7

Source: Table 14.1-17 in the CSR of Study V116-003 from the original BLA 125814/0.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In Cohort 1, the 5 most frequently reported medical history conditions (by preferred term) were: hypertension (38.5%), diabetes mellitus (16.7%), hyperlipidemia (12.9%), osteoarthritis (12.9%), and hypercholesterolemia (12.8%). In Cohort 2, the 5 most frequently reported medical history conditions (by preferred term) were: depression (11.0%), asthma (9.0%), anxiety (8.7%), seasonal allergy (8.0%), and hypertension (7.7%). Within each cohort, reported medical history conditions were generally comparable between intervention groups.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoints

Table 6 provides the postvaccination OPA GMTs on PP population for Cohort 1 and shows that for each of 10 common serotypes V116 met the predefined criterion for noninferiority to PCV20, i.e., lower bound of 95% CI of OPA GMT ratio [V116/PCV20]>0.5.

Table 6: Analysis of Postvaccination OPA GMTs for Common Serotypes (PP population) Cohort 1

Pneumococcal Serotype	V116 (N = 1179)		PCV20 (N = 1177)		GMT Ratio (V116 / PCV20) (95% CI)	p-Value (1-sided)
	n	GMT	n	GMT		
3	1154	274.0	1161	176.7	1.55 (1.40, 1.72)	<0.001
6A	1148	2302.0	1153	2972.5	0.77 (0.68, 0.88)	<0.001
7F	1152	3637.4	1158	3429.9	1.06 (0.95, 1.18)	<0.001
8	1155	2501.3	1158	1811.1	1.38 (1.25, 1.53)	<0.001
10A	1161	3893.4	1159	4678.0	0.83 (0.75, 0.93)	<0.001
11A	1145	3232.6	1150	2092.8	1.54 (1.39, 1.72)	<0.001
12F	1160	2641.2	1161	2499.6	1.06 (0.92, 1.21)	<0.001
19A	1159	2136.1	1162	2817.8	0.76 (0.69, 0.84)	<0.001
22F	1147	3874.5	1154	4770.1	0.81 (0.72, 0.92)	<0.001
33F	1154	13558.9	1157	11742.1	1.15 (1.01, 1.32)	<0.001

Source: Adapted from Table 14.2-1 in the CSR of Study V116-003 from the original BLA 125814/0.

Table 7 provides postvaccination OPA GMTs for the unique serotypes in V116 and shows that V116 met the predefined criteria for superiority to PCV20 for 10 of 11 serotypes unique to V116 at 30 days postvaccination. V116 did not meet the predefined criteria for superiority to PCV20 for serotype 15C as the lower bound of the 95% CI of OPA GMT ratio is 1.77.

Table 7: Analysis for Postvaccination OPA GMTs for Unique Serotypes (PP population) Cohort 1

Pneumococcal Serotype	V116 (N = 1179)		PCV20 (N = 1177)		GMT Ratio (V116 / PCV20) (95% CI)	p-Value (1-sided)
	n	GMT	n	GMT		
9N	1147	7470.7	1150	1640.4	4.55 (4.12, 5.04)	<0.001
15A	1107	5237.2	1102	1589.0	3.30 (2.91, 3.74)	<0.001
15C	1153	4216.2	1158	2072.3	2.03 (1.77, 2.34)	0.406
16F	1151	4868.2	1153	846.3	5.75 (5.16, 6.41)	<0.001
17F	1148	7764.9	1156	460.4	16.86 (14.90, 19.09)	<0.001
20A	1161	6099.2	1155	631.1	9.66 (8.66, 10.79)	<0.001
23A	1132	3737.2	1104	461.5	8.10 (6.86, 9.55)	<0.001
23B	1160	1082.5	1160	107.3	10.09 (8.48, 12.00)	<0.001
24F	1153	2728.6	1130	70.5	38.71 (33.87, 44.25)	<0.001
31	1153	3132.5	1154	144.4	21.69 (18.68, 25.18)	<0.001
35B	1153	8527.8	1159	1383.0	6.17 (5.59, 6.80)	<0.001

Source: Table 14.2-3 in the CSR of Study V116-003 from the original BLA 125814/0.

Table 8 shows that V116 met the predefined criteria for superiority to PCV20 for 10 of 11 serotypes unique to V116 based on the proportion of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination.

Table 8: Analysis of the Proportions of Participants with a ≥ 4 -Fold Rise in OPA Responses for Unique Serotypes (PP population) Cohort 1

Pneumo-coccal Serotype	V116 (N=1179)	PCV20 (N=1177)	Percentage Point Difference (V116 - PCV20)	
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI)	p-Value (1-sided)
9N	64.7 (595/920)	19.9 (195/978)	44.7 (40.7, 48.6)	<0.001
15A	66.7 (462/693)	35.8 (253/706)	30.9 (25.8, 35.8)	<0.001
15C	83.4 (794/952)	74.2 (695/937)	9.2 (5.6, 12.9)	0.665
16F	71.9 (654/910)	20.8 (200/961)	51.1 (47.1, 54.9)	<0.001
17F	75.8 (653/862)	9.5 (90/952)	66.3 (62.8, 69.6)	<0.001
20A	67.3 (675/1003)	9.6 (97/1011)	57.7 (54.2, 61.1)	<0.001
23A	78.9 (598/758)	36.8 (270/734)	42.2 (37.6, 46.6)	<0.001
23B	85.5 (873/1021)	49.6 (506/1021)	35.9 (32.1, 39.6)	<0.001
24F	80.5 (745/925)	6.3 (55/872)	74.2 (71.1, 77.1)	<0.001
31	76.5 (698/912)	17.9 (171/954)	58.6 (54.8, 62.1)	<0.001
35B	60.0 (550/917)	6.8 (67/988)	53.2 (49.6, 56.6)	<0.001

Source: Table 11-1 in the CSR of Study V116-003 from the original BLA 125814/0.

n= number of participants contributing to the analysis

m=number of participants with indicated responses.

Table 9 shows that the predefined immunobridging criteria for V116 were met in participants 18 to 49 YOA (Cohort 2) compared with V116 in participants 50 to 64 YOA in Cohort 1 for all 21 serotypes, as assessed by serotype-specific OPA GMTs at 30 days postvaccination.

Table 9: Analysis of Postvaccination OPA GMTs to Compare Participants 18-49 Years with Participants 50-64 Years for 21 Serotypes in V116 (PP population)

Pneumococcal Serotype	V116 18-49 Years (N = 200)		V116 50-64 Years (N = 589)		GMT Ratio (V116 18-49 Years / V116 50-64 Years) (95% CI)	p-Value (1-sided)
	n	GMT	n	GMT		
3	194	308.6	572	282.7	1.09 (0.90, 1.33)	<0.001
6A	196	5289.6	569	2572.9	2.06 (1.61, 2.62)	<0.001
7F	198	6447.2	571	4278.8	1.51 (1.23, 1.84)	<0.001
8	197	4516.0	571	3004.7	1.50 (1.26, 1.79)	<0.001
9N	197	17283.2	570	8791.4	1.97 (1.59, 2.43)	<0.001
10A	197	6808.1	575	4382.6	1.55 (1.26, 1.92)	<0.001
11A	196	5871.6	564	3785.8	1.55 (1.26, 1.91)	<0.001
12F	196	6150.4	574	3561.2	1.73 (1.37, 2.17)	<0.001
15A	184	11319.2	550	5901.2	1.92 (1.55, 2.37)	<0.001
15C	195	10194.0	570	5708.0	1.79 (1.36, 2.35)	<0.001
16F	193	8877.0	571	5720.0	1.55 (1.26, 1.91)	<0.001
17F	194	16070.6	568	10068.0	1.60 (1.26, 2.02)	<0.001
19A	198	2773.2	574	2374.6	1.17 (0.97, 1.40)	<0.001
20A	197	13150.0	575	7562.7	1.74 (1.39, 2.18)	<0.001
22F	198	9299.6	568	4683.6	1.99 (1.58, 2.49)	<0.001
23A	192	8848.7	561	4739.5	1.87 (1.43, 2.44)	<0.001
23B	198	2140.1	575	1420.9	1.51 (1.11, 2.04)	<0.001
24F	197	4137.6	570	3047.2	1.36 (1.10, 1.67)	<0.001
31	195	8005.6	570	3820.7	2.10 (1.63, 2.69)	<0.001
33F	197	34805.5	570	17607.4	1.98 (1.52, 2.57)	<0.001
35B	198	13933.4	573	9053.9	1.54 (1.26, 1.87)	<0.001

Source: Table 14.2-7 in the CSR of Study V116-003 from the original BLA 125814/0.

Reviewer's Comment: All four primary immunogenicity analyses were also conducted on the FAS population and the results were consistent with those observed in the PP population. Higher immune responses were observed in the V116 participants 18 to 49 years of age compared with the V116 participants 50 to 64 years of age during immunobridging.

6.1.11.2 Analyses of Secondary Endpoints

Table 10 shows that among the cross-reactive serotypes, 6C and 15B, V116 did not meet the predefined criterion for an acceptable antibody response for serotype 6C as the lower bound of the 95% CI of the percentage of participants with a ≥ 4 -fold rise in OPA responses was 46.0% (success criteria: lower bound of 95% CI > 50%).

Table 10: Analysis of the Proportions of Participants in V116 with a ≥ 4 -Fold Rise in OPA Responses for Serotypes 6C and 15B (PP population) (Cohort 1)

Pneumococcal Serotype	V116 Cohort 1 (N=1179)			
	n	m	Percent (95% CI)	p-Value
6C	912	450	49.3% (46.0, 52.6)	0.667
15B	883	571	64.7% (61.4, 67.8)	<0.001

Source: Table 14.2-9 in CSR of Study V116-003 from the original BLA 125814/0.

n= number of participants contributing to the analysis

m=number of participants with indicated responses.

For serotype 15B (cross reactive to serotype 15C), V116 in participants 18 to 49 years of age (Cohort 2) met the predefined criterion for immunobridging to V116 in participants 50 to 64 years of age (Cohort 1) (lower bound of the 95% CI of the OPA GMT ratio [V116 18 to 49 Years group/V116 50 to 64 Years group] >0.5) at 30 days postvaccination; the OPA GMT ratio was 2.02 (95% CI: 1.57, 2.60). For serotype 6C (cross reactive to serotype 6A), the immunobridging hypothesis was not tested in accordance with the statistical analysis plan. The OPA GMT ratio was 2.05 (95% CI: 1.52, 2.77).

Reviewer's Comment: Serotype-specific IgG GMCs at 30 days postvaccination for all serotypes in Cohort 1 were also computed and the results were consistent with the primary analysis based on OPA GMTs at 30 days postvaccination. For both OPA responses and IgG responses, 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 also comparable in both intervention groups for 10 common serotypes and higher in the V116 group for 11 serotypes unique to V116, compared to the PCV20 group.

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 V116 in Cohort 1 were analyzed based on the subgroups - age, sex, race, ethnicity, number of risk factors on PP population. OPA GMT ratios in adults 18 to 49 years (Cohort 2) compared to 50 to 64 years of age (Cohort 1) for all serotypes at 30 days postvaccination with V116 were also analyzed based on the subgroup categories - sex, race, ethnicity, and number of risk factors on the PP population.

Reviewer's Comment: Results from the subgroup analyses were consistent with those observed in the overall PP population.

6.1.12 Safety Analyses

Safety results are briefly summarized in this section.

6.1.12.1 Methods

All solicited AEs were summarized according to defined severity grading scales. Frequencies and percentages of subjects experiencing each AE were presented for each symptom severity. The unsolicited AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 and grouped by preferred terms (PTs) into frequency tables per system organ class (SOC). When an AE occurred more than once for a subject, the maximal severity and duration of the maximal severity were counted.

6.1.12.3 Deaths

In Cohort 1, there were 6 deaths reported during the study. 4 deaths were reported in the V116 group and were due to sepsis (Day 28), cerebrovascular accident (Day 44), myocardial infarction (Day 179), and hepatic cirrhosis and hepatic encephalopathy (Day 20). 2 deaths in the PCV20 group were due to cardiac arrest (Day 10) and abdominal abscess (Day 14). None of these deaths were considered related to study intervention. No death was reported in Cohort 2.

6.1.12.4 Overall Serious Adverse Events

There were 1177 and 1175 participants in APaT set for the V116 group and PCV20 group, respectively, in Cohort 1. There were 19 participants (1.6%) who experienced one or more SAEs in the V116 intervention group and 24 participants (2.0%) with one or more SAEs in the PCV20 group in Cohort 1. 200 and 100 participants were included in APaT set for V116 and PCV20 groups, respectively, in Cohort 2. Among them 1 participant (0.5%) in V116 and 3 participants (3.0%) in PCV20 group in Cohort 2 experienced one or more SAEs. None of these SAEs were considered to be related to study vaccine by the investigators.

6.1.12.5 Solicited Local and Systemic Adverse Events

Solicited local and systemic AEs from Day 1 through Day 5 postvaccination are summarized in Table 11.

Table 11: Individuals With Solicited Local and Systemic Adverse Events Within 5 Days Postvaccination in Pneumococcal Vaccine-Naïve Adults 18 through 49 Years of Age and 50 Years of Age and Older

		18 – 49 YOA		50 YOA and older	
		V116 n (%)	PCV20 n (%)	V116 n (%)	PCV20 n (%)
Individuals in population		200	100	1177	1175
One or more solicited AEs		161 (80.5)	78 (78.0)	600 (51.0)	708 (60.3)
Local AE	Severity				
Injection Site Pain	Total	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)

		18 – 49 YOA		50 YOA and older	
		V116 n (%)	PCV20 n (%)	V116 n (%)	PCV20 n (%)
	Severe	2 (1.0)	0 (0.0)	1 (0.1)	1 (0.1)
Injection Site Erythema	Total	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 (0.0)	2 (0.2)	2 (0.2)
	Unknown	-	-	1 (0.1)	1 (0.1)
Injection Site Swelling	Total	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 (0.0)	3 (0.3)	2 (0.2)
Systemic AE	Severity				
Fatigue	Total	81 (40.5)	34 (34.0)	237 (20.1)	230 (19.6)
Fatigue	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 (0.0)	5 (0.4)
Headache	Total	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 (0.0)	0 (0.0)	1 (0.1)
Myalgia	Total	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 (0.0)	1 (0.1)
Pyrexia	Total	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 (0.0)	7 (0.6)	7 (0.6)
	≥38.5°C (101.3°F) to <39.0°C (102.2°F)	2 (1.0)	0 (0.0)	6 (0.5)	5 (0.4)
	≥39.0°C (102.2°F) to <40.0°C (104.0°F)	2 (1.0)	1 (1.0)	1 (0.1)	3 (0.3)
	≥40.0°C (104.0°F)	-	-	1 (0.1)	0 (0.0)

Source: Adapted from Table 14.3-24 and Table 14.3-21 in CSR of Study V116-003 from the original BLA 125814/0.

6.1.12.6 Unsolicited Adverse Events

Within each cohort, the proportions of participants with unsolicited AEs reported Day 1 through Day 30 (excluding solicited AEs reported Day 1 through Day 5) were generally comparable across intervention groups. There were 251 (21.3%) participants in the V116 arm and 252 (21.4%) subjects in the PCV20 arm experienced one or more unsolicited AEs in Cohort 1. In Cohort 2, there were 52 (26%) participants in the V116 arm and 20 (20%) subjects in the PCV20 arm experienced one or more unsolicited AEs.

Reviewer's Comment: Safety analyses were also performed based on subgroups, i.e., age, sex, race, ethnicity, and number of risk factors in Cohorts 1 and 2. The results were comparable between intervention groups across subgroups.

6.2 Study V116-004 (Phase 3)

Title of the study: A Phase 3, randomized, double-blind, active comparator-controlled lot-to-lot consistency study to evaluate the safety, tolerability, and immunogenicity of V116 in adults 18 to 49 years of age

Study initiation date: August 12, 2022 (first participant first visit)

Study completion date: July 03, 2023 (last data available)

6.2.1 Objectives

Primary Objectives:

- To evaluate the safety and tolerability profile of V116 as assessed by the proportion of participants with adverse events (AEs).
- To compare the serotype-specific OPA GMTs at 30 days postvaccination across 3 different lots of V116 for all serotypes included in V116.

Secondary Objectives:

- To evaluate the serotype-specific OPA GMTs at 30 days postvaccination in combined lots of V116 compared with PPSV23 for all serotypes included in V116.
- To evaluate the serotype-specific IgG GMCs at 30 days postvaccination compared across the 3 different lots of V116 and evaluate combined lots of V116 compared with PPSV23 for all serotypes included in V116.
- To evaluate the serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise from baseline to 30 days postvaccination for both OPA and IgG responses separately for 3 different lots of V116 for all serotypes included in V116.
- To evaluate the serotype-specific OPA GMTs at 30 days postvaccination separately for 3 different lots of V116 for cross-reactive immune responses to serotypes within a serogroup.

Tertiary/Exploratory Objectives:

- To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination.

6.2.2 Design Overview

This was a randomized, active comparator-controlled, parallel-group, multisite, double-blind study of V116 in pneumococcal vaccine-naïve adults 18 to 49 years of age. Approximately 2040 participants who had not previously received any pneumococcal vaccine (vaccine-naïve) were randomized in a 1:1:1:1 ratio to receive a single dose of either V116 Lot 1, V116 Lot 2, V116 Lot 3, or PPSV23 on Day 1.

An eVRC was used by all participants to record solicited injection-site AEs, solicited systemic AEs, and daily body temperature from Day 1 through Day 5 postvaccination. Unsolicited AEs were collected through Day 30 postvaccination. Information for SAEs and deaths, regardless of whether the events were considered to be vaccine-related by the investigator, were collected until Day 180. Blood samples for immunogenicity assays were drawn on Day 1 and at 30 days postvaccination (Visit 3).

Because of the different appearance of V116 and PPSV23, a double-blinded technique with in-house blinding was used. V116 and PPSV23 were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. To avoid bias, contact between the unblinded study site personnel and study participants was strictly prohibited for any study-related procedures/assessments other than administration of study vaccines. Blinded site personnel were responsible for all other study procedures/assessments.

6.2.3 Population

Pneumococcal vaccine-naïve adult males and females, 18 to 49 YOA, at the time of informed consent were eligible for inclusion if they met the following criteria:

- The participant might have underlying chronic conditions if they were assessed to be stable as per the investigator's judgment.
- 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 WOCBP, or
 - A WOCBP and
 - Used an acceptable contraceptive method or was abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), during the intervention period and for at least 6 weeks after the last dose of study intervention.
 - Had a negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention.
 - Medical history, menstrual history, and recent sexual activity had been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- The participant (or legally acceptable representative) had provided documented informed consent for the study. The participant might also provide documented informed consent for FBR and/or assay development sample collection. However, the participant might be enrolled in the study without providing consent for FBR or assay development sample collection.

- The participant had the ability to complete eVRC data collection without assistance, based on judgment of the investigator.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Each lot of the test product V116 is a 21-valent conjugate pneumococcal vaccine which was injected as a single dose of 0.5 mL sterile solution (prefilled syringe) 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, 20, 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 sterile solution (prefilled syringe) 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, and 33F).

6.2.6 Sites and Centers

The study was conducted at 3 sites in Austria, 8 sites in Canada, 5 sites in Denmark, 7 sites in Finland, 6 sites in Israel, 5 sites in Poland, 6 sites in Spain, and 29 sites in United States.

6.2.7 Surveillance/Monitoring

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

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoints:

- *Safety endpoints*
 - Proportion of participants with solicited injection-site AEs from Day 1 through Day 5 postvaccination.
 - Proportion of participants with solicited systemic AEs from Day 1 through Day 5 postvaccination.
 - Proportion of participants with vaccine-related SAEs from Day 1 through the duration of participation in the study.
- *Immunogenicity endpoint*
 - Based on serotype-specific OPA responses, all 3 lots of V116 are equivalent as assessed by the serotype-specific OPA GMTs at 30 days postvaccination for all serotypes included in V116. The statistical success criterion for equivalence requires the bounds of the 95% CI of the OPA GMT ratio for each pairwise V116 lot-to-lot comparison to be within 0.5 to 2.0.

Secondary Endpoints:

- Serotype-specific OPA responses to evaluate the OPA GMTs at 30 days postvaccination in combined lots of V116 compared with PPSV23 for all serotypes included in V116.
- Serotype-specific IgG responses to evaluate the IgG GMCs at 30 days postvaccination compared across the 3 different lots of V116 and evaluate combined lots of V116 compared with PPSV23 for all serotypes included in V116.

- Serotype-specific OPA and IgG responses to evaluate the serotype-specific geometric mean fold rises (GMFRs) and proportions of participants with a ≥ 4 -fold rise from baseline to 30 days postvaccination for both OPA and IgG responses separately for 3 different lots of V116 for all serotypes included in V116.
- Serotype-specific OPA responses to evaluate the serotype-specific OPA GMTs at 30 days postvaccination separately for 3 different lots of V116 for cross-reactive immune responses to serotypes within a serogroup.

Tertiary Endpoint:

- Serotype-specific OPA and IgG responses to evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination.

6.2.9 Statistical Considerations & Statistical Analysis Plan

All consented participants were given a unique screening number that was used to identify the participant for all procedures that occur before randomization. All eligible participants were randomly allocated and received a treatment/randomization number. The treatment/randomization number was used to identify the participant for all procedures occurring after treatment randomization.

Analysis Sets:

- *PP population*: The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. Potential deviations that might result in the exclusion of a participant from the PP population for all immunogenicity analyses included:
 - Failure to receive any study vaccine at Visit 1 (Day 1),
 - Failure to receive correct clinical material as per randomization schedule at Visit 1 (Day 1),
 - Receipt of prohibited medication or prohibited vaccine before study vaccination.

Additional potential deviations that might result in the exclusion of a participant's measurement from a specific time point assessment in the PP population for immunogenicity analyses included:

- Receipt of prohibited medication or prohibited vaccine before a blood sample collection,
 - Collection of blood sample outside the prespecified window.
- *FAS population*: The FAS population consists of all randomized participants who received 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 immunogenicity data using the FAS population.
- *APaT population*: APaT consists of all randomized participants who received study intervention. Participants were included in the group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. At least 1 temperature measurement obtained subsequent to study intervention was required for inclusion in the analyses of temperature.

Primary Immunogenicity Analysis:

The primary immunogenicity analysis was carried out on the PP population and supportive analysis was provided on the FAS population. The primary objective to compare the serotype-specific OPA GMTs at 30 days postvaccination across the 3 different lots of V116 for all serotypes included in V116 was assessed via the primary hypothesis, i.e., $H_0: \text{GMT}_x/\text{GMT}_y \leq 0.5 \text{ or } \text{GMT}_x/\text{GMT}_y \geq 2.0$ versus $H_1: 0.5 < \text{GMT}_x/\text{GMT}_y < 2.0$, where GMT_x is serotype-specific OPA GMT for one of the V116 lots and GMT_y is serotype-specific OPA GMT for another V116 lot. Each possible pairwise comparison of lots was made (Lot 1 to Lot 2, Lot 1 to Lot 3, and Lot 2 to Lot 3) for each serotype. Each pairwise comparison of lots consisted of two 1-sided tests at the type 1 error = 0.025 level. Rejecting the null hypothesis of nonequivalence for any test is equivalent to requiring the bounds of the 95% CI on the pairwise lot-to-lot comparison of the GMT ratios to be between 0.5 and 2.0. Estimation of the serotype-specific OPA GMT ratios and 95% CIs were conducted using the cLDA method by Liang, K-Y and Zeger, S. L. (2000). In the model, the response vector consisted of the log-transformed antibody titers at baseline and 30 days postvaccination. The repeated-measures model included terms for vaccination group (V116 Lot 1, V116 Lot 2, and V116 Lot 3), time, and the interaction of time-by-vaccination group. This model restricted the baseline mean to be the same for all V116 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 are missing either the baseline or postbaseline measurements.

The study is considered to have met the primary objective if success is achieved for all 3 pairwise comparisons for V116 lots for all serotypes contained in V116. Comparisons were made individually for each serotype and for each pairwise comparison to control the overall type 1 error rate at 0.05 (2-sided), and no multiplicity adjustment was used.

Primary Safety Analyses:

Safety analyses were based on the APaT set. Safety analyses included 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 M&N method (1985).

Sample Size and Power for Primary Immunogenicity Analysis:

For the primary hypothesis on all serotypes contained in V116, this study would have > 90% power to demonstrate equivalent immunogenicity across the 3 V116 lots as assessed by the OPA GMTs at 30 days postvaccination at an overall type 1 error = 0.05 (2-sided) level, based on the following assumptions:

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

Sample Size and Power for Safety Analyses:

Assuming 100% of the randomized participants would be evaluable for safety analyses, there is an 80% chance of observing at least 1 SAE among 1530 participants in the V116 group (Lot 1, Lot 2, Lot 3 combined) if the underlying incidence of an SAE is 0.11% (1 of every 951 participants receiving the vaccine), and a 50% chance of observing at least 1 SAE among 1530 participants in the V116 group if the underlying incidence of an SAE is 0.046% (1 of every 2208 participants receiving the vaccine). If no SAEs were observed among 1530 participants, this study would provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.24% (1 in every 415 participants) in the V116 group (Lot 1, Lot 2, Lot 3 combined).

Subgroup Analyses:

Subgroup analyses were performed for selected safety endpoints as well as primary immunogenicity endpoints based on chronic medical condition, sex, race and ethnicity, if there were more than 5% of the total vaccinated participants in each vaccination group.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

There was 1 premature unblinding event in this study. The unblinding was limited to a single study center staff member who was not involved in assessment of the participant. This event was classified as a protocol deviation, but not an important protocol deviation. The participant was not excluded from analysis. Important protocol deviations were reported for 126 participants in V116 combined lots and for 38 subjects in PPSV23 arm. Also, among them 101 subjects in V116 combined lots had important protocol deviations and 33 in PPSV23 arm had important protocol deviations, which were considered clinically important. Table 12 shows the subject disposition for Study V116-004.

Table 12: Subject Disposition

	V116 Lot 1	V116 Lot 2	V116 Lot 3	V116 (Combined)	PPSV23	Total
Randomized participants	541	540	541	1622	540	2162
Vaccinated at Visit 1						
V116 Lot 1	538	1	0	539	0	539
V116 Lot 2	0	536	0	536	0	536
V116 Lot 3	1	0	540	541	0	541
PPSV23	0	1	0	1	540	541
Trial disposition						
Completed	521	520	525	1566	526	2092
Discontinued	20	20	16	56	14	70
Death	0	0	0	0	1	1
Lost to follow-up	16	11	11	38	11	49
Randomized by mistake without study treatment	0	1	0	1	0	1
Withdrawal by subject	4	8	3	15	1	16

	V116 Lot 1	V116 Lot 2	V116 Lot 3	V116 (Combined)	PPSV23	Total
Other	0	0	2	2	1	3
Participants included in OPA analyses (PP set) by timepoints						
Day 1	525	533	533	1591	530	2121
Day 30	481	491	491	1463	499	1962
At least one timepoint	528	534	533	1595	538	2133
Both Day 1 and Day 30 timepoint	478	490	491	1459	491	1950

Source: Adapted from Table 10-1 and Table 14.1-5 in the CSR of Study V116-004 from the original BLA 125814/0.

6.2.10.1.1 Demographics

Demographic characteristics of the enrolled participants were generally well-balanced across vaccine arms. Please see Table 13.

Table 13: Vaccinated Participant Characteristics by Vaccination Groups and Manufacturing Lots

	V116 Lot 1	V116 Lot 2	V116 Lot 3	V116 (Combined)	PPSV23	Total
Participants	539	538	540	1617	540	2157
Sex (n, %)						
Male	235 (43.6)	219 (40.7)	230 (42.6)	684 (42.3)	230 (42.6)	914 (42.4)
Female	304 (56.4)	319 (59.3)	310 (57.4)	933 (57.7)	310 (57.4)	1243 (57.6)
Age in Years (n, %)						
18-49	539 (100)	538 (100)	540 (100)	1617 (100)	540 (100)	2157 (100)
Mean	34.8	34.8	34.3	34.7	34.4	34.6
SD	9.3	9.2	9.3	9.3	9.2	9.3
Median	35.0	35.5	35.0	35.0	34.0	35.0
Range	18-49	18-49	18-49	18-49	18-49	18-49
Race (n, %)						
American Indian or Alaska Native	6 (1.1)	2 (0.4)	4 (0.7)	12 (0.7)	4 (0.7)	16 (0.7)
Asian	9 (1.7)	12 (2.2)	6 (1.1)	27 (1.7)	8 (1.5)	35 (1.6)
Black or African American	48 (8.9)	43 (8.0)	55 (10.2)	146 (9.0)	48 (8.9)	194 (9.0)
Multiple	16 (3.0)	23 (4.3)	16 (3.0)	55 (3.4)	26 (4.8)	81 (3.8)
Native Hawaiian or Other	2 (0.4)	1 (0.2)	0 (0.0)	3 (0.2)	1 (0.2)	4 (0.2)

	V116 Lot 1	V116 Lot 2	V116 Lot 3	V116 (Combined)	PPSV23	Total
Pacific Islander						
White	457 (84.8)	457 (84.9)	457 (84.6)	1371 (84.8)	453 (83.9)	1824 (84.6)
Missing	1 (0.2)	0 (0.0)	2 (0.4)	3 (0.2)	0 (0.0)	3 (0.1)
Ethnicity (n, %)						
Hispanic or Latino	98 (18.2)	104 (19.3)	113 (20.9)	315 (19.5)	107 (19.8)	422 (19.6)
Not Hispanic or Latino	438 (81.3)	432 (80.3)	419 (77.6)	1289 (79.7)	430 (79.6)	1719 (79.7)
Not Reported	3 (0.6)	1 (0.2)	7 (1.3)	11 (0.7)	3 (0.6)	14 (0.6)
Unknown	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)	0 (0.0)	2 (0.1)
Country (n, %)						
Austria	34 (6.3)	22 (4.1)	30 (5.6)	86 (5.3)	27 (5.0)	113 (5.2)
Canada	31 (5.8)	25 (4.6)	30 (5.6)	86 (5.3)	25 (4.6)	111 (5.1)
Denmark	27 (5.0)	36 (6.7)	27 (5.0)	90 (5.6)	30 (5.6)	120 (5.6)
Finland	32 (5.9)	37 (6.9)	33 (6.1)	102 (6.3)	35 (6.5)	137 (6.4)
Israel	74 (13.7)	71 (13.2)	64 (11.9)	209 (12.9)	71 (13.1)	280 (13.0)
Poland	35 (6.5)	29 (5.4)	28 (5.2)	92 (5.7)	29 (5.4)	121 (5.6)
Spain	52 (9.6)	56 (10.4)	58 (10.7)	166 (10.3)	61 (11.3)	227 (10.5)
United States	254 (47.1)	262 (48.7)	270 (50.0)	786 (48.6)	262 (48.5)	1048 (48.6)

Source: Table 10-2 in the CSR of Study V116-004 from the original BLA 125814/0.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Reported medical history conditions were generally comparable between the V116 (combined lots) and the PPSV23 intervention groups. The 5 most frequently 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%).

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoints

Table 14 shows that all 3 lots of V116 met the equivalence criteria as assessed by serotype-specific OPA GMTs at 30 days postvaccination for all serotypes included in V116. The bounds of the 95% CI of the serotype-specific OPA GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all serotypes included in V116.

Table 14: Analysis of Postvaccination OPA GMTs (Comparison Across V116 Lots, PP population)

Pneu- moco- ccal Serotype	Group A vs. Group B	V116						GMT Ratio Group A/Group B (95% CI)	p-Values for Equivalence		Serotype Specific Conclusion
		Group A			Group B				Lower	Upper	
		N	n	Estimated GMT	N	n	Estimated GMT				
3	Lot 1 vs. Lot 2	539	524	327.2	538	525	299.0	1.09 (0.96, 1.24)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	524	327.2	540	525	318.8	1.03 (0.90, 1.17)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	525	299.0	540	525	318.8	0.94 (0.83, 1.06)	<0.001	<0.001	Equivalent
6A	Lot 1 vs. Lot 2	539	515	6901.9	538	523	6014.9	1.15 (0.97, 1.35)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	515	6901.9	540	524	6641.2	1.04 (0.88, 1.22)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	523	6014.9	540	524	6641.2	0.91 (0.77, 1.06)	<0.001	<0.001	Equivalent
7F	Lot 1 vs. Lot 2	539	522	7219.8	538	531	6201.8	1.16 (1.01, 1.34)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	522	7219.8	540	527	6657.0	1.08 (0.94, 1.25)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	531	6201.8	540	527	6657.0	0.93 (0.81, 1.07)	<0.001	<0.001	Equivalent
8	Lot 1 vs. Lot 2	539	527	3935.5	538	530	3812.8	1.03 (0.92, 1.16)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	527	3935.5	540	528	3765.8	1.05 (0.93, 1.18)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	530	3812.8	540	528	3765.8	1.01 (0.90, 1.14)	<0.001	<0.001	Equivalent
9N	Lot 1 vs. Lot 2	539	526	18747.4	538	533	17201.6	1.09 (0.94, 1.26)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	526	18747.4	540	531	18557.8	1.01 (0.87, 1.17)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	533	17201.6	540	531	18557.8	0.93 (0.80, 1.07)	<0.001	<0.001	Equivalent
10A	Lot 1 vs. Lot 2	539	524	7570.2	538	529	7796.9	0.97 (0.85, 1.11)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	524	7570.2	540	533	7330.4	1.03 (0.91, 1.18)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	529	7796.9	540	533	7330.4	1.06 (0.93, 1.21)	<0.001	<0.001	Equivalent
11A	Lot 1 vs. Lot 2	539	518	6396.0	538	531	6630.9	0.96 (0.84, 1.11)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	518	6396.0	540	532	6374.5	1.00 (0.87, 1.16)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	531	6630.9	540	532	6374.5	1.04 (0.90, 1.20)	<0.001	<0.001	Equivalent
12F	Lot 1 vs. Lot 2	539	523	7478.5	538	532	6803.0	1.10 (0.96, 1.26)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	523	7478.5	540	528	7329.9	1.02 (0.89, 1.17)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	532	6803.0	540	528	7329.9	0.93 (0.81, 1.07)	<0.001	<0.001	Equivalent

Pneu- moco- ccal Serotype	Group A vs. Group B	V116						GMT Ratio Group A/Group B (95% CI)	p-Values for Equivalence		Serotype Specific Conclusion
		Group A			Group B				Lower	Upper	
		N	n	Estimated GMT	N	n	Estimated GMT				
15A	Lot 1 vs. Lot 2	539	502	10698.5	538	505	10253.9	1.04 (0.89, 1.22)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	502	10698.5	540	513	10692.3	1.00 (0.86, 1.17)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	505	10253.9	540	513	10692.3	0.96 (0.82, 1.12)	<0.001	<0.001	Equivalent
15C	Lot 1 vs. Lot 2	539	522	13133.8	538	527	11441.3	1.15 (0.95, 1.38)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	522	13133.8	540	522	11177.1	1.18 (0.97, 1.42)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	527	11441.3	540	522	11177.1	1.02 (0.85, 1.23)	<0.001	<0.001	Equivalent
16F	Lot 1 vs. Lot 2	539	521	9239.1	538	521	9550.8	0.97 (0.84, 1.11)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	521	9239.1	540	521	9530.1	0.97 (0.84, 1.11)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	521	9550.8	540	521	9530.1	1.00 (0.87, 1.15)	<0.001	<0.001	Equivalent
17F	Lot 1 vs. Lot 2	539	525	17185.3	538	531	17718.6	0.97 (0.85, 1.11)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	525	17185.3	540	532	16886.7	1.02 (0.89, 1.17)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	531	17718.6	540	532	16886.7	1.05 (0.92, 1.20)	<0.001	<0.001	Equivalent
19A	Lot 1 vs. Lot 2	539	527	3187.1	538	533	3123.3	1.02 (0.91, 1.15)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	527	3187.1	540	533	3386.0	0.95 (0.84, 1.07)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	533	3123.3	540	533	3368.0	0.93 (0.82, 1.04)	<0.001	<0.001	Equivalent
20A	Lot 1 vs. Lot 2	539	524	16339.3	538	525	16676.2	0.98 (0.84, 1.14)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	524	16339.3	540	525	15302.4	1.07 (0.92, 1.24)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	525	16676.2	540	525	15302.4	1.09 (0.94, 1.27)	<0.001	<0.001	Equivalent
22F	Lot 1 vs. Lot 2	539	521	11638.5	538	523	10614.3	1.10 (0.93, 1.29)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	521	11638.5	540	529	11346.7	1.03 (0.87, 1.21)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	523	10614.3	540	529	11346.7	0.94 (0.80, 1.10)	<0.001	<0.001	Equivalent
23A	Lot 1 vs. Lot 2	539	509	8437.4	538	521	8459.8	1.00 (0.85, 1.17)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	509	8437.4	540	520	8322.8	1.01 (0.86, 1.19)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	521	8459.8	540	520	8322.8	1.02 (0.87, 1.19)	<0.001	<0.001	Equivalent
23B	Lot 1 vs. Lot 2	539	526	2964.1	538	530	2435.5	1.22 (1.00, 1.48)	<0.001	<0.001	Equivalent

Pneu- moco- ccal Serotype	Group A vs. Group B	V116						GMT Ratio Group A/Group B (95% CI)	p-Values for Equivalence		Serotype Specific Conclusion
		Group A			Group B				Lower	Upper	
		N	n	Estimated GMT	N	n	Estimated GMT				
	Lot 1 vs. Lot 3	539	526	2964.1	540	527	3035.5	0.98 (0.80, 1.19)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	530	2435.5	540	527	3035.5	0.80 (0.66, 0.97)	<0.001	<0.001	Equivalent
24F	Lot 1 vs. Lot 2	539	522	4861.3	538	522	4783.4	1.02 (0.88, 1.18)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	522	4861.3	540	524	4758.8	1.02 (0.88, 1.18)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	522	4783.4	540	524	4758.8	1.01 (0.87, 1.16)	<0.001	<0.001	Equivalent
31	Lot 1 vs. Lot 2	539	516	9052.0	538	527	8831.6	1.02 (0.87, 1.20)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	516	9052.0	540	522	8870.7	1.02 (0.87, 1.20)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	527	8831.6	540	522	8870.7	1.00 (0.85, 1.17)	<0.001	<0.001	Equivalent
33F	Lot 1 vs. Lot 2	539	521	37994.1	538	529	34227.3	1.11 (0.93,1.33)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	521	37994.1	540	526	35182.5	1.08 (0.90, 1.29)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	529	34227.3	540	526	35182.5	0.97 (0.81, 1.16)	<0.001	<0.001	Equivalent
35B	Lot 1 vs. Lot 2	539	523	12971.8	538	528	12586.6	1.03 (0.91, 1.17)	<0.001	<0.001	Equivalent
	Lot 1 vs. Lot 3	539	523	12971.8	540	527	12494.5	1.04 (0.91, 1.18)	<0.001	<0.001	Equivalent
	Lot 2 vs. Lot 3	538	528	12586.6	540	527	12494.5	1.01 (0.89, 1.14)	<0.001	<0.001	Equivalent

Source: Table 14.2-1 in CSR of Study V116-004 from the original BLA 125814/0.

Reviewer's Comment: The primary immunogenicity analysis was also conducted on the FAS population and the results were consistent with those in the PP population.

6.2.11.2 Analyses of Secondary Endpoints

Table 15 and Table 16 show that serotype-specific OPA GMTs at 30 days postvaccination were generally comparable between the V116 (combined lots) and PPSV23 intervention groups for the common serotypes and higher in the V116 (combined lots) group for the serotypes unique to V116, respectively.

Table 15: Analysis of Postvaccination OPA GMTs for Common Serotypes (V116 Combined lots and PPSV23) on PP population

Pneumococcal Serotype	V116 (Combined Lots) (N = 1617)		PPSV23 (N = 540)		GMT Ratio (95% CI) (V116 (Combined Lots) /PPSV23)
	n	GMT	n	GMT	
3	1574	316.5	534	339.8	0.93 (0.84, 1.03)
7F	1580	6702.2	531	5058.1	1.33 (1.18, 1.49)
8	1585	3847.3	537	4543.3	0.85 (0.77, 0.93)
9N	1590	18166.7	533	19031.9	0.95 (0.85, 1.08)
10A	1586	7618.2	534	5763.0	1.32 (1.18, 1.48)
11A	1581	6494.4	534	3728.0	1.74 (1.56, 1.95)
12F	1583	7196.9	534	5207.5	1.38 (1.22, 1.56)
17F	1588	17330.5	536	10159.9	1.71 (1.53, 1.91)
19A	1593	3222.9	533	3474.7	0.93 (0.84, 1.03)
20A	1574	16183.8	533	10994.2	1.47 (1.30, 1.67)
22F	1573	11118.1	530	8308.0	1.34 (1.17, 1.53)
33F	1576	35684.3	533	42515.6	0.84 (0.73, 0.97)

Source: Table 14.2-3 in the CSR of Study V116-004 from the original BLA 125814/0.

Table 16: Analysis of Postvaccination OPA GMTs for Unique Serotypes in V116 (V116 Combined lots and PPSV23) on PP population

Pneumococcal Serotype	V116 (Combined Lots) (N = 1617)		PPSV23 (N = 540)		GMT Ratio (95% CI) (V116 (Combined Lots) /PPSV23)
	n	GMT	n	GMT	
6A	1562	6491.7	529	1866.4	3.48 (3.01, 4.02)
15A	1520	10520.0	512	2608.5	4.03 (3.56, 4.56)
15C	1571	11922.3	529	4112.0	2.90 (2.49, 3.38)
16F	1563	9415.3	527	2532.2	3.72 (3.32, 4.17)
23A	1550	8428.3	519	1056.1	7.98 (6.84, 9.31)
23B	1583	2825.4	533	119.1	23.72 (19.71, 28.55)
24F	1568	4892.9	518	250.3	19.55 (16.70, 22.88)
31	1565	8865.6	531	654.5	13.55 (11.68, 15.71)

Pneumococcal Serotype	V116 (Combined Lots) (N = 1617)		PPSV23 (N = 540)		GMT Ratio (95% CI) (V116 (Combined Lots) /PPSV23)
	n	GMT	n	GMT	
35B	1578	12798.6	537	3452.1	3.71 (3.36, 4.09)

Source: Table 14.2-4 in the CSR of Study V116-004 from the original BLA 125814/0.

Reviewer's Comment: Serotype-specific IgG GMCs at 30 days postvaccination with V116 for all serotypes were also computed, and the results were comparable across the 3 lots and consistent with the primary analysis based on OPA GMTs at 30 days postvaccination. Serotype-specific IgG GMCs at 30 days postvaccination were also computed between the V116 (combined lots) and PPSV23 intervention groups and the results were consistent with the primary analysis based on OPA GMTs. Both OPA responses and IgG responses, serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold rise in serotype-specific OPA and IgG responses from baseline to 30 days postvaccination were also comparable across 3 lots of V116 for all serotypes in V116.

6.2.11.3 Subpopulation Analyses

Subgroup analyses were carried out based on sex, race, ethnicity, and number of risk factors.

Reviewer's Comment: Results from subgroup analyses were consistent with those observed in overall PP population.

6.2.12 Safety Analyses

Safety results are briefly summarized in this section.

6.2.12.1 Methods

All solicited AEs were summarized according to defined severity grading scales. Frequencies and percentages of subjects experiencing each AE were presented for each symptom severity. The unsolicited AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 and grouped by preferred terms (PTs) into frequency tables per system organ class (SOC). When an AE occurred more than once for a subject, the maximal severity and duration of the maximal severity were counted.

6.2.12.3 Deaths

Only 1 death due to road traffic accident was reported in the PPSV23 arm and the event was considered not related to the study vaccine by the investigator.

6.2.12.4 Overall Serious Adverse Events

There were a total of 1616 participants in the APaT population for V116 combined lots and 541 participants in APaT for PPSV23 arm. The proportion of participants with SAEs was low; 0.9% (14 subjects) in the V116 (combined lots) and 1.1% (6 subjects) in the PPSV23 intervention groups. None of the SAEs were considered by the investigator to be vaccine related.

6.2.12.5 Solicited Local and Systemic Adverse Events

Solicited local and systemic AEs from Day 1 through Day 5 postvaccination are summarized in Table 17.

Table 17: Individuals With Solicited Local and Systemic Adverse Events Within 5 Days Postvaccination in Pneumococcal Vaccine-Naïve Adults 18 through 49 Years of Age

		V116 (combined lots) n (%)	PPSV23 n (%)
Individuals in population		1616	541
One or more solicited AEs		1263 (78.2)	387 (71.5)
Local AE	Severity		
Injection Site Pain	Total	1184 (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)
Injection Site Erythema	Total	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)
Injection Site Swelling	Total	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 AE	Severity		
Fatigue	Total	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	Total	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	Total	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	Total	48 (3.0)	12 (2.2)
	≥38.0°C (100.4°F) to <38.5°C (101.3°F)	31 (1.9)	4 (0.7)
	≥38.5°C (101.3°F) to <39.0°C (102.2°F)	11 (0.7)	2 (0.4)
	≥39.0°C (102.2°F) to <40.0°C (104.0°F)	4 (0.2)	5 (0.9)
	≥40.0°C (104.0°F)	2 (0.1)	1 (0.2)

Source: Adapted from Table 14.3-12 in CSR of Study V116-004 from the original BLA 125814/0.

6.2.12.6 Unsolicited Adverse Events

The proportions of participants with unsolicited AEs reported within 30 days of vaccination (excluding solicited AEs reported Day 1 through Day 5 postvaccination) were generally comparable between the V116 (combined lots) and PPSV23 intervention groups. 442 (27.4%) subjects in the V116 (combined lots) arm and 142 (26.2%) subjects in the PPSV23 arm experienced one or more unsolicited AEs.

Reviewer's Comment: Subgroup analyses based on sex, race, ethnicity, and number of risk factors were performed if there were more than 5% of participants who received V116 or PPSV23 in each intervention group within that subgroup. Safety results for each subgroup analyzed were generally consistent with those in the overall population. In some AE categories, lower proportions of participants with AEs were observed in the Black or African American (compared with white) and Hispanic or Latino (compared with Not Hispanic or Latino) subgroups, regardless of the intervention groups. That is, there were lower proportions of Black or African American compared to proportions of White who experienced injection site erythema, injection site pain, fatigue, headache, myalgia, and pyrexia irrespective of intervention groups. In the PPSV23 intervention group, the proportions of Black or African American compared to White were higher in injection site swelling and SAEs. Similarly, proportions of Hispanic or Latino compared to Not Hispanic or Latino were lower in injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, and pyrexia across all intervention groups, except for SAEs in the PPSV23 intervention group.

6.3 Study V116-005 (Phase 3)

Title of the study: A Phase 3, randomized, double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, and immunogenicity of V116 when administered concomitantly with influenza vaccine in adults 50 years of age or older

Study initiation date: September 23, 2022 (first participant first visit)

Study completion date: June 28, 2023 (last data available)

6.3.1 Objectives

Primary Objectives:

- To evaluate the safety and tolerability of V116 when administered concomitantly with quadrivalent influenza vaccine (QIV) compared with V116 administered sequentially with QIV as assessed by the proportion of participants with AEs.
- To compare the serotype-specific OPA GMTs at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV.
- To compare the strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV administered concomitantly with V116 compared with QIV administered sequentially with V116.

Secondary Objectives:

- To evaluate serotype-specific IgG GMCs at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV.
- Within each vaccination group, to evaluate the serotype-specific GMFRs and the proportion of participants who achieve a serotype-specific ≥ 4 -fold rise from baseline to 30 days postvaccination with V116 for both OPA and IgG responses for participants administered V116 concomitantly with QIV and participants administered V116 sequentially with QIV.
- Within each vaccination group, to evaluate the strain-specific (1) GMFRs from baseline to 30 days postvaccination with QIV, (2) proportions of participants with an HAI titer $\geq 1:40$ at 30 days postvaccination with QIV, and (3) proportions of participants that seroconvert at 30 days postvaccination with QIV for participants administered QIV concomitantly with V116 and participants administered QIV sequentially with V116.

Tertiary/Exploratory Objectives:

- To evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV.

6.3.2 Design Overview

This was a randomized, placebo-controlled, parallel-group, multisite, double-blind study of V116 in adults ≥ 50 years of age who receive V116 administered concomitantly with QIV or V116 administered sequentially with QIV. Approximately 1000 participants were randomly assigned in a 1:1 ratio to receive either V116 administered concomitantly with QIV or V116 administered sequentially with QIV. Randomization was stratified by participant age at enrollment (50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥ 85 years) and by pneumococcal vaccination status (PCV13- and PPSV23-naïve, prior receipt of PCV13 only, prior receipt of PPSV23 only, and prior receipt of both PCV13 and PPSV23). At least 50% of participants will be ≥ 65 years of age and at least 50% of participants will be naïve to PCV13 and PPSV23. At the end of the study, 50% of participants were ≥ 65 YOA and 70.6% participants were PCV13- and PPSV23-naïve.

An eVRC was used by all participants to record solicited injection-site AEs, solicited systemic AEs, and daily body temperature from Day 1 through Day 5 postvaccination. Unsolicited AEs were collected through Day 30 postvaccination. Information for SAEs and deaths, regardless of whether the events were considered to be vaccine-related by the investigator, were collected through Day 180.

Blood samples for immunogenicity assays were drawn on Day 1 and at 30 days after each vaccination.

Because of the different appearance of V116 and placebo, a double-blinded technique with in-house blinding was used. V116 and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. Although QIV was provided open label in this study, it was also prepared and/or dispensed and administered

by the unblinded study-site personnel for consistency. To avoid bias, contact between the unblinded study site personnel and study participants was strictly prohibited for any study-related procedures/assessments other than administration of study vaccines. Blinded site personnel were responsible for all other study procedures/assessments.

6.3.3 Population

Adult males or females, ≥ 50 YOA, at the time of informed consent were eligible for inclusion if they met the following criteria:

- The participant might have underlying chronic conditions if they were assessed to be stable as per the investigator's judgment.
- 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 WOCBP, or
 - A WOCBP and
 - Used an acceptable contraceptive method or was abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), during the intervention period and for at least 6 weeks after the last dose of study intervention.
 - Had a negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention.
 - Medical history, menstrual history, and recent sexual activity had been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- The participant (or legally acceptable representative) had provided documented informed consent for the study. The participant might also provide documented informed consent for FBR and/or assay development sample collection. However, the participant might be enrolled in the study without providing consent for FBR or assay development sample collection.
- The participant had the ability to complete eVRC data collection without assistance, based on judgment of the investigator.

6.3.4 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 μ g of each PnPs antigen (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B). The QIV vaccine was injected as a single dose of 0.5 mL suspension intramuscularly. For the placebo, a single dose of 0.5 mL sterile saline solution was prepared and administered intramuscularly.

6.3.6 Sites and Centers

This study was conducted at 56 sites within United States.

6.3.7 Surveillance/Monitoring

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

6.3.8 Endpoints and Criteria for Study Success

Primary Endpoints:

- *Safety endpoints*
 - Proportion of participants with solicited injection-site AEs from Day 1 through Day 5 postvaccination.
 - Proportion of participants with solicited systemic AEs from Day 1 through Day 5 postvaccination.
 - Proportion of participants with vaccine-related SAEs from Day 1 through the duration of participation in the study.
- Immunogenicity endpoints
 - Serotype-specific OPA GMTs at 30 days postvaccination with V116. V116 administered concomitantly with QIV is noninferior to V116 administered sequentially with QIV as assessed by serotype-specific OPA GMTs at 30 days postvaccination with V116. The statistical success criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the OPA GMT ratio [concomitant group/sequential group] to be >0.50 .
 - Strain-specific HAI GMTs at 30 days postvaccination with QIV. QIV administered concomitantly with V116 is noninferior to QIV administered sequentially with V116 as assessed by strain-specific HAI GMTs at 30 days postvaccination with QIV. The statistical criterion for noninferiority requires the lower bound of the 2-sided 95% CI of the HAI GMT ratio [concomitant group/sequential group] to be greater than 0.67.

Secondary Endpoints:

- Serotype-specific IgG GMCs at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV.
- Serotype-specific OPA and IgG responses within each vaccination group, to evaluate the serotype-specific GMFRs and the proportion of participants who achieve a serotype-specific ≥ 4 -fold rise from baseline to 30 days postvaccination with V116 for both OPA and IgG responses for participants in concomitant and sequential groups.
- Strain-specific HAI responses within each vaccination group, to evaluate the strain-specific (1) GMFRs from baseline to 30 days postvaccination with QIV, (2) proportions of participants with an HAI titer $\geq 1:40$ at 30 days postvaccination with QIV, and (3) proportions of participants that seroconvert at 30 days postvaccination with QIV for participants in concomitant and sequential groups.

Tertiary/Exploratory Objectives:

- Serotype-specific OPA and IgG responses to evaluate the cross-reactive immune responses to serotypes within a serogroup at 30 days postvaccination with V116 administered concomitantly with QIV compared with V116 administered sequentially with QIV.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Intervention randomization occurred centrally using an IRT system. Participants were assigned randomly in a 1:1 ratio to receive V116 administered concomitantly with QIV or V116 administered sequentially with QIV. Intervention randomization was stratified according to the following factors:

- *Participants age at time of randomization*: 50 to 64 YOA, 65 to 74 YOA, 75 to 84 YOA, ≥ 85 YOA. At least 50% of participants were supposed to be ≥ 65 YOA.
- *Prior pneumococcal vaccination status*: PCV13- and PPSV23-naïve, prior receipt of PCV13 only, prior receipt of PPSV23 only, prior receipt of PCV13 and PPSV23. At least 50% of participants were supposed to be naïve to PCV13 and PPSV23.

Analysis Sets:

- *PP population*: The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. Potential deviations that might result in the exclusion of a participant from the PP population for all immunogenicity analyses included:
 - Failure to receive the assigned regimen as per randomization schedule at Visit 1 (Day 1),
 - Receipt of prohibited medication or prohibited vaccine before study vaccination.

Additional potential deviations that might result in the exclusion of a participant's measurement from a specific time point assessment in the PP population for immunogenicity analyses included:

- Failure to receive study vaccine at Visit 3 (Day 30),
 - Failure to receive correct clinical material as per randomization schedule at Visit 3 (Day 30),
 - Receipt of prohibited medication or prohibited vaccine before a blood sample collection,
 - Collection of blood sample outside the prespecified window. As an exception, participants who return for postvaccination blood sample collection 1 day before or 1 day after the prespecified window will be included in the PP population for immunogenicity analyses.
- *FAS population*: The FAS population consists 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 immunogenicity data using the FAS population.
- *ApaT population*: ApaT consists of all randomized participants who received at least 1 dose of study vaccines. Participants were included in the group corresponding to the study intervention they actually received for the analysis of safety data using the ApaT population. At least 1 temperature measurement obtained subsequent to study intervention was required for inclusion in the analyses of temperature.

Primary Immunogenicity Analyses:

Primary immunogenicity analyses were conducted for each serotype separately on the PP set and supportive analyses were carried out on FAS. The following primary hypotheses

were tested. First, suppose GMT₁ is the serotype-specific OPA GMT for V116 in the concomitant group and GMT₂ is the serotype-specific OPA GMT for V116 in the sequential group. Also, let GMT₃ be the strain-specific HAI GMT in the concomitant group and GMT₄ be the strain-specific HAI GMT in sequential group.

H1: Noninferiority hypotheses for serotypes in V116

For each of 21 serotypes in V116, the primary noninferiority hypothesis (H1) regarding OPA GMTs between concomitant and sequential groups, H₀: GMT₁/ GMT₂ ≤ 0.50 versus H₁: GMT₁/ GMT₂ > 0.50 was conducted at 1-sided α=0.025.

H2: Noninferiority hypotheses for strains in QIV

For each of 4 strains in QIV, the primary noninferiority hypothesis (H2) regarding HAI GMTs between concomitant and sequential groups, H₀: GMT₃/ GMT₄ ≤ 0.67 versus H₁: GMT₃/ GMT₄ > 0.67 was conducted at 1-sided α=0.025.

To address the 2 primary immunogenicity objectives, the serotype-specific estimation of OPA GMTs at 30 days postvaccination with V116 and strain-specific estimation of HAI GMTs at 30 days postvaccination with QIV, 95% CI, and the hypothesis test (ie, 1-sided p-value) were calculated using the cLDA method proposed by Liang and Zeger (2000). The model considered the log-transformed antibody titers at baseline and 30 days postvaccination as response vector. The repeated-measures model included terms for vaccination group, time, the interaction of time-by-vaccination group, age stratum at baseline, prior pneumococcal vaccination status, the interaction of age stratum-by-time, and the interaction of prior pneumococcal vaccination status-by-time. This model allowed for different baseline means for each stratum but restricted the baseline mean within both the age stratum levels and the prior pneumococcal vaccination status stratum levels 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 are missing either the baseline or postbaseline measurements.

This study would be considered to have met its primary immunogenicity objectives if noninferiority was demonstrated with respect to OPA GMTs for the 21 serotypes in V116 and HAI GMTs for the 4 influenza strains in QIV at a 1-sided 2.5% alpha-level. The comparisons were made individually for each of the 21 serotypes and the 4 influenza strains to control the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment was made.

Primary Safety Analyses:

Safety analyses were based on the ApaT set. Safety analyses included 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 M&N method (1985).

Sample Size and Power for Immunogenicity Analyses:

For the primary hypotheses, this study was assumed to have approximately 90% power for demonstrating noninferiority of the serotype-specific OPA GMT ratios for the 21

pneumococcal serotypes included in V116 and >99% power for demonstrating noninferiority of the strain-specific HAI GMT ratios for the 4 influenza strains in QIV at an overall 1-sided 2.5% alpha-level, based on the following assumptions:

- 90% evaluability rate (approximately 450 evaluable participants per treatment group) for both primary endpoints (OPA GMT ratios and HAI GMT ratios).
- The underlying OPA GMT ratio was assumed to be 0.80 (concomitant group/sequential group) for the 21 pneumococcal serotypes. The assumption for this ratio was 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 considered to be same as those observed in V116-001 Phase 2. The standard deviations of the natural log titers for the 21 pneumococcal serotypes in V116 ranged from 1.06 to 1.95.
- The underlying HAI GMT ratio were assumed to be 1.0 (concomitant group/sequential group) for the 4 influenza strains. The variabilities for HAI titers in both concomitant and sequential groups were considered to be same as that observed in V114-021. The standard deviations of the natural log titers for the 4 influenza strains ranged from 1.08 to 1.41 in the concomitant group.

The two hypotheses were assumed to be independent leading the overall power for the primary immunogenicity hypotheses to be approximately 90% ($=0.909 \times >0.992$) to achieve the prespecified noninferiority statistical criteria for the 21 serotypes in V116 and the 4 influenza strains in QIV.

Sample Size and Power for Safety Analyses:

Assuming 100% of the randomized participants to be evaluable for safety analyses, there was an 80% chance of observing at least 1 SAE among 500 participants in the concomitant group if the underlying incidence of an SAE was 0.32% (1 of every 311 participants receiving the vaccine), and a 50% chance of observing at least 1 SAE among 500 participants in the concomitant group if the underlying incidence of an SAE was 0.14% (1 of every 721 participants receiving the vaccine). If no SAEs were observed among 500 participants in the concomitant group, this study would provide 97.5% confidence that the underlying percentage of participants with an SAE was <0.74% (1 in every 136 participants) in the concomitant group.

Subgroup Analyses:

Subgroup analyses were performed for the primary immunogenicity endpoints and selected safety endpoints (summary of AEs and summary of solicited AEs). Subgroup analyses were planned based on age, sex, race, ethnicity and prior pneumococcal vaccination status. The ≥ 85 years of age group would be combined with the 75 to 84 years of age group if the number of vaccinated participants in ≥ 85 years of age group was $\leq 5\%$ in either vaccination group.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

The following two unblinding incidents were reported in Study V116-005.

- A document that did not have the correct permission and security setting in the regulatory content management repository was opened by a Sponsor clinical director. This document contained unblinding information for a single participant. Following this, the Sponsor clinical director did not have further involvement in data review of the study. This unblinding event was considered a single incident due to process failure.
- An unblinded pharmacist marked the administered vaccine on the administration log which was visible to the site primary study coordinator and lead clinical research associate. This resulted in unblinding for a single participant. Corrective action was implemented to retrain the study site personnel. The site study coordinator who was unblinded did not have any further contact with or involvement in safety assessment of the participant.

The Applicant did not exclude any participant data from analysis, as neither of these events were classified as important protocol deviations by the Applicant.

Important protocol deviations were reported for 155 (14.4%) participants – 73 (13.5%) in the concomitant group and 82 (15.2%) in the sequential group. Of these, 130 (59 subjects in the concomitant group and 71 in the sequential group) participants had important protocol deviations that were considered to be clinically important. Table 18 shows the subject disposition for study V116-005.

Table 18: Subject Disposition

	Concomitant Group	Sequential Group	Total
Randomized participants	540	540	1080
Vaccinated at Visit 1			
QIV	536	536	1072
V116	534	0	534
Placebo	0	535	535
Vaccinated at Visit 3			
Placebo	522	0	522
V116	0	518	518
Trial Disposition			
Completed	510	507	1017
Discontinued	30	33	63
Death	1	2	3
Lost to follow-up	17	15	32
Physician Decision	0	1	1
Randomized by mistake without study treatment	0	0	1
Withdrawal by subject	12	12	24

	Concomitant Group	Sequential Group	Total
Other	0	2	2
Participants included in OPA analyses (PP set) by timepoints			
Baseline	517	491	1008
Postvaccination	490	449	939
At least one timepoint	525	500	1025
Both baseline and post-vaccination	482	440	922
Participants included in HAI analyses (PP set) by timepoints			
Baseline	515	518	1033
Postvaccination	495	490	985
At least one timepoints	526	526	1052
Both baseline and post-vaccination	484	482	966

Source: Adapted from Table 10-1, Table 14.1-5 and Table 14.1-7 from the CSR of Study V116-005 from the original BLA 125814/0.

6.3.10.1.1 Demographics

Demographic characteristics of the enrolled participants were comparable between the concomitant and sequential groups. Please see Table 19.

Table 19: Vaccinated Participant Characteristics

	Concomitant		Sequential		Total	
	n	Percent	n	Percent	n	Percent
Vaccinated Participants	536	-	536	-	1072	-
Sex						
Male	239	44.6	249	46.5	488	45.5
Female	297	55.4	287	53.5	584	54.5
Age (Years)						
50 to 64	268	50.0	268	50.0	536	50.0
65 to 74	207	38.6	209	39.0	416	38.8
75 to 84	54	10.1	53	9.9	107	10.0
≥85	7	1.3	6	1.1	13	1.2
Mean	64.2	-	64.2	-	64.2	-
SD	8.4	-	8.4	-	8.4	-
Median	64.5	-	64.5	-	64.5	-
Range	50-91	-	50-91	-	50-91	-
Race						
American Indian or Alaska Native	1	0.2	4	0.7	5	0.5
Asian	3	0.6	10	1.9	13	1.2
Black or African American	107	20.0	101	18.8	208	19.4
Multiple	13	2.4	8	1.5	21	2.0
Native Hawaiian or Other Pacific Islander	1	0.2	1	0.2	2	0.2

	Concomitant		Sequential		Total	
	n	Percent	n	Percent	n	Percent
White	410	76.5	412	76.9	822	76.7
Missing	1	0.2	0	0.0	1	0.1
Ethnicity						
Hispanic or Latino	127	23.7	125	23.3	252	23.5
Not Hispanic or Latino	403	75.2	409	76.3	812	75.7
Not reported	4	0.7	2	0.4	6	0.6
Unknown	2	0.4	0	0.0	2	0.2
Country						
United States	536	100.0	536	100.0	1072	100.0
Prior pneumococcal vaccination status						
PCV13- and PPSV23-naive	376	70.1	381	71.1	757	70.6
Prior receipt of PCV13 only	29	5.4	29	5.4	58	5.4
Prior receipt of PPSV23 only	72	13.4	68	12.7	140	13.1
Prior receipt of PCV13 and PPSV23	59	11.0	58	10.8	117	10.9

Source: Table 10-2 from the CSR of Study V116-005 from the original BLA 125814/0.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Reported medical history conditions were generally comparable between the concomitant and sequential intervention groups. The 5 most frequently reported medical history conditions overall (by preferred term) were hypertension (38.8%), osteoarthritis (21.0%), diabetes mellitus (20.4%), gastroesophageal reflux disease (18.3%), and seasonal allergy (17.4%).

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoints

Table 20 shows that V116 administered concomitantly with QIV met the criterion for noninferiority to V116 administered sequentially with QIV (lower bound of the 2-sided 95% CI of the OPA GMT ratio [concomitant/sequential] >0.5) for 20 of 21 pneumococcal serotypes at 30 days postvaccination with V116. Serotype 23B did not meet the noninferiority criterion as the lower bound of the 95% CI of the OPA GMT ratio was 0.44.

Table 20: Analysis of Postvaccination OPA GMTs (PP Population)

Pneumococcal Serotype	Concomitant (N=536)		Sequential (N=536)		GMT Ratio, 95% CI (Concomitant/ Sequential)	p-Value (1-sided)
	n	GMT	n	GMT		
3	519	209.2	497	250.1	0.84 (0.72, 0.97)	<0.001
6A	521	2056.4	496	2608.2	0.79 (0.66, 0.94)	<0.001
7F	521	2399.2	496	3275.4	0.73 (0.63, 0.85)	<0.001
8	519	1508.9	497	2135.7	0.71 (0.61, 0.82)	<0.001

Pneumococcal Serotype	Concomitant (N=536)		Sequential (N=536)		GMT Ratio, 95% CI (Concomitant/ Sequential)	p-Value (1-sided)
	n	GMT	n	GMT		
9N	522	5075.6	499	7566.6	0.67 (0.57, 0.79)	<0.001
10A	524	3033.6	499	3966.2	0.76 (0.65, 0.91)	<0.001
11A	519	2576.3	499	4051.1	0.64 (0.54, 0.75)	0.002
12F	525	1869.9	499	2449.5	0.76 (0.62, 0.94)	<0.001
15A	511	4670.6	458	6559.7	0.71 (0.60, 0.85)	<0.001
15C	522	3426.0	493	4832.6	0.71 (0.58, 0.87)	<0.001
16F	522	5371.5	498	7757.2	0.69 (0.59, 0.81)	<0.001
17F	520	5783.8	497	7924.3	0.73 (0.62, 0.86)	<0.001
19A	524	1830.1	498	2453.3	0.75 (0.65, 0.85)	<0.001
20A	522	5172.8	498	6986.9	0.74 (0.63, 0.87)	<0.001
22F	517	3194.9	490	4158.2	0.77 (0.65, 0.91)	<0.001
23A	511	3358.2	486	4319.9	0.78 (0.63, 0.96)	<0.001
23B	522	934.3	498	1664.5	0.56 (0.44, 0.72)	0.177
24F	517	2996.5	494	4143.1	0.72 (0.61, 0.86)	<0.001
31	522	2997.4	499	4390.6	0.68 (0.56, 0.83)	<0.001
33F	520	9032.5	492	10765.1	0.84 (0.70, 1.01)	<0.001
35B	522	7701.4	495	9940.2	0.77 (0.67, 0.89)	<0.001

Source: Table 14.2-1 from the CSR of Study V116-005 from the original BLA 125814/0.

Table 21 shows that QIV administered concomitantly with V116 met the criterion for noninferiority to QIV administered sequentially with V116 (lower bound of the 2-sided 95% CI of the GMT ratio [concomitant/sequential] >0.67) for 3 of 4 influenza strains at 30 days postvaccination with QIV. Influenza strain A/H3N2 did not meet the noninferiority criterion as the lower bound of the 95% CI of the HAI GMT ratio was 0.67 (rounded from 0.6659). A trend toward lower strain-specific HAI GMTs for all influenza strains was observed when QIV was administered concomitantly with V116 compared with QIV administered alone.

Table 21: Analysis of Postvaccination HAI GMTs (PP Population)

Influenza Strain	Concomitant (N=536)		Sequential (N=536)		GMT Ratio 95% CI (Concomitant/ Sequential)	p-Value (1-sided)
	n	GMT	n	GMT		
A/H1N1	526	268.23	526	325.06	0.83 (0.70, 0.97)	0.007
A/H3N2	526	128.07	526	163.06	0.79 (0.67, 0.93)	0.030
B/Victoria	526	70.02	526	85.66	0.82 (0.70, 0.95)	0.005
B/Yamagata	526	31.80	526	35.86	0.89 (0.78, 1.00)	<0.001

Source: Table 14.2-3 from the CSR of Study V116-005 from the original BLA 125814/0.

Reviewer's Comment: Table 20 shows a trend toward lower serotype-specific OPA GMTs for all serotypes when V116 was administered concomitantly with QIV compared with V116 administered alone. Table 21 shows a trend toward lower strain-specific HAI GMTs for all influenza strains when QIV was administered concomitantly with V116 compared with QIV administered alone. The primary immunogenicity analyses were also conducted on FAS population and the results were consistent with those observed in PP population.

6.3.11.2 Analyses of Secondary Endpoints

One of the secondary immunogenicity analyses included serotype-specific IgG GMCs at 30 days postvaccination with V116 and results were consistent with the trends observed for primary analysis of OPA GMTs.

Reviewer's Comment: For both V116 OPA and IgG responses, a trend toward lower serotype-specific GMFRs and proportions of participants with a ≥ 4 -fold increase from baseline to 30 days postvaccination with V116 was observed for most serotypes when V116 was administered concomitantly with QIV compared with V116 administered alone. Strain-specific GMFRs, the proportions of participants with HAI titers $\geq 1:40$, and the proportions of participants who seroconverted from baseline to 30 days postvaccination with QIV were generally comparable between the concomitant and sequential intervention groups for all 4 influenza strains.

6.3.11.3 Subpopulation Analyses

Subgroup analyses were carried out based on age, sex, race, ethnicity and prior pneumococcal vaccination status, and the estimate of the between-group intervention effect was only calculated within each subgroup if there were more than 5% of the total vaccinated participants in each intervention group.

Reviewer's Comment: Results from subgroup analyses based on sex, race, and ethnicity were generally consistent with those from the overall population. In the subgroup analysis based on age, the age groups 75 to 84 YOA and ≥ 85 YOA were combined. Serotype-specific OPA GMT ratios and strain-specific HAI GMT ratios (concomitant/sequential) within each age subgroups (50 to 64, 65 to 74, and ≥ 75 years of age) were generally consistent with the ratios observed in the overall population, but within each intervention group, there was a trend toward lower serotype-specific OPA GMTs 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), except for serotype 31 in concomitant group and serotypes 24F and 35B in sequential group for age group 65 to 74 YOA, and serotypes 3 and 24F in sequential group for age group ≥ 75 YOA. For subgroup analysis based on prior pneumococcal vaccination status, Serotype-specific OPA GMT ratios [concomitant/sequential] within each subgroup based on prior pneumococcal vaccination status were generally consistent with the ratios observed in the overall population, but Strain-specific HAI GMT ratios [concomitant/sequential] were higher in participants with prior receipt of PCV13 and PPSV23 vaccination status than the other subgroups and overall population.

6.3.12 Safety Analyses

Safety results are briefly summarized in this section.

6.3.12.1 Methods

All solicited AEs were summarized according to defined severity grading scales. Frequencies and percentages of subjects experiencing each AE were presented for each symptom severity. The unsolicited AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 and grouped by preferred terms (PTs) into frequency tables per system organ class (SOC). When an AE occurred more than once for a subject, the maximal severity and duration of the maximal severity were counted.

6.3.12.3 Deaths

Three deaths were reported in Study V116-005. One (0.2%) death occurred in the concomitant group (metastatic malignant melanoma), and 2 (0.4%) deaths occurred in the sequential group (septic shock and victim of homicide). None of the events were considered by the investigator to be related to study vaccine.

6.3.12.4 Overall Serious Adverse Events

There were 534 participants in ApaT for the concomitant group and 535 participants in ApaT for the sequential group. The proportion of participants with SAEs was low; 1.9% (10 subjects) in the concomitant group and 3.2% (17 subjects) in the sequential groups following any vaccination. One participant in the sequential group had an SAE of bronchospasm that was considered vaccine-related by the investigator. The event occurred within 30 minutes following Vaccination 2 (V116), required medical intervention, and was assessed by the investigator as an SAE/other important medical event (medically significant but not life threatening or requiring hospitalization). The event resolved after approximately 24 hours.

6.3.12.5 Solicited Local and Systemic Adverse Events

Solicited local and systemic AEs from Day 1 through Day 5 postvaccination are summarized in Table 22.

Table 22: Individuals With Solicited Local and Systemic Adverse Events Within 5 Days Postvaccination Following Any Vaccination

		Concomitant Group n (%)	Sequential Group n (%)
Individuals in population		534	535
One or more solicited AEs		361 (67.6)	348 (65.0)
Local AE	Severity		
Injection Site Pain	Total	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)
	Total	61 (11.4)	59 (11.0)
	Mild	47 (8.8)	47 (8.8)

		Concomitant Group n (%)	Sequential Group n (%)
Injection Site Erythema	Moderate	11 (2.1)	11 (2.1)
	Severe	3 (0.6)	1 (0.2)
Injection Site Swelling	Total	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 AE	Severity		
Fatigue	Total	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	Total	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	Total	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	Total	10 (1.9)	13 (2.4)
	≥38.0°C (100.4°F) to <38.5°C (101.3°F)	5 (0.9)	7 (1.3)
	≥38.5°C (101.3°F) to <39.0°C (102.2°F)	2 (0.4)	4 (0.7)
	≥39.0°C (102.2°F) to <40.0°C (104.0°F)	3 (0.6)	2 (0.4)

Source: Table 14.3-19 from the CSR of Study V116-005 from the original BLA 125814/0.

6.3.12.6 Unsolicited Adverse Events

The proportions of participants with unsolicited AEs reported within 30 days of vaccination (excluding solicited AEs reported Day 1 through Day 5 postvaccination) was ≤31.4% and generally comparable between concomitant and sequential groups. There were 144 (27%) subjects in the concomitant group and 168 (31.4%) subjects in the sequential group experienced one or more unsolicited AEs.

Reviewer's Comment: Subgroup analyses based on age, sex, race, ethnicity and prior pneumococcal vaccination status were performed if there were more than 5% of the total participants in each intervention group within that subgroup. Safety results for each subgroup analyzed were generally consistent with those in the overall population. A trend toward lower proportions of participants with solicited AEs was observed in older age groups (65 to 74 and ≥75 years of age) compared with younger age groups (50 to 64 years of age) in the concomitant group. A trend toward higher proportions of participants with AEs was observed in female participants compared with male participants in both intervention groups. A trend toward lower proportions of participants with AEs was observed in participants who were Black or

African American compared with participants who were White in the concomitant group. A trend toward lower proportions of participants with AEs was observed in participants who were Hispanic or Latino compared with participants who were not Hispanic or Latino in both intervention groups. A trend toward higher proportions of participants with AEs was observed in participants with prior receipt of PCV13 and PPSV23 compared with PCV13- and PPSV23-naïve participants in both intervention groups.

6.4 Study V116-006 (Phase 3)

Title of the study: A Phase 3 clinical study to evaluate the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-experienced adults 50 years of age or older

Study initiation date: July 12, 2022 (first participant first visit)

Study completion date: June 22, 2023 (last data available)

6.4.1 Objectives

Primary Objectives:

- To evaluate the safety and tolerability of V116 as assessed by the proportion of participants with AEs.
- To evaluate the serotype-specific OPA GMTs at 30 days postvaccination for all serotypes included in V116.

Secondary Objectives:

- To evaluate the serotype-specific IgG GMCs at 30 days postvaccination for all serotypes included in V116.
- To evaluate the serotype-specific GMFR and the proportion of participants who achieve a serotype-specific ≥ 4 -fold increase from baseline to 30 days postvaccination for both OPA and IgG responses for all serotypes included in V116.

Tertiary/Exploratory Objective:

- To evaluate the cross-reactive immune responses to serotypes within a serogroups 30 days postvaccination.

6.4.2 Design Overview

This Phase 3 study was conducted in participants ≥ 50 years of age who were pneumococcal vaccine experienced and eligible for enrollment if they received either PCV13, PCV15, PCV20, PPSV23, PCV13+PPSV23, PCV15+PPSV23, or PPSV23+PCV13 ≥ 1 year before enrollment. Approximately 700 participants were enrolled into 1 of 3 parallel cohorts based on the participant's prior pneumococcal vaccination history:

- *Cohort 1:* Approximately 300 participants who were vaccinated with PPSV23 ≥ 1 year prior to enrollment were randomized in a 2:1 ratio to receive either V116 or PCV15 on Day 1. Cohort 1 was double-blind, parallel group, and active comparator-controlled.
- *Cohort 2:* Approximately 300 participants who were vaccinated with PCV13 ≥ 1 year prior to enrollment were randomized in a 2:1 ratio to receive either V116 or PPSV23 on Day 1. Cohort 2 was double-blind, parallel group, and active comparator-controlled.

In Cohort 1 and Cohort 2, randomization was stratified by participant age at enrollment and time since prior pneumococcal vaccination. Study enrollment might be considered complete if at least 250 participants were enrolled into each of these 2 cohorts and if at least 50% of participants in Cohorts 1 and 2 (combined) were ≥ 65 years of age.

- *Cohort 3:* Approximately 100 participants who were vaccinated with PCV13+PPSV23, PCV15+PPSV23, PCV15, PCV20, or PPSV23+PCV13 ≥ 1 year prior to enrollment received V116 on Day 1. Cohort 3 was open-label and single group and enrolled participants until the target enrollment of 100 participants was achieved or until Cohorts 1 and 2 had completed their enrollment.

An eVRC was used by all participants to record solicited injection-site AEs, solicited systemic AEs, and daily body temperature from Day 1 through Day 5 postvaccination. Unsolicited AEs were recorded through Day 30 postvaccination. Information for SAEs and deaths, regardless of whether the events were considered to be vaccine-related by the investigator, were collected through completion of participation in the study. Blood samples for immunogenicity assays were drawn on Day 1 and at 30 days postvaccination (Visit 3).

This study was conducted as a hybrid randomized and blinded, and nonrandomized open label study depending on each specific cohort. Because of the different appearance of V116 and PPSV23/PCV15, a double-blinded technique with in-house blinding was used for Cohort 1 and Cohort 2.

Cohort 3 was open-label. The participants, investigators, and Sponsor personnel were aware of participant treatment assignments after each participant was enrolled and treatment was assigned.

6.4.3 Population

Adult males and females, ≥ 50 YOA, at the time of informed consent were eligible for inclusion if they met the following criteria:

- The participant might have underlying chronic conditions if they were 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.
- 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 WOCBP, or
 - A WOCBP and
 - Used an acceptable contraceptive method or was abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), during the intervention period and for at least 6 weeks after the last dose of study intervention.

- Had a negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention.
- Medical history, menstrual history, and recent sexual activity had been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- The participant (or legally acceptable representative) had provided documented informed consent for the study. The participant might also provide documented informed consent for FBR and/or assay development sample collection. However, the participant might be enrolled in the study without providing consent for FBR or assay development sample collection.
- The participant had the ability to complete eVRC data collection without assistance, based on judgment of the investigator.

6.4.4 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 sterile solution (prefilled syringe) 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, 20, 22F, 23A, 23B, 24F, 31, 33F, and 35B). The comparator product PCV15 is a 15-valent conjugate pneumococcal vaccine which was injected as a single dose of 0.5 mL suspension (prefilled syringe) intramuscularly. Each unit dose consists of 2 µg of each PnPs antigen (1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) and 4 µg of PnPs antigen 6B. The comparator product PPSV23 is a 23-valent conjugate pneumococcal vaccine which was injected as a single dose of 0.5 mL sterile solution (prefilled syringe) 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, and 33F).

6.4.6 Sites and Centers

There were 4 sites in Canada, 1 site in France, 7 sites in Israel, 2 sites in Japan, 6 sites in South Korea, 4 sites in Spain, 2 sites in Taiwan, and 11 sites in United States for Cohort 1. Cohort 2 was conducted at 4 sites in Canada, 1 site in France, 3 sites in Israel, 4 sites in Italy, 2 sites in Japan, 5 sites in South Korea, 3 sites in Spain, 2 sites in Taiwan, and 14 sites in United States. Lastly, there were 2 sites in Canada, 6 sites in Israel, 2 sites in Taiwan, and 10 sites in United States for Cohort 3.

6.4.7 Surveillance/Monitoring

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

6.4.8 Endpoints and Criteria for Study Success

Primary Endpoints:

- *Safety endpoints*
 - Proportion of participants with solicited injection-site AEs from Day 1 through Day 5 postvaccination.
 - Proportion of participants with solicited systemic AEs from Day 1 through Day 5 postvaccination.

- Proportion of participants with vaccine-related SAEs from Day 1 through the duration of participation in the study.
- *Immunogenicity endpoints*
 - Serotype-specific OPA GMTs at 30 days postvaccination.

Secondary Endpoints:

- Serotype-specific OPA GMTs and IgG GMCs at 30 days postvaccination and proportion of participants who received a serotype-specific ≥ 4 -fold increase from baseline to 30 days postvaccination for all serotypes included in V116.

Tertiary/Exploratory Endpoints:

- Serotype-specific OPA and IgG responses to evaluate the cross-reactive immune responses to serotypes within a serogroup 30 days postvaccination.

6.4.9 Statistical Considerations & Statistical Analysis Plan

All consented participants were given a unique screening number that was used to identify the participant for all procedures that occur before randomization. All eligible participants were randomly allocated and received a treatment/randomization number. The treatment/randomization number was used to identify the participant for all procedures occurring after treatment randomization.

Analysis Sets:

- *PP population:* The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. 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 Visit 1 (Day 1),
 - Failure to receive correct clinical material as per randomization schedule,
 - Failure to receive pneumococcal vaccine ≥ 1 year prior to enrollment, as per each specific cohort,
 - Receipt of a prohibited medication or prohibited vaccine prior to study vaccination.

Additional potential deviations that might result in the exclusion of a participant's measurement from a specific time point assessment in the PP population for immunogenicity analyses included:

- Receipt of a prohibited medication or prohibited vaccine prior to a blood sample collection,
- Collection of a blood sample outside of the prespecified window. As an exception, participants who returned to postvaccination blood sample collection 1 day before or 1 day after the prespecified window would be included in the PP population for immunogenicity analyses.
- *FAS population:* The FAS population consists of all randomized participants who received 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 immunogenicity data using the FAS population.

- *APaT population:* APaT consists of all randomized/allocated participants who received at least 1 dose of study intervention. Participants were included in the group corresponding to the study vaccination they actually received for the analysis of safety data using the APaT population. If a participant received a study vaccine that did not belong to the assigned cohort, (eg, a participant from Cohort 1 received PPSV23, or a participant from Cohort 2 received PCV15), this participant was excluded from the APaT population. For Cohort 3, if a participant received an incorrect study vaccination, this participant was excluded from the APaT population. At least 1 temperature measurement obtained subsequent to study intervention was required for inclusion in the analyses of temperature.

Primary Immunogenicity Analyses:

Immunogenicity analyses were conducted on the PP population for each of the 21 pneumococcal serotypes included in V116. To address the primary immunogenicity objective, the evaluation of the OPA GMTs at 30 days postvaccination included descriptive summaries and within-group 95% CIs. The within-group 95% CIs were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

Primary Safety Analyses:

Safety analyses was based on the APaT set. Safety analyses included 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. Within-group CI was calculated using the Clopper Pearson method (1934).

Sample Size and Power for Primary Immunogenicity Analysis:

This was a descriptive study that consists of 3 cohorts, enrolling approximately 700 participants. It was assumed that 90% of the participants will be evaluable for PP immunogenicity analyses at 30 days postvaccination in each cohort.

Sample Size and Power for Safety Analyses:

Assuming 100% of the enrolled participants to be evaluable for safety analyses and 200 participants in Cohort 1 receive V116, there was an 80% chance of observing at least 1 SAE among 300 participants if the underlying incidence of a SAE was 0.80% (1 of every 125 participants receiving the vaccine), and a 50% chance of observing at least 1 SAE among 200 participants if the underlying incidence of a SAE was 0.35% (1 of every 289 participants receiving the vaccine). If no SAEs were observed among the 300 participants, this study would provide 97.5% confidence that the underlying percentage of participants with a SAE was <1.83% (1 in every 55 participants).

Assuming 100% of the enrolled participants to be evaluable for safety analyses and 100 participants in Cohort 2 (Cohort 3) receive V116, there was an 80% chance of observing at least 1 SAE among 100 participants if the underlying incidence of a SAE was 1.60% (1 of every 63 participants receiving the vaccine). There was a 50% chance of observing at least 1 SAE among 100 participants if the underlying incidence of a SAE was 0.69% (1 of every 145 participants receiving the vaccine). If no SAEs were observed among the 100

participants, this study would provide 97.5% confidence that the underlying percentage of participants with a SAE was <3.62% (1 in every 28 participants).

Subgroup Analyses:

Subgroup analyses were performed for selected safety endpoints as well as primary immunogenicity endpoints based on age, sex, race, ethnicity, and time since last prior pneumococcal vaccination. Participants had the last prior pneumococcal vaccination ≥ 10 years were combined to the 5 to 9 years group as the number of vaccinated participants in the ≥ 10 years group was $\leq 5\%$ in either vaccination group. For Cohort 3, subgroup analyses were also carried out based on prior pneumococcal vaccination history (PCV15, PCV20, PCV13+PPSV23, PCV15+PPSV23, PPSV23+PCV13).

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

In the safety database, the pharmacovigilance team unblinded 1 participant in Cohort 1, who received V116, due to a vaccine-related SAE. The Sponsor and site study team remained blinded. There was no impact to the assessment of study data. This event was not classified as an important protocol deviation, nor was the participant excluded from analysis. Important protocol deviations were noted for 23 (4.5%) subjects who received V116, 3 (2.5%) subjects who received PCV15, and 7 (8.2%) subjects who received PPSV23 in this study. Among them, 21 (4.1%) protocol deviations in V116, 2 (1.7%) protocol deviations in PCV15 and 4 (4.7%) protocol deviations in PPSV23 were considered to be clinically important. Table 23 shows the subject disposition of Study V116-006.

Table 23: Disposition of Participants by Cohort

	Cohort 1		Cohort 2		Cohort 3	Total
	V116	PCV15	V116	PPSV23	V116	
Randomized participants	231	119	176	85	106	717
Vaccinated at Visit 1						
V116	229	1	174	0	105	509
PCV15	0	117	0	0	0	117
PPSV23	0	1	0	85	0	86
Trial disposition						
Completed	229	118	173	85	105	710
Discontinued	2	1	3	0	1	7
Lost to follow-up	0	0	1	0	0	1
Randomized by Mistake without study treatment	0	0	1	0	1	2
Withdrawal by subject	2	1	1	0	0	4
Participants included in OPA analyses by time point (PP population)						
Day 1	223	115	169	82	104	693

	Cohort 1		Cohort 2		Cohort 3	Total
	V116	PCV15	V116	PPSV23	V116	
Day 30	215	115	166	78	99	673
At least one time-point	226	115	171	84	105	701
Both Day 1 and Day 30 timepoint	212	115	164	76	98	665

Source: Adapted from Table 10-1, Table 14.1-10, Table 14.1-12 and Table 14.1-14 in the CSR of Study V116-006 from the original BLA 125814/0.

6.4.10.1.1 Demographics

In Cohort 1 and Cohort 2, demographic characteristics of the enrolled participants were generally well-balanced between intervention groups. Please see Table 24 for demographic characteristics for Cohort 1, Cohort 2 and Cohort 3.

Table 24: Vaccinated Participants Characteristics by Cohort

	Cohort 1		Cohort 2		Cohort 3	Total
	V116	PCV15	V116	PPSV23	V116	
Participants	229	119	174	85	105	712
Sex (n, %)						
Male	112 (48.9)	59 (49.6)	74 (42.5)	36 (42.4)	50 (47.6)	331 (46.5)
Female	117 (51.1)	60 (50.4)	100 (57.5)	49 (57.6)	55 (52.4)	381 (53.5)
Age in Years (n, %)						
50-64	48 (21.0)	25 (21.0)	80 (46.0)	39 (45.9)	17 (16.2)	209 (29.4)
≥65	181 (79.0)	94 (79.0)	94 (54.0)	46 (54.1)	88 (83.8)	503 (70.6)
Mean	68.7	69.0	65.5	65.4	71.0	67.9
SD	7.5	7.1	7.8	6.6	7.6	7.7
Median	69.0	69.0	66.0	65.0	71.0	68.0
Range	50-86	51-88	50-83	51-81	53-91	50-91
Race (n, %)						
Asian	96 (41.9)	47 (39.5)	55 (31.6)	25 (29.4)	13 (12.4)	236 (33.1)
Black or African American	6 (2.6)	3 (2.5)	3 (1.7)	1 (1.2)	6 (5.7)	19 (2.7)
Multiple	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	3 (0.4)
White	125 (54.6)	69 (58.0)	116 (66.7)	59 (69.4)	85 (81.0)	454 (63.8)
Ethnicity (n, %)						
Hispanic or Latino	21 (9.2)	17 (14.3)	34 (19.5)	16 (18.8)	14 (13.3)	102 (14.3)
Not Hispanic	206 (90.0)	102 (85.7)	140 (80.5)	69 (81.2)	91 (86.7)	608 (85.4)

	Cohort 1		Cohort 2		Cohort 3	Total
	V116	PCV15	V116	PPSV23	V116	
or Latino						
Not Reported	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Unknown	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Country (n, %)						
Canada	23 (10.0)	10 (8.4)	21 (12.1)	14 (16.5)	7 (6.7)	75 (10.5)
France	1 (0.4)	1 (0.8)	0 (0.0)	2 (2.4)	0 (0.0)	4 (0.6)
Israel	46 (20.1)	25 (21.0)	3 (1.7)	3 (3.5)	22 (21.0)	99 (13.9)
Italy	0 (0.0)	0 (0.0)	24 (13.8)	7 (8.2)	0 (0.0)	31 (4.4)
Japan	31 (13.5)	19 (16.0)	11 (6.3)	2 (2.4)	0 (0.0)	63 (8.8)
South Korea	51 (22.3)	22 (18.5)	17 (9.8)	10 (11.8)	0 (0.0)	100 (14.0)
Spain	17 (7.4)	12 (10.1)	15 (8.6)	6 (7.1)	0 (0.0)	50 (7.0)
Taiwan	13 (5.7)	5 (4.2)	25 (14.4)	13 (15.3)	11 (10.5)	67 (9.4)
United States	47 (20.5)	25 (21.0)	58 (33.3)	28 (32.9)	65 (61.9)	223 (31.3)
Time since last pneumococcal vaccination						
1-4 years	108 (47.2)	54 (45.4)	135 (77.6)	66 (77.6)	78 (74.3)	441 (61.9)
5-9 years	85 (37.1)	45 (37.8)	33 (19.0)	18 (21.2)	27 (25.7)	208 (29.2)
≥10 years	36 (15.7)	20 (16.8)	6 (3.4)	1 (1.2)	0 (0.0)	63 (8.8)

Source: Adapted from Table 10-2 in the CSR of Study V116-006 from the original BLA 125814/0.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In Cohort 1, the 5 most frequently reported medical history conditions (by preferred term) were: hypertension (44.3%), diabetes mellitus (28.4%), hyperlipidemia (20.4%), hypercholesterolemia (16.1%), and gastroesophageal reflux disease (10.9%). In Cohort 2, the 5 most frequently reported medical history conditions (by preferred term) were: hypertension (36.7%), diabetes mellitus (22.0%), hyperlipidemia (15.1%), osteoarthritis (14.3%), and hypercholesterolemia (13.9%). In Cohorts 1 and 2, reported medical history conditions were generally comparable between intervention groups. In Cohort 3, the 5 most frequently reported medical history conditions (by preferred term) were: hypertension (57.1%), hyperlipidemia (38.1%), diabetes mellitus (26.7%), osteoarthritis (21.9%), and hypercholesterolemia (19.0%).

6.4.11 Immunogenicity Analyses

6.4.11.1 Analyses of Primary Endpoints

Table 25 and Table 26 show that V116 elicited immune responses that were generally comparable to PCV15 for the 6 common serotypes and higher than PCV15 for the 15 serotypes unique to V116, as assessed by OPA GMTs at 30 days postvaccination, respectively, in Cohort 1. Table 27 and Table 28 show that V116 elicited immune responses

that were generally comparable to PPSV23 for the 12 common serotypes and higher than PPSV23 for the 9 serotypes unique to V116, as assessed by OPA GMT at 30 days postvaccination, respectively, in Cohort 2. Across all 3 cohorts, V116 was immunogenic for all 21 serotypes contained in the vaccine as assessed by serotype-specific OPA GMTs at 30 days postvaccination.

Table 25: Within Group Analysis of Postvaccination OPA GMTs for Common Serotypes (PP population in Cohort 1)

Pneumococcal Serotypes	V116 (N=229)			PCV15 (N=119)		
	n	GMT	95% CI	n	GMT	95 % CI
3	197	262.1	(224.0, 306.8)	103	226.3	(182.0, 281.4)
6A	191	1653.5	(1347.2, 2029.4)	94	2076.1	(1571.4, 2742.8)
7F	209	2184.4	(1891.4, 2522.8)	110	1750.3	(1404.7, 2181.0)
19A	204	1513.8	(1318.4, 1738.1)	109	2022.9	(1634.1, 2504.3)
22F	206	1983.8	(1698.3, 2317.4)	108	1595.6	(1227.1, 2074.6)
33F	188	4311.9	(3625.1, 5128.9)	99	3397.2	(2665.3, 4330.0)

Source: Table 14.2-1 in the CSR of Study V116-006 from the original BLA 125814/0.

Table 26: Within Group Analysis of Postvaccination OPA GMTs for Unique Serotypes (PP population in Cohort 1)

Pneumococcal Serotypes	V116 (N=229)			PCV15 (N=119)		
	n	GMT	95% CI	n	GMT	95% CI
8	208	1273.0	(1115.1, 1453.3)	113	345.8	(250.5, 477.5)
9N	191	3805.1	(3324.0, 4356.0)	111	2176.5	(1809.6, 2617.9)
10A	209	1986.2	(1637.7, 2408.9)	112	467.5	(337.0, 648.5)
11A	197	1998.5	(1696.9, 2353.8)	100	335.6	(228.9, 491.8)
12F	212	981.8	(782.4, 1232.1)	114	80.5	(54.0, 120.1)
15A	175	4184.9	(3548.3, 4935.6)	93	877.2	(616.2, 1248.7)
15C	206	2307.8	(1878.4, 2835.4)	110	539.6	(371.1, 784.6)
16F	187	3060.5	(2633.8, 3556.3)	107	392.3	(301.3, 510.8)
17F	194	3599.8	(3134.5, 4134.3)	108	939.6	(693.7, 1272.6)
20A	195	2847.4	(2433.3, 3331.8)	110	1058.9	(829.9, 1351.1)
23A	202	2363.9	(1857.4, 3008.5)	91	310.2	(202.1, 476.0)
23B	197	673.2	(517.1, 876.4)	110	153.0	(98.7, 237.1)
24F	201	1822.6	(1411.6, 2353.3)	97	106.6	(69.7, 162.9)
31	194	3018.4	(2473.6, 3683.3)	108	113.2	(74.5, 172.1)
35B	194	6703.1	(5732.7, 7837.8)	107	1019.1	(739.9, 1403.7)

Source: Table 14.2-2 in the CSR of Study V116-006 from the original BLA 125814/0.

Table 27: Within Group Analysis of Postvaccination OPA GMTs for Common Serotypes (PP population in Cohort 2)

Pneumococcal Serotypes	V116 (N=174)			PPSV23 (N=85)		
	n	GMT	95% CI	n	GMT	95% CI
3	149	391.1	(332.8, 459.6)	75	583.1	(453.5, 749.6)
7F	150	3129.8	(2609.9, 3753.3)	70	4057.0	(3211.2, 5125.6)
8	161	2320.1	(1987.3, 2708.7)	75	2723.2	(2197.4, 3374.8)
9N	143	7214.4	(6062.9, 8584.6)	58	6482.5	(4908.9, 8560.7)
10A	155	3976.8	(3360.7, 4705.8)	73	1797.6	(1136.2, 2843.9)
11A	142	2846.6	(2411.0, 3360.8)	71	1736.6	(1367.1, 2206.0)
12F	160	2552.6	(2120.5, 3072.9)	73	1402.5	(912.2, 2156.4)
17F	125	5963.8	(5036.6, 7061.7)	67	4367.3	(3372.5, 5655.7)
19A	158	2528.9	(2201.7, 2904.9)	74	3241.5	(2646.0, 3971.0)
20A	138	6005.5	(4919.8, 7330.8)	72	3393.9	(2536.9, 4540.5)
22F	143	4389.2	(3541.1, 5440.3)	71	2524.0	(1834.5, 3472.5)
33F	131	8162.9	(6407.2, 10399.7)	59	8761.9	(6157.4, 12468.1)

Source: Table 14.2-3 in the CSR of Study V116-006 from the original BLA 125814/0.

Table 28: Within Group Analysis of Postvaccination OPA GMTs for Unique Serotypes (PP population in Cohort 2)

Pneumococcal Serotypes	V116 (N=174)			PPSV23 (N=85)		
	n	GMT	95% CI	n	GMT	95% CI
6A	152	3624.0	(3099.2, 4237.7)	74	1812.3	(1226.6, 2677.6)
15A	134	6185.2	(5179.3, 7386.6)	63	1668.2	(1234.4, 2254.5)
15C	152	4334.4	(3563.8, 5271.5)	72	1470.4	(978.6, 2209.3)
16F	146	4626.5	(3861.8, 5542.6)	74	832.8	(604.3, 1147.6)
23A	156	4253.4	(3417.6, 5293.5)	60	433.6	(247.5, 759.5)
23B	160	1530.7	(1196.5, 1958.3)	75	203.9	(127.6, 325.6)
24F	151	2746.1	(2257.9, 3339.9)	63	48.5	(28.6, 82.1)
31	146	4413.5	(3530.2, 5517.7)	68	171.8	(99.9, 295.6)
35B	148	8143.5	(6761.4, 9808.1)	76	1527.7	(1169.5, 1995.5)

Source: Table 14.2-4 in the CSR of Study V116-006 from the original BLA 125814/0.

Table 29: Within Group Analysis of Postvaccination OPA GMTs for 21 Serotypes in V116 (PP population in Cohort 3)

Pneumococcal Serotypes	V116 (N=105)		
	n	GMT	95% CI
3	85	318.3	(250.0, 405.3)
6A	93	2097.3	(1693.4, 2597.6)
7F	96	2051.3	(1630.2, 2581.0)

Pneumococcal Serotypes	V116 (N=105)		
	n	GMT	95% CI
8	98	1486.8	(1230.5, 1796.6)
9N	90	4054.5	(3389.4, 4850.2)
10A	96	2564.0	(1959.1, 3355.6)
11A	87	2373.0	(1905.4, 2955.4)
12F	99	1235.3	(948.3, 1609.2)
15A	86	4328.6	(3378.7, 5545.7)
15C	89	2191.9	(1573.2, 3053.9)
16F	89	2477.0	(1887.2, 3251.2)
17F	82	3836.7	(3063.4, 4805.1)
19A	93	1533.8	(1272.4, 1848.9)
20A	88	2433.4	(1880.5, 3148.9)
22F	99	1913.5	(1453.5, 2519.0)
23A	86	3967.2	(2764.8, 5692.7)
23B	97	844.0	(608.2, 1171.4)
24F	90	2041.5	(1500.8, 2777.1)
31	90	3285.5	(2485.0, 4343.8)
33F	88	4654.3	(3532.1, 6133.1)
35B	90	5836.8	(4693.6, 7258.6)

Source: Table 14.2-5 in the CSR of Study V116-006 from the original BLA 125814/0.

Reviewer's Comment: The primary immunogenicity analysis was also conducted on the FAS population and the results were consistent with those of the PP population.

6.4.11.2 Analyses of Secondary Endpoints

Serotype-specific IgG GMCs at 30 days postvaccination with V116 for all serotypes were also computed, and the results were consistent with the primary analysis based on OPA GMTs at 30 days postvaccination. Both OPA responses and IgG responses, 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 also computed and comparable across 3 cohorts for all serotypes in V116.

6.4.11.3 Subpopulation Analyses

Subgroup analyses were carried out based on age, sex, race, ethnicity, time since last vaccination and prior pneumococcal vaccination history. There were no notable differences within each of the cohort-specific subgroup categories analyzed as assessed by OPA GMTs at 30 days postvaccination for all 21 serotypes contained in V116.

6.4.12 Safety Analyses

Safety results are briefly summarized in this section.

6.4.12.1 Methods

All solicited AEs were summarized according to defined severity grading scales. Frequencies and percentages of subjects experiencing each AE were presented for each symptom severity. The unsolicited AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 and grouped by preferred terms (PTs) into frequency tables per system organ class (SOC). When an AE occurred more than once for a subject, the maximal severity and duration of the maximal severity were counted.

6.4.12.3 Deaths

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

6.4.12.4 Overall Serious Adverse Events

There were 230 participants in the APaT set for V116 and 117 participants in the APaT set for PCV15 in Cohort 1. In Cohort 1, there were 2 (0.9%) participants in the V116 arm and 4 (3.4%) participants in PCV15 who experienced one or more SAEs. There were 174 subjects in the APaT set for V116 and 85 subjects in the APaT set for PPSV23 in Cohort 2. In Cohort 2, there were 2 (1.1%) participants in the V116 arm and 3 (3.5%) participants in PPSV23 who experienced one or more SAEs. There were 105 participants in the APaT set in Cohort 3 for V116 and 2 (1.9%) of them experienced one or more SAEs.

One participant in the V116 group of Cohort 1 experienced an SAE of injection-site cellulitis that was considered vaccine related by the investigator. The participant completed the study per protocol. None of the SAEs were considered vaccine related by the investigator for participants in Cohort 2 and Cohort 3.

6.4.12.5 Solicited Local and Systemic Adverse Events

Solicited local and systemic AEs from Day 1 through Day 5 postvaccination are summarized in Table 30, Table 31 and Table 32 for Cohort 1, Cohort 2 and Cohort 3, respectively.

Table 30: Individuals With Solicited Local and Systemic Adverse Events Within 5 Days Postvaccination in Cohort 1

		V116 n (%)	PCV15 n (%)
Individuals in population		230	117
One or more solicited AEs		107 (46.5)	65 (55.6)
Local AE	Severity		
Injection Site Pain	Total	82 (35.7)	51 (43.6)
	Mild	65 (28.3)	43 (36.8)
	Moderate	16 (7.0)	8 (6.8)
	Severe	1 (0.4)	0 (0.0)
Injection Site Erythema	Total	17 (7.4)	9 (7.7)
	Mild	10 (4.3)	6 (5.1)
	Moderate	5 (2.2)	2 (1.7)
	Severe	2 (0.9)	1 (0.9)

		V116 n (%)	PCV15 n (%)
Injection Site Swelling	Total	19 (8.3)	10 (8.5)
	Mild	15 (6.5)	9 (7.7)
	Moderate	4 (1.7)	1 (0.9)
Systemic AE	Severity		
Fatigue	Total	33 (14.3)	20 (17.1)
	Mild	25 (10.9)	11 (9.4)
	Moderate	8 (3.5)	9 (7.7)
Headache	Total	16 (7.0)	11 (9.4)
	Mild	10 (4.3)	9 (7.7)
	Moderate	5 (2.2)	2 (1.7)
	Severe	1 (0.4)	0 (0.0)
Myalgia	Total	17 (7.4)	3 (2.6)
	Mild	9 (3.9)	2 (1.7)
	Moderate	8 (3.5)	1 (0.9)
Pyrexia	Total	4 (1.7)	3 (2.6)
	≥38.0°C (100.4°F) to <38.5°C (101.3°F)	2 (0.9)	0 (0.0)
	≥38.5°C (101.3°F) to <39.0°C (102.2°F)	2 (0.9)	2 (1.7)
	≥39.0°C (102.2°F) to <40.0°C (104.0°F)	0 (0.0)	1 (0.9)

Source: Adapted from Table 14.3-30 in the CSR of Study V116-006 from the original BLA 125814/0.

Table 31: Individuals With Solicited Local and Systemic Adverse Events Within 5 Days Postvaccination in Cohort 2

		V116 n (%)	PPSV23 n (%)
Individuals in population		174	85
One or more solicited AEs		86 (49.4)	52 (61.2)
Local AE	Severity		
Injection Site Pain	Total	72 (41.4)	40 (47.1)
	Mild	52 (29.9)	30 (35.3)
	Moderate	20 (11.5)	10 (11.8)
Injection Site Erythema	Total	13 (7.5)	8 (9.4)
	Mild	5 (2.9)	2 (2.4)
	Moderate	6 (3.4)	6 (7.1)
	Severe	2 (1.1)	0 (0.0)
Injection Site Swelling	Total	8 (4.6)	14 (16.5)
	Mild	6 (3.4)	7 (8.2)
	Moderate	2 (1.1)	7 (8.2)
Systemic AE	Severity		
Fatigue	Total	33 (19.0)	11 (12.9)
	Mild	24 (13.8)	6 (7.1)
	Moderate	8 (4.6)	5 (5.9)
	Severe	1 (0.6)	0 (0.0)
Headache	Total	18 (10.3)	10 (11.8)

		V116 n (%)	PPSV23 n (%)
	Mild	10 (5.7)	7 (8.2)
	Moderate	8 (4.6)	3 (3.5)
Myalgia	Total	17 (9.8)	8 (9.4)
	Mild	7 (4.0)	4 (4.7)
	Moderate	9 (5.2)	4 (4.7)
	Severe	1 (0.6)	0 (0.0)
Pyrexia	Total	5 (2.9)	1 (1.2)
	≥38.0°C (100.4°F) to <38.5°C (101.3°F)	1 (0.6)	0 (0.0)
	≥38.5°C (101.3°F) to <39.0°C (102.2°F)	2 (1.1)	1 (1.2)
	≥39.0°C (102.2°F) to <40.0°C (104.0°F)	2 (1.1)	0 (0.0)

Source: Adapted from Table 14.3-31 in the CSR of Study V116-006 from the original BLA 125814/0.

Table 32: Individuals With Solicited Local and Systemic Adverse Events Within 5 Days Postvaccination in Cohort 3

		V116 n (%)
Individuals in population		105
One or more solicited AEs		51 (48.6)
Local AE	Severity	
Injection Site Pain	Total	46 (43.8)
	Mild	37 (35.2)
	Moderate	9 (8.6)
Injection Site Erythema	Total	8 (7.6)
	Mild	4 (3.8)
	Moderate	3 (2.9)
	Severe	1 (1.0)
Injection Site Swelling	Total	11 (10.5)
	Mild	6 (5.7)
	Moderate	4 (3.8)
	Severe	1 (1.0)
Systemic AE	Severity	
Fatigue	Total	23 (21.9)
	Mild	19 (18.1)
	Moderate	4 (3.8)
Headache	Total	9 (8.6)
	Mild	9 (8.6)
Myalgia	Total	9 (8.6)
	Mild	7 (6.7)
	Moderate	2 (1.9)

Source: Adapted from Table 14.3-32 in the CSR of Study V116-006 from the original BLA 125814/0.

6.4.12.6 Unsolicited Adverse Events

Across all 3 cohorts, <18% of participants in each intervention group reported unsolicited

AEs from Day 1 through Day 30 postvaccination (excluding solicited AEs reported Day 1 through Day 5). In Cohort 1, 32 (13.9%) subjects who received V116 and 21 (17.9%) subjects who received PCV15 experienced one or more unsolicited AEs. In Cohort 2, 22 (12.6%) subjects in the V116 arm and 14 (16.5%) subjects in the PPSV23 arm experienced one or more unsolicited AEs. In Cohort 3, 11 (10.5%) participants experienced one or more unsolicited AEs.

Within Cohorts 1 and 2, the proportions of participants with unsolicited AEs (excluding solicited AEs reported Day 1 through Day 5) were generally comparable in both intervention groups.

Reviewer's Comment: Safety analyses within each cohort based on subgroups - age, sex, race, ethnicity, time since last pneumococcal vaccination, and prior pneumococcal vaccination history (only for Cohort 3) were generally consistent with those in the overall cohort population.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

To support evaluation of specific safety endpoints, in the supportive integrated safety analysis (ISS), data were integrated by pooling the participants who received V116 into one group, and by combining active comparator-controlled groups across studies into one collapsed control group. Safety endpoints included unsolicited AEs, vaccine-related AEs (solicited and unsolicited AEs), SAEs, vaccine-related SAEs, SAE within 30 minutes following the vaccination, and AEs resulting in death. Discontinuation from study intervention due to an AE was not summarized as an endpoint in the integrated analysis. Point estimates and within-group 95% CIs for the percentages of participants with the event were provided for these events. The number and percentage of participants with specific AEs were provided following the formula: $\pi_j = (n_{1j} + n_{2j} + n_{3j} + n_{4j})/N_j$, where n_{ij} is the number participants with a specific AE in the i^{th} study for the j^{th} treatment group, N_j is the total number of participants in the j^{th} treatment group, $i = 1, 2, 3, 4$ indicating each of the 4 studies included in the plan for integrated analyses, $j = 1$ indicating the V116 group, $j = 2$ indicating the collapsed control group. Within-group CIs were calculated based on the exact binomial method proposed by Clopper and Pearson (1934).

Subgroup analysis was performed within each individual study based on factors including age and/or prior pneumococcal vaccination status. In addition, to assess whether the treatment effect for the safety endpoints was consistent across the age groups (18 to 49 or ≥ 50 years of age) of the study populations, the pooled number and percentage of participants with the event by age group were also provided for all safety endpoints.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Integrated safety analyses were based on Studies V116-003, V116-004 (lots 1, 2 and 3 of V116 were considered as a single group of V116), V116-006 and the sequential group from V116-005 where V116 was the last dose of study vaccine administered.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 6038 participants were included in the ISS analysis. Table 33 shows the number of participants included from different studies.

Table 33: Number of Participants Considered in ISS Analyses Who Received V116 or Control

Population	Study Number	V116	Control
Pneumococcal vaccine-naïve adults 18-49	V116-003	200	100
	V116-004	1616	541
Pneumococcal vaccine-naïve adults ≥50	V116-003	1177	1175
	V116-005	364	N/A
Pneumococcal vaccine-experienced adults ≥50	V116-005	154	N/A
	V116-006	509	202
Total		4020	2018

Source: Adapted from Table 5.3.5.3.3-AdultPCV:1 in the Integrated Summary of Safety (ISS) from the original BLA 125814/0.

Table 34 shows the disposition of participants by age groups.

Table 34: Disposition of Participants by Age Groups

Participants in population	18 to 49 YOA			50 YOA and older		
	V116	Control	Total	V116	Control	Total
	1816	641	2457	2204	1377	3581
Vaccination with (n, %)						
V116	1816 (100 %)	0 (0.0%)	1816 (73.9%)	2204 (100%)	0 (0.0%)	2204 (61.5%)
PCV15	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	117 (8.5%)	117 (3.3%)
PCV20	0 (0.0%)	100 (15.6%)	100 (4.1%)	0 (0.0%)	1175 (85.3%)	1175 (32.8%)
PPSV23	0 (0.0%)	541 (84.4%)	541 (22.0%)	0 (0.0%)	85 (6.2%)	85 (2.4%)
Trial Disposition (n, %)						
Completed	1760 (96.9%)	623 (97.2%)	2383 (97.0%)	2171 (98.5%)	1351 (98.1%)	3522 (98.4%)
Discontinued	56 (3.1%)	18 (2.8%)	74 (3.0%)	33 (1.5%)	26 (1.9%)	59 (1.6%)
Death	0 (0.0%)	1 (0.2%)	1 (0.0%)	6 (0.3%)	2 (0.1%)	8 (0.2%)
Lost to follow-up	42 (2.3%)	14 (2.2%)	56 (2.3%)	19 (0.9%)	15 (1.1%)	34 (0.9%)

Participants in population	18 to 49 YOA			50 YOA and older		
	V116	Control	Total	V116	Control	Total
	1816	641	2457	2204	1377	3581
Physician decision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Withdrawal by subject	12 (0.7%)	2 (0.3%)	14 (0.6%)	7 (0.3%)	8 (0.6%)	15 (0.4%)
Other	2 (0.1%)	1 (0.2%)	3 (0.1%)	1 (0.0%)	0 (0.0%)	1 (0.0%)

Source: Table 5.3.5.3.3-AdultPCV:3 in the Integrated Summary of Safety (ISS), pp. 8, from the original BLA 125814/0.

Table 35: Selected Demographic Characteristics of All Participants as Treated Population

	V116		Control		Total	
	n	%	n	%	n	%
Participants	4020	-	2018	-	6038	-
Sex						
Male	1711	42.6%	867	43.0%	2578	42.7%
Female	2309	57.4%	1151	57.0%	3460	57.3%
Age (Years)						
18-49	1816	45.2%	641	31.8%	2457	40.7%
50-64	984	24.5%	649	32.2%	1633	27.0%
65-74	942	23.4%	572	28.3%	1514	25.1%
75-84	249	6.2%	140	6.9%	389	6.4%
≥85	29	0.7%	16	0.8%	45	0.7%
Mean	51.3	-	54.9	-	52.5	-
SD	17.5	-	16.4	-	17.2	-
Median	53.0	-	58.0	-	55.0	-
Range	18-91	-	18-97	-	18-97	-
Race						
American Indian or Alaska Native	20	0.5%	9	0.4%	29	0.5%
Asian	388	9.7%	262	13.0%	650	10.8%
Black or African American	385	9.6%	180	8.9%	565	9.4%
Multiple	101	2.5%	62	3.1%	163	2.7%
Native Hawaiian Or Pacific Islander	22	0.5%	19	0.9%	41	0.7%
White	3100	77.1%	1486	73.6%	4586	76.0%
Missing	4	0.1%	0	0.0%	4	0.1%
Ethnicity						
Hispanic Or Latino	821	20.4%	405	20.1%	1226	20.6%

	V116		Control		Total	
	n	%	n	%	n	%
Not Hispanic Or Latino	3170	78.9%	1597	79.1%	4767	78.6%
Not reported	22	0.5%	13	0.6%	35	0.6%
Unknown	7	0.2%	3	0.1%	10	0.2%
Prior Pneumococcal Vaccination Status						
Vaccine-naïve	3357	83.5%	1816	90.0%	5173	85.7%
Vaccine-experienced	663	16.5%	202	10.0%	865	14.3%
Region						
Asia	632	15.7%	354	17.5%	986	16.3%
Australia	183	4.6%	202	10.0%	385	6.4%
Europe	784	19.5%	362	17.9%	1146	19.0%
North America	2345	58.3%	1041	51.6%	3386	56.1%
South America	76	1.9%	59	2.9%	135	2.2%

Source: Table 5.3.5.3.3-AdultPCV:6 in the Integrated Summary of Safety (ISS), pp. 14-15, from the original BLA 125814/0.

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

In the 18-49 YOA group, only vaccine-naïve subjects were considered. Subgroup analysis based on age group (18-49 YOA and ≥ 50 YOA) was considered.

8.4 Safety Results

8.4.1 Deaths

A total of 9 deaths were reported in the pooled datasets: 6 deaths in the V116 group and 3 deaths in the control group. Among participants who received V116, deaths were due to myocardial infarction (1), hepatic cirrhosis and hepatic encephalopathy (1), sepsis (1), sepsis shock (1), cerebrovascular accident (1), and victim of homicide (1). In the control groups, the deaths were due to cardiac arrest (1), abdominal abscess (1) and road traffic accident (1). None of the deaths were considered to be related to the study vaccines by the investigator.

8.4.2 Nonfatal Serious Adverse Events

56 (1.4%) participants who received V116 experienced one or more SAEs from Day 1 through month 6 postvaccination and in control groups, there were 40 (2.0%) such participants. One participant in the sequential group in Study V116-005 had an SAE of bronchospasm that was considered vaccine-related by the investigator and the event occurred within 30 minutes following vaccination 2, i.e., V116. One participant in the V116 group of Cohort 1 in Study V116-006 experienced an SAE of injection-site cellulitis that was considered vaccine related by the investigator.

8.4.3 Study Dropouts/Discontinuations

There were 89 participants who received V116 and 44 participants in control groups discontinued from the studies. Please see the review memo of the clinical reviewer for further details.

8.4.4 Common Adverse Events

Please see the review memo of the clinical reviewer for further details.

8.4.5 Clinical Test Results

Please see the review memo of the clinical reviewer for further details.

8.4.6 Systemic Adverse Events

There were 1481 (36.8%) and 646 (32.0%) subjects who received V116 and the comparators, respectively, experienced solicited systemic AEs. There were 1088 (27.1%), 741 (18.4%), 455 (11.3%) and 87 (2.2%) subjects experienced fatigue, headache, myalgia, and pyrexia, respectively in the V116 group. In the control groups, there were 479 (23.7%), 313 (15.5%), 151 (7.5%) and 32 (1.6%) subjects who had fatigue, headache, myalgia, and pyrexia, respectively.

8.4.7 Local Reactogenicity

There were 2294 (57.1%) and 1141 (56.5%) subjects who received V116 and the comparators, respectively, experienced solicited injection site AEs. There were 396 (9.9%), 2236 (55.6%), and 393 (9.8%) subjects experienced injection site erythema, injection site pain and injection site swelling, respectively in the V116 group. In the control groups, there were 145 (7.2%), 1100 (54.5%) and 177 (8.8%) subjects who had injection site erythema, injection site pain and injection site swelling, respectively.

8.4.8 Unsolicited Adverse Events

There were 898 (22.3%) and 449 (22.2%) subjects who received V116 and the comparators, respectively, experienced one or more unsolicited AEs from Day 1 through Day 30 postvaccination.

Reviewer's Comment: The integrated safety summary based on age groups (18-49 YOA and ≥ 50 YOA) shows that proportion of solicited and unsolicited AEs was higher in the 18-49 age group. There were 1816 participants of 18 to 49 YOA who received V116 and percentages of participants experienced injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, pyrexia and unsolicited AEs were 13.8%, 73.1%, 13.3%, 36.0%, 27.5%, 16.4%, 3.0% and 27.2%, respectively. Similarly, there were 2204 participants ≥ 50 YOA who received V116 and percentages of participants experienced injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, pyrexia, and unsolicited AEs were 6.6%, 41.2%, 6.9%, 19.7%, 11.0%, 7.2%, 1.5% and 18.3%, respectively. In the control group, there were 641 participants 18 to 49 YOA and percentages of participants experienced injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, pyrexia, and unsolicited AEs

were 8.4%, 62.7%, 8.6%, 34.0%, 21.8%, 9.5%, 2.0% and 25.3%, respectively. Similarly, there were 1377 participants ≥ 50 YOA in the control group and percentages of participants experienced injection site erythema, injection site pain, injection site swelling, fatigue, headache, myalgia, pyrexia, and unsolicited AEs were 6.6%, 50.7%, 8.9%, 19.0%, 12.6%, 6.5%, 1.4% and 20.8%, respectively.

8.5 Additional Safety Evaluations

N/A.

8.6 Safety Conclusions

AE profiles were similar across treatment arms and there was no clear safety signal in either vaccination arm.

9. ADDITIONAL STATISTICAL ISSUES

N/A.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Demonstration of immunogenicity of V116 was based on four studies. In the V116-003 study, for adults ≥ 50 YOA V116 met the predefined GMT noninferiority criteria compared with PCV20 for each of 10 common serotypes at 30 days postvaccination, and V116 met the predefined superiority criteria compared with PCV20 for each of 10 serotypes out of 11 serotypes unique to V116. V116 did not meet the predefined criterion for superiority to PCV20 for serotype 15C. Similarly for adults ≥ 50 YOA, V116 met the predefined criteria for superiority to PCV20 for 10 (except serotype 15C) of 11 serotypes unique to V116 based on the proportion of participants with a ≥ 4 -fold rise in serotype-specific OPA responses from baseline to 30 days postvaccination. The predefined criteria for immunobridging were also met for V116 in participants 18 to 49 YOA compared with V116 in participants 50 to 64 YOA for all 21 serotypes as assessed by serotype-specific OPA GMTs at 30 days postvaccination.

In Study V116-004, lot-to-lot consistency was demonstrated among 3 lots of V116. The predefined equivalence criteria were met.

In Study V116-005, V116 administered concomitantly with QIV met the predefined criterion for noninferiority to V116 administered sequentially with QIV for 20 of 21 pneumococcal serotypes in V116 at 30 days postvaccination, except for serotype 23B. QIV administered concomitantly with V116 met the predefined criterion for noninferiority to QIV administered sequentially with V116 for 3 of 4 influenza strains in QIV at 30 days postvaccination, except for strain A/H3N2.

In Study V116-006, V116 was administered to vaccine-experienced adults and compared with PCV15 or PPSV23. Overall, V116 was immunogenic for all 21 serotypes contained in the vaccine as assessed by serotype-specific OPA GMTs at 30 days postvaccination and elicited immune responses to cross-reactive serotypes 6C and 15B in adults.

V116 was generally well tolerated when administered as a single dose in pneumococcal vaccine-naïve and pneumococcal vaccine-experienced individuals ≥ 18 years of age, with a safety profile generally comparable to currently licensed pneumococcal vaccines. V116 was also well tolerated in adults when administered concomitantly with inactivated influenza vaccine, with a safety profile that was generally consistent with the safety profile of V116 administered alone. Two vaccine-related SAEs were reported. One of them was in the sequential group in Study V116-005, reporting an SAE of bronchospasm that was considered vaccine-related by the investigator and occurred within 30 minutes following vaccination 2, i.e., V116. The other was in the V116 group of Cohort 1 in Study V116-006, an SAE of injection-site cellulitis that was considered vaccine related by the investigator.

Results related to primary and secondary immunogenicity analyses, solicited AEs, and unsolicited AEs for all four studies were verified using R 4.3.1 and SAS 9.4. Results in integrated safety were also verified.

10.2 Conclusions and Recommendations

Overall, based on the four studies submitted to this BLA, V116 appears to elicit comparable immune responses to licensed pneumococcal vaccines for the common serotypes and higher GMTs at 30 days postvaccination for the serotypes unique to V116. In Study V116-003, the superiority test showed that the LB of GMT ratio [V116/PCV20] for serotype 15C in Cohort 1 to be < 2 , which implied that the superiority criteria were not met for serotype 15C when compared to PCV20.

Considering the totality of the evidence, based on my review of the statistical analyses and results presented in this original BLA, I recommend approval of V116 for the proposed indication in adults ≥ 18 years of age.