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Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)
PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

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To: Tatiana Claro da Silva, PhD
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OVR, CBER, FDA

Through: Christopher Jason, MD,
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Sponsor: Merck Sharp & Dohme LLC.

Product¹: Pneumococcal 21- valent Conjugate Vaccine
[CRM 197 Protein]; PCV 21 vaccine

Application Type / Number BLA / STN 125814/0

Proposed Indication Active immunization for the prevention of
invasive disease caused by Streptococcus
pneumoniae serotypes 3, 6A, (b) (4), 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.

Submission Date: October 18, 2023

Action Due Date: Priority Review April 18, 2024/Standard Review:
October 17, 2024

¹ The product was referred to as V116 in the clinical development program.

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA/ STN125814/0 based on the safety profile of Pneumococcal 21-valent Conjugate Vaccine [CRM 197 protein], also referred to as V116 (the name used in the clinical development program). Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for PCV 21 vaccine should the indication for this product be approved. Please refer to Appendix 1 for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Pneumococcal disease (PD) is classified as invasive (IPD) or non-invasive disease (non-IPD). IPD refers to an infection caused by *S. pneumoniae* in a normally sterile body site, such as blood, cerebrospinal fluid, pleural fluid, synovial fluid, or pericardial fluid. Non-IPD mainly consists of nonbacteremic pneumococcal pneumonia (nonbacteremic PP), sinusitis, and acute otitis media.

It is estimated that 30 to 40 percent of children in the U.S. are colonized with *Streptococcus pneumoniae* (*S pneumoniae*), with the prevalence exceeding 50% in children attending daycare settings. About 5 to 10 percent of adults are colonized with *S pneumoniae* and these rates have not changed significantly since the advent of conjugate polysaccharide pneumococcal vaccine. Invasive pneumococcal disease (IPD) occurs more frequently from October through March (and is rare in July and August) with the mechanism behind the seasonal variation not understood. Risk factors for invasive disease include colonization, extremes of age, frailty, race and ethnicity, crowded living arrangements, and immunocompromising conditions and other medical comorbidities (e.g., alcoholism, CSF leak, chronic heart, kidney, liver or lung disease, cigarette smoking, cochlear implant, diabetes mellitus).

The most common presentation of *S pneumoniae* infection is bacteremic pneumococcal pneumonia with or without empyema, followed by pneumococcal bacteremia in which no source is identified (primary pneumococcal bacteremia). Antimicrobial therapy and drainage/debridement is the goal of treatment. Beta-lactam antibiotics are the primary treatment. Alternative antibiotics (carbapenems, fluoroquinolones, vancomycin, and linezolid) may be utilized for patients with serious penicillin allergy. The duration of antibiotic therapy is dictated by the underlying site of infection. Generally, antimicrobial treatment should be administered until clinical signs of infection have resolved. Pneumococcal vaccination is the most effective way of preventing IPD. Other preventive measures include smoking cessation and optimizing care of predisposing conditions such as asthma and chronic obstructive pulmonary disease (COPD).

3 PRODUCT INFORMATION

3.1 Product Description

V116 (Pneumococcal 21 valent Conjugate Vaccine [CRM 197 Protein], is a sterile solution of purified capsular polysaccharides from *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B individually conjugated to CRM 197 carrier protein. CRM 197 is a nontoxic mutant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.

V116 is a suspension for intramuscular injection supplied in a 0.5 mL single-dose prefilled syringe. Each 0.5 mL dose contains a total of 84 mcg of pneumococcal polysaccharide antigen (4 mcg each of polysaccharide serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) conjugated to approximately 65 mcg of CRM197 carrier protein (a mutant of diphtheria toxin), 1.55 mg L-histidine, 0.50 mg of polysorbate 20, 4.49 mg sodium chloride, and water for injection. V116 does not contain any preservatives.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125814/0 is: "The target indication for V116 is active immunization for the prevention of invasive pneumococcal disease (IPD) and pneumonia caused by *Streptococcus pneumoniae* serotypes (3, 6A, (b) (4), 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".

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

The Sponsor submitted an original BLA/STN 125814/0 for V116 on October 18, 2023. Under IND 19316, the V116 program for IPD and pneumonia in adults ≥ 18 years of age was granted Fast Track designation on December 13, 2019, and Breakthrough Therapy Designation on January 10, 2022. On December 15, 2023, the FDA classified the BLA as Priority Review.

5 DESCRIPTION OF V116 (Pneumococcal 21-valent Conjugate Vaccine) CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data reviewed are from the Clinical Summary of Safety, Integrated Summary of Safety and Clinical Trial Reports submitted to STN125814/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions

pertaining to pharmacovigilance planning, should this BLA 125814/0 be approved. Please refer to the package insert for the final clinical safety data.

5.1.1 Study Designs

The clinical development program to support V116 licensure in adults includes safety results from five clinical studies: one Phase 1/Phase 2 study (V116-001) and four Phase 3 studies (V116-003, V116-004, V116-005, V116-006) (Table 1). Each study was a multisite, randomized, double blind controlled study to evaluate safety, tolerability, and immunogenicity of V116. One study (V116-005), which evaluated concomitant administration of V116 with inactivated influenza vaccine, was placebo controlled. Three studies were active-comparator controlled with PCV20 (study V116-003), with PPSV23 (study V116-004), or with PPSV23 or PCV 15 (study V116-006). One of the active comparator-controlled studies (V116-004) was a lot consistency study.

Table 1. Summary of Clinical Studies Supporting the Safety of V116 *

Study	N	Description
V116-001	510	Phase 2 study of pneumococcal vaccine naïve adults \geq 50 years old randomly assigned in 1:1 ratio to receive single V116 dose (containing 4 ug of each pneumococcal polysaccharide (PnPs) antigen per 1.0 ml) or PPSV23.
V116-003	2,356	Phase 3 study that compared safety and immunogenicity of V116 with PVC 20 in vaccine naïve adults \geq 18 years of age.
V116-004	2,157	Phase 3 study: Clinical lot consistency study comparing safety and immunogenicity of 3 manufacturing lots of V116 in vaccine naïve adults 18-49 years of age.
V116-005	1,072	Phase 3 study with concomitant use of V116 with inactivated quadrivalent influenza vaccine in adults \geq 50 years of age
V116-006	712	Phase 3 study included 3 cohorts that studied safety and immunogenicity of V116 in participants \geq 50 years of age who previously received a pneumococcal vaccination \geq 1 year prior to enrollment.

*Adapted from: Table 2.7.4 Summary of Clinical Safety Studies with V116 (2.7.4 Summary of Clinical Safety) and Table of all Clinical Trials (5.2 Tabular Listing of All Clinical Trials) and 5.3.5.1, STN125814/0, Module X

5.1.2 Study Populations

The clinical studies included adults \geq 18 years of age from 21 different countries across different races and ethnicities with and without prior pneumococcal vaccination. About one-third of the participants were \geq 65 years of age and one-third of the study population had stable medical conditions (e.g., chronic heart, kidney, lung, or liver disease; diabetes mellitus, alcoholism, or smoking) associated with an increased risk of pneumococcal disease. Demographics and baseline characteristics were generally

comparable across intervention groups. Specific demographic data of the five clinical study populations is shown in Table 1 below.

Table 2. Study Sites and Demographics of Vaccinated Participants in the Five Clinical Studies Supporting the Safety of V116 *

Study Number	Number Study Sites (Location)	Study Population
V-116-001	81 (U.S.)	<p>Pneumococcal vaccine naïve adults \geq 50 years old</p> <p><u>Sex</u>: 227 (44.7%) M /281 (55.3%) F (Total= 508)</p> <p><u>Median Age</u>: 61.0 years</p> <p><u>Age Range</u>: 50-64 years: n= 361(71.1%) 65-74 years: n=119 (23/4%) 75-88 years: n= 28 (5.5%)</p> <p><u>Ethnicity</u>: 293 (57.7%) not Hispanic or Latino, 213 (41.9%) Hispanic or Latino, 1 (0.2%) not reported, 1 (0.2%) unknown</p> <p><u>Race</u>: 3 (0.6%) American Indian or Alaska Native, 5 (1.0%) Asian, 55 (10.8%) black or African American, 2 (0.4%) multiple, 1 (0.2%) Native Hawaiian or other Pacific Islander, 442 (87.0%) white.</p>
V116-003	112 (Australia, Belgium, Chile, Germany, Korea, New Zealand, Puerto Rico, Sweden, Taiwan, Turkey, U.S.A.)	<p>Overall demographics of the study:</p> <p><u>Median Age (range)</u>: 63.0 yrs. (18-97 yrs)</p> <p><u>Sex</u>: 1098 (41.3%) M/1558 (58.7%) female (Total = 2656)</p> <p><u>Ethnicity</u>: 2048 (77.1%) not Hispanic or Latino, 583 (22.0%) Hispanic or Latino, 18 (0.7%) not reported, 7 (0.3%) unknown.</p> <p><u>Race</u>: 9 (0.3%) American Indian or Alaska Native, 369 (13.9%) Asian, 258 (9.7%) black or African American, 71 (2.7%) multiple, 36 (1.4%) Native Hawaiian or other Pacific Islander, 1912 (72.0%) white, 1 (0.0%) missing.</p> <p><u>Cohort 1 Demographics</u></p> <p>Pneumococcal vaccine naïve adults \geq 50 years old</p>

		<p><u>Sex</u>: 999 M / 1357 F (Total= 2,356) <u>Median Age</u>: 65.0 years <u>Age Range</u>: 50-64 years:n=1176 65-74 years:n= 928 75-85 years:n= 225 ≥ 85 years:n= 27</p> <p><u>Cohort 2 Demographics</u> Pneumococcal vaccine naïve adults 18-49 years old</p> <p><u>Sex</u>: 99 M / 201 F (Total= 300) <u>Median Age</u>: 35.0 years <u>Age Range</u>: 18-49 years:n= 300</p>
V116-004	72 (Austria, Canada, Denmark, Finland, Israel, Poland, Spain, U.S.A.)	<p>Pneumococcal vaccine- naïve adults 18-49 years old</p> <p><u>Sex</u>: 914 (42.4%) M / 1243 (57.6%) F (Total= 2,157) <u>Median Age</u>: 35.0 years <u>Age Range</u>: 18-49 years <u>Ethnicity</u>: 1719 (79.7%) not Hispanic or Latino, 422 (19.6%) Hispanic or Latino, 14 (0.6%) not reported, 2 (0.1%) Unknown <u>Race</u>: 35 (1.6%) Asian, 194 (9.0%) black or African American, 4 (0.2%) 3 (0.1%) missing, 81 (3.8%) multiple, Native Hawaiian or Other Pacific Islander, 1824 (84.6%) white.</p>
V116-005	56 (U.S.A.)	<p>Pneumococcal vaccine naïve and vaccine experienced (PCV 13 and/or PPSV 23) adults ≥ 50 years old.</p> <p><u>Sex</u>: 488 (45.5%) M / 584 (54.5%) F (Total= 1,072) <u>Median Age</u>: 64.5 years <u>Age Range</u>: 50-64 years: 536 65-74 years: 416 75-84 years: 107 ≥ 85 years: 13</p> <p><u>Ethnicity</u>: 812 (75.7%) not Hispanic or Latino, 252 (23.5%) Hispanic or Latino, 6 (0.6%) not reported, 2 (0.2%) unknown. <u>Race</u>: 5 (0.5%) American Indian or Alaska Native, 13 (1.2%) Asian, 208 (19.4%) Black or</p>

		<p>African American, 21 (2.0%) multiple, 2 (0.2%) Native Hawaiian or Other Pacific Islander, 822 (76.7%) White, 1 (0.1%) missing.</p> <p><u>Prior pneumococcal vaccination status:</u> PCV13 & PPSV23 naïve: 757 (70.6%) Prior receipt PCV 13 only: 58 (5.4%) Prior receipt PPSV23 only: 140 (13.1%) Prior receipt PCV 13 & PPSV23: 117 (10.9%)</p>
V116-006	51 (Canada, France, Israel, Italy, Japan, Korea, Spain, Taiwan, U.S.A.) %0	<p>Pneumococcal vaccine-experienced adults ≥ 50 years old</p> <p><u>Cohort 1</u> <u>Sex:</u> 171 M / 177 F (Total= 348) <u>Median age:</u> 69.0 years <u>Age Range:</u> 50-64 years: 73 ≥ 65 years: 275 <u>Time since last pneumococcal vaccination:</u> 1-4 years: 162 5-9 years: 130 ≥ 10 years: 56</p> <p><u>Cohort 2</u> <u>Sex:</u> 110 M / 149 F (Total= 259) <u>Median Age:</u> 66.0 years <u>Age Range:</u> 50-64 years: 119 ≥ 65 years: 140 <u>Time since last pneumococcal vaccination:</u> 1-4 years: 201 5-9 years: 51 ≥ 10 years: 7</p> <p><u>Cohort 3</u> <u>Sex:</u> 50 M / 55 F (Total= 105) <u>Median age:</u> 71.0 years</p> <p><u>Ethnicity:</u> 608 (85.4%) not Hispanic or Latino, 102 (14.3%) Hispanic or Latino, 1 (0.1%) not reported, 1 (0.1%) unknown <u>Race:</u> 236 (33.1%) Asian, 19 (2.7%) Black or African American, 3 (0.4%) other/multiple, 454 (63.8%) White.</p>

* Adapted from Sponsor Table 2.5 (2.5 Clinical Overview; page 17, STN 125814/0).

5.1.3 Exposure

Results from the five completed studies (1 Phase 2 study [V116-001] and four Phase 3 studies [V116-003, V116-004, V116-005, V116-006]) conducted across 291 clinical study sites in 21 countries, included approximately 6,500 adults ranging in age from 18-97 years of age from across different races and ethnicities. Approximately 4,800 adults received V116 in these studies including those with and without prior pneumococcal exposure, and with and without increased risk of pneumococcal disease due to chronic medical conditions.

The Phase 3 studies enrolled adults with stable underlying chronic medical conditions (including chronic heart, kidney, liver and lung disease, diabetes mellitus, alcoholism and current tobacco use). Participants with end stage renal disease (CKD Stage 4 or 5) were not included in the studies. A total of 1,990 (33%) had at least 1 or more chronic medical conditions associated with an increased risk of pneumococcal disease; 1,602 (26.5%) of participants had one chronic medical condition, and 388 (6.4%) had 2 or more chronic medical conditions. Individuals immunocompromised due to congenital or acquired immunodeficiencies were not included in the Phase 3 studies.

Reviewer Comment: V116 was studied in diverse populations and adequately reflects intended use of the vaccine in adults, with the exception of immunocompromised patients. Although Phase 3 studies (V116-003; V116-004; V116-005) enrolled adults \geq 18 years of age with (and without) increased risk of pneumococcal disease due to chronic medical conditions, patients immunocompromised due to congenital or acquired immunodeficiencies, functional or anatomic asplenia, autoimmune disease, and those receiving immunosuppressive therapy or treatments associated with organ or bone marrow transplantation were not represented in the studies. But based upon post marketing data from other previously licensed pneumococcal vaccines, this reviewer does not believe the safety profile of V116 would be different in immunocompromised individuals. See discussion below in Section 8.3 (Important Missing Information). Also excluded from the studies were pregnant and lactating women, and children. However, V116 is not intended for use in these populations at this time.

5.2 Adverse events

Safety evaluation methods were uniform across all five studies in the clinical development program. After administration of the study vaccine, all participants were observed for at least 30 minutes for any immediate reactions. Postvaccination safety evaluations were reported on electronic vaccination report cards (eVRC) with the following information reported daily by participants:

- Solicited Injection-site AEs (injection-site pain, erythema, swelling), systemic AEs (fatigue, headache, myalgia), and oral body temperature from Day 1 through Day 5 postvaccination.
- A solicited body temperature \geq 100.4 degrees Fahrenheit was considered a solicited systemic event of pyrexia from Day 1 through Day 5 postvaccination.
- Unsolicited AEs were collected through 30 days post-vaccination.

- SAEs were collected throughout the duration of the study (up to approximately six months after receiving V116 or control vaccines).

For complaints reported on the electronic vaccination report card, the investigator reviewed the data with the participant and reported events meeting the AE definition in the clinical database. Investigators also assessed intensity, toxicity, and seriousness of AEs according to protocol-specified criteria. Duration of follow up for serious AEs (SAEs) was at least 6 months in all 4 of the Phase 3 studies and in the Phase 2 study. Duration of follow up for nonserious AEs in all 5 studies was 30 days.

Safety results were presented by the sponsor in an integrated safety analysis and by individual study. For integrated analysis of adverse events, the sponsor pooled safety data from the four Phase 3 studies involving participants who received V116 into one group (V116-003, V116-004, V116-006 and the sequential group in V116-005) and by pooling the participants who received an active comparator (PCV 15, PCV 20, or PPSV 23) into one combined control group.

Reviewer comment: There was consistent assessment of AEs across the five clinical studies. The 6-month duration of follow up for SAEs in the four Phase 3 studies was adequate. Pooling of studies for the integrated population is appropriate given these studies had similar study designs and study populations.

The occurrence of SAEs was low and overall comparable across intervention groups. The investigator only considered a few of the SAEs to be vaccine related and there were few discontinuations due to AEs. There were few deaths in either intervention group; none of the deaths were considered to be vaccine related by the investigator.

5.2.1 Clinical study V116-003

Study description

V116-003 was a Phase 3, randomized, double-blind, active comparator-controlled, study conducted at 112 centers in 11 countries to assess the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-naïve adults ≥ 18 years of age. There were 2,663 participants enrolled into 1 of 2 cohorts based on age at time of enrollment. Participants with underlying chronic medical conditions associated with an increased risk of pneumococcal disease were enrolled if the conditions were judged to be stable by the study investigator.

Cohort 1

2,362 participants ≥ 50 years of age were randomized in a 1:1 ratio to receive either V116 (n= 1181) or PCV20 (n= 1181). Randomization was stratified by participant age at enrollment (50-64 years, 65-74 years, 75-84 years, and ≥ 85 years).

For the V116 group, 1181 participants were randomized, 1179 were vaccinated, 1160 completed the study, and 21 discontinued the study. Discontinuations were due to

deaths (4 [0.3%]), lost to follow-up (10 [0.8%]), randomized by mistake without study treatment (1 [0.1%]); withdrawal by subject (4 [0.3%]), and “other” (2 [0.2%]).

For the PCV20 group, 1181 randomized, 1177 vaccinated, 1152 completed the study, and 29 discontinued the study. Discontinuations were due to deaths (2 [0.2%]), lost to follow-up (15 [1.3%]), physician decision (2 [0.2%]), randomized by mistake without safety treatment (2 [0.2%]), and withdrawal by subject (8 [0.7%]).

Approximately 38% of all participants who received V116 had ≥ 1 prespecified medical history condition associated with an increased risk of pneumococcal disease (i.e., alcoholism [0.3%], chronic heart disease [2.1%], chronic kidney disease [2.2%], chronic liver disease [1.8%], chronic lung disease [11.5%], diabetes [18.0%], current smoker [11.8%]).

Approximately 35% of all participants who received PCV20 had ≥ 1 prespecified medical history condition associated with an increased risk of pneumococcal disease (i.e., alcoholism [0.3%], chronic heart disease [1.4%], chronic kidney disease [1.9%], chronic liver disease [1.9%], chronic lung disease [11.1%], diabetes [15.5%], current smoker [11.3%]).

Cohort 2:

301 participants 18-49 years of age were randomized in a 2:1 ratio to receive either V116 (n= 201) or PCV20 (n= 100).

For the V116 group, 201 randomized, 200 vaccinated, 195 completed the study, 6 discontinued the study. Discontinuations were due to lost to follow-up (5 [2.5%]) and withdrawal by subject (1 [0.5%]).

For the PCV20 group, 100 randomized, 100 vaccinated, 96 completed the study, and 4 discontinued the study. Discontinuations were due to loss to follow-up (3 [3.0%]) and withdrawal by subject (1 [1.0%]).

Approximately 24% of all participants who received V116 had ≥ 1 prespecified medical history condition associated with an increased risk of pneumococcal disease (i.e., chronic kidney disease [0.0 %], chronic liver disease [1.5%], chronic lung disease [9.5%], diabetes [3.5%], current smoker [11.5%]).

Approximately 19% of all participants who received PCV20 had ≥ 1 prespecified medical history condition associated with an increased risk of pneumococcal disease (i.e., chronic kidney disease [1.0 %], chronic liver disease [0.0%], chronic lung disease [8.0%], diabetes [4.0%], current smoker [8.0%]).

Overall, the number of prespecified medical history conditions associated with an increased risk of pneumococcal disease between participants 18-49 years of age (Cohort 2) and 50-64 years of age (Cohort 1) were generally comparable in each

intervention group, with the exception of diabetes, which was higher in the 50-64 years age group.

Summary of Adverse Events in Cohorts 1 and 2

Overall, the proportion of participants that reported one or more adverse events (AEs) was comparable between the V116 and PCV 20 groups in Cohort 1 (58.2% vs 66.2%) and V116 and PCV20 groups in Cohort 2 (82.0% vs 79.0%). See Table 3.

Cohort 1

Overall, the proportion of participants in the V116 and PCV20 groups experienced comparable systemic AEs (39.2% vs 40.0%), vaccine related systemic AEs (27.4% vs 26.9%), SAEs (1.6% vs 2.0%) and deaths (0.3% vs 0.2%). None of the SAEs or deaths (4 in V116 group and 2 in PCV20 group) were considered vaccine related.

There were less injection- site AEs (including vaccine related injection-site AEs) in the V116 group vs PCV 20 group (42.9% vs 54.6%). See Table 3.

Cohort 2

Overall, the proportion of participants in the V116 and PCV20 groups experienced comparable injection site AEs (73.0% vs 75%), systemic AEs (59.0% vs 50.05%), vaccine related injection site (73.0% vs 75.0%) and systemic (51.0% vs 42.0%) AEs. V116 participants reported less SAEs than the PCV20 participants (0.5% vs 3.0%), none of which were considered vaccine related. There were no deaths reported in this cohort. See Table 3.

Table 3. Summary of Adverse Events in All Treated Participants in Cohorts 1 & 2*

	COHORT 1 (\geq 50 years of age)		COHORT 2 (18-49 years of age)	
	<u>V116</u> n (%)	<u>PCV20</u> n (%)	<u>V116</u> n (%)	<u>PCV20</u> n (%)
# Participants	1,177	1,175	200	100
w/ \geq 1 AEs	685 (58.2)	778 (66.2)	164 (82.0)	79 (79.0)
injection site	505 (42.9)	642 (54.6)	146 (73.0)	75 (75.0)
systemic	461 (39.2)	470 (40.0)	118 (59.0)	50 (50.0)
Vaccine related ^a AEs	609 (51.7)	715 (60.9)	159 (79.5)	78 (78.0)
injection site	505 (42.9)	642 (54.6)	146 (73.0)	75 (75.0)
systemic	322 (27.4)	316 (26.9)	102 (51.0)	42 (42.0)
Serious AEs (up to 6 mo.)	19 (1.6)	24 (2.0)	1 (0.5)	3 (3.0)
Serious vaccine related AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Deaths	4 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)
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* Adapted from Sponsor Table 12-1 and 12-2. (Clinical Study Report P003V116; page 70 & 71, STN 125814/0).

^a Determined by investigator to be related to the vaccine. All injection site AEs and pyrexia (maximum temperature > 100.4 F (38.0 C) solicited from Day 1 through Day 5 postvaccination) are considered to be vaccine related.

PCV20 = pneumococcal 20-valent conjugate vaccine.

Most common AEs:

The most frequently reported AEs (experienced by more than 5% of participants) following V116 or PCV20 within each cohort were the solicited AEs of injection-site pain, fatigue, headache, injection-site erythema, injection-site swelling, and myalgia, which were generally comparable between the intervention groups except for injection-site pain, which was lower in the V116 group than the PCV20 group (40.0% vs 51.7%). See Table 4.

Table 4. Participants with AEs in V116 Group (Incidence > 5% in One or More Vaccination Groups) All Treated Participants in Cohort 1 and Cohort 2*

	COHORT 1 (≥ 50 years of age)		COHORT 2 (18-49 years of age)	
	<u>V116</u> n (%)	<u>PCV20</u> n (%)	<u>V116</u> n (%)	<u>PCV20</u> n (%)
# Participants	1,177	1,175	200	100
w/ ≥ 1 AE	685 (58.2)	778 (66.2)	164 (82.0)	79 (79.0)
Injection site pain	471 (40.0)	608 (51.7)	143 (71.5)	74 (74.0)
Fatigue	240 (20.4)	235 (20.0)	81 (40.5)	34 (34.0)
Headache	162 (13.8)	174 (14.8)	59 (29.5)	26 (26.0)
Injection site erythema	82 (7.0)	86 (7.3)	32 (16.0)	13 (13.0)
Injection site swelling	79 (6.7)	103 (8.8)	28 (14.0)	14 (14.0)
Myalgia	75 (6.4)	82 (7.0)	33 (16.5)	14 (14.0)

* Adapted from Sponsor Table 14.3-4 and Table 14.3-5 (Clinical Study Report P003V116; page 501 & 502, STN 125814/0).

Solicited Adverse Events

Overall, the majority (>50%) of participants in the V116 and PCV20 groups in both cohorts reported ≥ 1 solicited adverse event, including solicited injection site AEs (41.4% vs 53.6% in Cohort 1; 72.0% vs 75% in Cohort 2) and systemic AEs (28.4% vs 32.5% in Cohort 1; 53.5% vs 44.0% in Cohort 2). See Table 5.

Injection -site AEs

Cohort 1

For specific injection site AEs, following PCV, V116 participants reported less injection site pain (39.4% vs 51.7%) than the PCV20 group. Other solicited injection site AEs were comparable between the V116 and PCV 20 participants, including injection site erythema (5.4% vs 6.3%) and injection site swelling (6.0% vs 8.3%). Most solicited injection site AEs following PCV were mild or moderate in intensity and of short duration (≤ 3 days). See Table 5.

Cohort 2

For specific injection site AEs following PCV, V116 participants reported comparable injection site pain (71.5% vs 74.0%), injection site erythema (15.5% vs 13.0%), and injection site swelling (14.0% vs 14.0%) compared to PCV20 participants. Most solicited injection site AEs following PCV were mild or moderate in intensity and of short duration (≤ 3 days). See Table 5.

Systemic AEs

Cohort 1

For specific solicited systemic AEs following PCV, V116 participants reported comparable fatigue (20.1% vs 19.6%), headache (11.5% vs 12.9%), myalgia (5.9% vs 6.7%) and pyrexia (1.3% vs 1.3%) to PCV 20 participants. Most solicited systemic AEs following PCV were mild or moderate in intensity and of short duration (≤ 3 days). See Table 5.

Cohort 2

For specific solicited AEs following PCV, V116 participants reported more fatigue (40.5% vs 34.0%) than the PCV20 group. Other solicited systemic AEs were comparable between the V116 and PCV20 participants, including headache (29.5% vs 24.0%), and myalgia (16.5% vs 14.0%). V116 participants reported more pyrexia (3.5% vs 1.0%) than the PCV 20 group. Most solicited systemic AEs following PCV were mild or moderate in intensity and of short duration (≤ 3 days). See Table 5.

Table 5. Treated Participants with Solicited Adverse Events in Cohort 1 and Cohort 2 (Incidence > 0% in One or More Vaccination Groups)*

	Cohort 1 (≥ 50 years of age)		Cohort 2 (18-49 years of age)	
	V116 n (%)	PCV 20 n (%)	V116 n (%)	PCV20 n (%)
#Participants	1,177	1,175	200	100
w/ ≥ 1 AEs	600 (51.0)	708 (60.3)	161 (80.5)	78 (78.0)
Solicited injection site AEs	487 (41.4)	630 (53.6)	144 (72.0)	75 (75.0)
Pain	464 (39.4)	607 (51.7)	143 (71.5)	74 (74.0)

Erythema	64 (5.4)	74 (6.3)	31 (15.5)	13 (13.0)
Swelling	71 (6.0)	98 (8.3)	28 (14.0)	14 (14.0)
Solicited systemic AEs	334 (28.4)	323 (27.5)	107 (53.5)	44 (44.0)
Fatigue	237 (20.1)	230 (19.6)	81 (40.5)	34 (34.0)
Headache	135 (11.5)	152 (12.9)	59 (29.5)	24 (24.0)
Myalgia	70 (5.9)	79 (6.7)	33 (16.5)	14 (14.0)
Pyrexia	15 (1.3)	15 (1.3)	7 (3.5)	1 (1.0)

*Adapted from Sponsor Table 12-3 and 12-4 (Clinical Study Report P003V116; page 72 and 73, STN 125814/0).

Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through 5 post vaccination. Pyrexia was defined as maximum temperature ≥ 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination.

PCV20 = pneumococcal 20-valent conjugate vaccine.

SAEs:

Overall, the proportions of participants with serious adverse events (SAEs) were low ($\leq 3\%$) within each cohort and generally comparable between the V116 and PCV20 participants (1.6% vs 2.0%) in Cohort 1. In Cohort 2, V116 participants reported less frequent SAEs (0.5% vs 3.0%) than PCV20 participants. None of the SAEs were considered to be vaccine related (most noteworthy V116 SAE cases listed below). See Table 6.

Abdominal Wall Abscess: 56-year-old female (participant # (b) (6)) with history of obesity, hypertension, hyperlipidemia, post menopause, drug hypersensitivity, osteoarthritis, hypothyroidism, COPD and diabetes mellitus, who was hospitalized for chills and reported drainage from abscess in the abdominal pannus region. She was diagnosed with abdominal wall abscess (onset Day 146) considered to be caused due to skin laying over the pannus region. On Day 152 she had abdominal panniculectomy (I&D of abdominal wall pannus). On Day 154 wound closure performed with vacuum placement. On Day 156 abdominal wall abscess reported as resolved and participant discharged from hospital with wound vacuum in place and on appropriate antibiotic treatment. On Day 184 abdominal wall abscess resolution confirmed. As of Day 169 participant had completed the study.

Sepsis: 54-year-old male (participant # (b) (6)) with history of type 1 diabetes mellitus (on insulin), below the knee amputation with right leg prosthesis, recurrent cellulitis in leg amputation stump and hypertension (on hydrochlorothiazide (+) lisinopril and furosemide). On Day 71 participant hospitalized with complaint of pain and swelling in right leg stump. During hospitalization he was diagnosed with poorly controlled diabetes mellitus, acute kidney injury (AKI) and sepsis due to abscess associated with distal osteomyelitis of the right leg stump, and acute pyelonephritis (due to bacterial UTI). Participant treated with appropriate antibiotics and corrective insulin and discharged on Day 78. On Day 120 sepsis resolved. As of Day 201, the participant had completed the study.

Alcoholism, Duodenal ulcer perforation, peritonitis, delirium tremens, cerebrovascular accident: 66-year-old male (participant # (b) (6)) with history of obesity, psoriasis, headache, hypertension, COPD, emphysema, alcoholism, was hospitalized, on Day 118, due to relapse of alcoholism after abstinence. No treatment or further details reported. On Day 144 relapse of alcoholism resolved and participant discharged from hospital. On Day 153 participant c/o abdominal pain, and hospitalized on Day 154 found to have duodenal ulcer perforation and peritonitis. He was hospitalized on Day 154 and diagnosed with duodenal ulcer perforation and peritonitis. He underwent laparotomy for duodenal sewing, cholecystectomy and atypical removal of liver segment III. No histopathological abnormalities found. Participant had prolonged stay in ICU due to delay of extubation (d/t history of COPD), onset of severe delirium tremens (due to alcoholism), and cerebrovascular accident (d/t embolic event from newly diagnosed paroxysmal atrial fibrillation) with right arm hemiparesis. By Day 181, when the participant left the hospital against medical advice, the duodenal ulcer perforation, CVA, and peritonitis were considered resolved. As of Day 182 the participant had completed the study and the right arm hemiparesis was ongoing.

Dizziness: 89-year-old female (participant # (b) (6)) with history of irritable bowel syndrome and osteoarthritis (treated with paracetamol, codeine, and pregabalin), had her pregabalin switched to amitriptyline on Day 53 due to a supply issue, and subsequently developed dizziness and unsteadiness on her feet. Symptoms progressively worsened and on Day 59 she presented to ED with difficulty standing and was admitted for hospitalization. Lab results unremarkable, and on same day amitriptyline was stopped, and symptoms gradually subsided. On Day 62 dizziness resolved and participant discharged with a diagnosis of adverse reaction to amitriptyline and famotidine. As of Day 171, the participant had completed the study.

Dyspnea: 72-year-old female (participant # (b) (6)) with history of UTI, GERD, sinus bradycardia, nausea, cardiac pacemaker insertion, cholecystectomy, was diagnosed with moderate COVID-19 on Day 23. She was treated with nirmatrelvir (+) ritonavir and on Day 29 the COVID-19 was resolved. On Day 51 participant c/o dyspnea, she had increased D-Dimer and participant was hospitalized due to suspected pulmonary embolus, which was later ruled out. On Day 52 dyspnea was resolved and participant discharged from hospital with diagnosis of SOB post COVID, normal D-Dimer and “nil” pulmonary embolism. As of Day 187, the participant had completed the study.

Table 6. Summary of Serious Adverse Events (Incidence > 0% in One or More Vaccination Groups) in All Treated Participants in Cohorts 1 & 2*

	COHORT 1 (≥ 50 years of age)		COHORT 2 (18-49 years of age)	
	V116 n (%)	PCV20 n (%)	V116 n (%)	PCV20 n (%)
# Participants	1,177	1,175	200	100
w/ ≥ 1 SAEs	19 (1.6)	24 (2.0)	1 (0.5)	3 (3.0)
Cardiac disorders	2 (0.2)	6 (0.5)		
Cardiac arrest	1 (0.1)	1 (0.1)		

	COHORT 1 (≥ 50 years of age)		COHORT 2 (18-49 years of age)	
	<u>V116</u> n (%)	<u>PCV20</u> n (%)	<u>V116</u> n (%)	<u>PCV20</u> n (%)
Coronary artery embolism	0 (0.0)	1 (0.1)		
Myocardial infarction	1 (0.1)	4 (0.3)		
Ear & Labyrinth disorders	0 (0.0)	1 (0.1)		
Vertigo	0 (0.0)	1 (0.1)		
Gastrointestinal disorders	4 (0.3)	3 (0.3)	0 (0.0)	1 (1.0)
Abdominal pain	0 (0.0)	1 (0.1)		
Abdominal pain upper	1 (0.1)	0 (0.0)		
Colitis	0 (0.0)	1 (0.1)		
Duodenal ulcer perforation	1 (0.1)	0 (0.0)		
Inguinal hernia	1 (0.1)	0 (0.0)		
Jejunal perforation			0 (0.0)	1 (1.0)
Oral mucosa erosion	1 (0.1)	0 (0.0)		
Small intestinal obstruction	0 (0.0)	1 (0.1)		
General disorders & administrative site conditions	0 (0.0)	1 (0.1)		
Non-cardiac chest pain	0 (0.0)	1 (0.1)		
Hepatobiliary disorders	2 (0.2)	0 (0.0)		
Hepatic cirrhosis	1 (0.1)	0 (0.0)		
Hepatic necrosis	1 (0.1)	0 (0.0)		
Subcapsular hepatic hematoma	1 (0.1)	0 (0.0)		
Immune system disorders	0 (0.0)	1 (0.1)		
Drug hypersensitivity	0 (0.0)	1 (0.1)		
Infections & infestations	7 (0.6)	4 (0.3)	1 (0.5)	1 (1.0)
Abdominal abscess	0 (0.0)	1 (0.1)		
Abdominal wall abscess	1 (0.1)	0 (0.0)		
Appendicitis	1 (0.1)	0 (0.0)		
Cellulitis			0 (0.0)	1 (1.0)
Diverticulitis	1 (0.1)	0 (0.0)		
Encephalitis viral	0 (0.0)	1 (0.1)		
Gastroenteritis	0 (0.0)	1 (0.1)		
Peritonitis	1 (0.1)	0 (0.0)		
Pneumonia	0 (0.0)	1 (0.1)		
Pneumonia aspiration	1 (0.1)	0 (0.0)		
Sepsis	2 (0.2)	0 (0.0)		
Septic shock	1 (0.1)	0 (0.0)		
Tooth Abscess			1 (0.5)	0 (0.0)
Injury, poisoning & procedural complications	1 (0.1)	2 (0.2)	0 (0.0)	1 (1.0)
Brain contusion	0 (0.0)	1 (0.1)		
Hip fracture	0 (0.0)	1 (0.1)		
Lower limb fracture			0 (0.0)	1 (1.0)

	COHORT 1 (≥ 50 years of age)		COHORT 2 (18-49 years of age)	
	<u>V116</u> n (%)	<u>PCV20</u> n (%)	<u>V116</u> n (%)	<u>PCV20</u> n (%)
Upper limb fracture	1 (0.1)	0 (0.0)		
Metabolism & nutrition disorders	2 (0.2)	0 (0.0)		
Diabetes mellitus inadequate control	1 (0.1)	0 (0.0)		
Hyponatremia	1 (0.1)	0 (0.0)		
Musculoskeletal & connective tissue disorders	1 (0.1)	1 (0.1)		
Lumbar spinal stenosis	0 (0.0)	1 (0.1)		
Osteoarthritis	1 (0.1)	0 (0.0)		
Neoplasms benign, malignant & unspecified (including cysts & polyps)	2 (0.2)	1 (0.1)		
Invasive ductal breast carcinoma	1 (0.1)	0 (0.0)		
Prostate cancer	0 (0.0)	1 (0.1)		
Rectal adenocarcinoma	1 (0.1)	0 (0.0)		
Nervous system disorders	4 (0.3)	4 (0.3)		
Cerebrovascular accident	2 (0.2)	0 (0.0)		
Dizziness	1 (0.1)	0 (0.0)		
Encephalopathy	0 (0.0)	1 (0.1)		
Hepatic encephalopathy	1 (0.1)	0 (0.0)		
Ischemic stroke	0 (0.0)	1 (0.0)		
Metabolic encephalopathy	0 (0.0)	1 (0.1)		
Radial nerve palsy	0 (0.0)	1 (0.1)		
Product Issues	1 (0.1)	0 (0.0)		
Device occlusion	1 (0.1)	0 (0.0)		
Psychiatric disorders	1 (0.1)	1 (0.1)		
Alcohol withdrawal syndrome	0 (0.0)	1 (0.1)		
Alcoholism	1 (0.1)	0 (0.0)		
Delirium tremens	1 (0.1)	0 (0.0)		
Renal & urinary disorders	1 (0.1)	2 (0.2)		
Acute kidney injury	0 (0.0)	1 (0.1)		
Nephrolithiasis	1 (0.1)	1 (0.1)		
Respiratory, thoracic & mediastinal disorders	2 (0.2)	0 (0.0)		
Acute respiratory failure	1 (0.1)	0 (0.0)		
Dyspnea	1 (0.1)	0 (0.0)		

* Adapted from Sponsor Table 14.3-48 and 14.3-49. (Clinical Study Report P003V116; page 612-615, STN 125814/0).

Every participant is counted a single time for each applicable row and column. Reported serious adverse events occurred from Day 1 through the duration of participation in the study. MedDRA version 26.0 was used in the reporting of this study.

PCV20 = pneumococcal 20-valent conjugate vaccine.

Deaths:

Cohort 1

Six deaths were reported: four participants died in the V116 group (0.3%) and two participants died in the PCV20 group (0.2%). None of the deaths were considered by the study investigator to be related to study vaccination:

- In the V116 group, deaths included:
 - 1) A 54-year-old female (participant # (b) (6)) with history of arthralgia and asthma died from cerebrovascular accident on Day 44. No further information was provided. This reviewer agrees with the study investigator that this death was not related to the study vaccination.
 - 2) A 56-year-old female (participant # (b) (6)) with history of hypertriglyceridemia died from MI on Day 179. No further information was reported. This reviewer agrees with the study investigator that this death was not related to the study vaccination.
 - 3) A 75-year-old male (participant # (b) (6)) with history of obesity, sinusitis, hypertension and asthma, was hospitalized (on Day 20) s/p fall and development of dizziness and confusion. Although spinal and head CTs normal, abdominal CT showed ascites. Following discharge on Day 22, the participant was readmitted to the hospital due to recurrent confusion and diagnosed (on Day 27) with hepatic cirrhosis and hepatic encephalopathy (onset Day 20). A complicated hospital course followed during which the participant had an upper GI bleed due to erosive stomatitis, developed aspiration pneumonia, and worsening hepatic encephalopathy. On Day 129 the participant died due to hepatic cirrhosis and hepatic encephalopathy. This reviewer agrees with the study investigator that this death was not related to the study vaccination.
 - 4) A 70-year-old female (participant # (b) (6)) with history of atrial fibrillation, epilepsy, obesity, spinal compression fracture, hypertension and glaucoma died from sepsis on Day 127 following multiple hospitalizations (x 3) and a complicated medical course due to subcapsular hepatic hematoma s/p liver biopsy (on Day 26), that developed into liver abscess, hepatic necrosis and caused septic shock (Days 28 and 87) with cardiac arrest (Day 29). Hepatic fluid drainage catheter placed (Day 37) which later occluded and required readmission to the hospital (Day 67) and caused the second episode of septic shock (Day 87). The patient's final hospital discharge occurred on Day 112, with discharge diagnoses of subcapsular hematoma, bilateral pleural effusion, liver necrosis, aortic stenosis atrial fibrillation sepsis/septic shock. Electrolyte imbalance, aortic stenosis, atrial fibrillation (all with onset on Day 29) and hepatic necrosis were not considered resolved, while the outcome of subcapsular hepatic hematoma and septic shock (onset Day 28)

was reported as unknown. The participant was discharged with oral antibiotics and on Day 127 reportedly died due to sepsis. This reviewer agrees with the study investigator that this death was not related to the study vaccination.

- In the PCV20 group, deaths included:
 - 1) 75-year-old male (participant # (b) (6)) with a history of COPD and cardiac pacemaker (condition for its insertion unknown) who died from cardiac arrest on Day 10. No further information was provided. This reviewer agrees with the study investigator that this death was not related to the study vaccination.
 - 2) 67-year-old female (participant # (b) (6)) with history of hypothyroidism and gastroenteritis that died from an abdominal abscess after hospital admission (on Day 14) for 1.5-month history of nausea, vomiting abdominal pain and weight loss. Abdominal CT performed which showed intra-abdominal abscess. During participant's hospitalization she had paracentesis drainage catheter placed in RLQ for abdominal cavity drainage (Day 15), another abdominal CT (Day 18) to rule out intra-abdominal abscess perforation, followed by laparotomy ("no focus was identified") and positive blood culture for *E. faecium* (Day 29). Due to leukocytosis (Day 56) Infectious Disease consult sought and fluconazole added to antimicrobial treatment regimen. On Day 63 participant had acute respiratory failure and cardiac arrest and died due to abdominal abscess. This reviewer agrees with the study investigator that this death was not related to the study vaccination.

Cohort 2

No deaths were reported.

Reviewer Comment: The overall safety for V116 is comparable to PCV20 in this study, although V116 participants experienced less injection site pain in Cohort 1 (participants ≥ 50 years old) than in Cohort 2 (participants 18-49 years old). This study suggests that V116 has an acceptable safety profile in immunocompetent pneumococcal vaccine-naïve adults ≥ 18 years of age with risk factors for pneumococcal disease. Strengths of this study include the large number of participants who received V116 across two cohorts ($n=1,379$) and the high proportion of V116 participants with ≥ 1 prespecified medical history condition (chronic heart, kidney, liver and lung disease, diabetes mellitus, alcoholism or current smoker) associated with an increased risk of pneumococcal disease (38% in Cohort 1; and 24% in Cohort 2). A limitation of this study is the exclusion of immunocompromised participants.

5.2.2 Clinical study (V116-001)

Study description:

V116-001 was a Phase 2 randomized, double-blind, comparator-controlled study conducted at 18 centers in the U.S. to assess the safety, tolerability, and immunogenicity of V116 compared to PPSV23 in healthy adults* ≥ 50 years of age who were pneumococcal vaccine naïve. A total of 510 participants were randomized in a 1:1 ratio and 508 participants received a pneumococcal conjugated vaccine (PCV). In the PPSV23 group, two of the randomized participants withdrew from the study prior to receiving PCV.

In the V116 group, 254 participants were randomized and 254 (100.0%) were vaccinated. Most participants, 244 (96.1%), completed the study while 10 (3.9%) discontinued the study (1 death, 7 lost to follow-up, and 2 withdrew from the study).

In the PPSV23 group, 256 participants were randomized, 254 (99.2%) were vaccinated, 247 (96.5%) completed the study, and 9 (3.5%) discontinued the study (5 lost to follow-up and 4 withdrew from the study).

Reviewer Comment: *The reported medical history conditions of the participants were generally comparable between the V116 and PPSV23 group, with the 5 most frequently reported medical conditions being hypertension (46.7%), osteoarthritis (23.8%), hypercholesterolemia (22.6%), gastroesophageal reflux disease (22.2%) and post menopause (18.9%).

Summary of Adverse Events (AEs)

Following vaccination, nonserious AEs were collected from Day 1 to Day 30, and serious adverse events were collected from Day 1 through the duration of the study.

Overall, the proportion of participants reporting at least one or more adverse events was comparable between the V116 and PPSV23 groups (66.5% vs 59.4%). Injection site AEs (including vaccine-related injection-site AEs) were higher in the V116 group (51.6% vs 40.9%) compared to the PPSV23 group. Systemic AEs were comparable between the V116 and PPSV23 groups (44.5% vs 43.75%) while vaccine related systemic AEs were higher in the V116 participants than the PPSV23 participants (34.3% vs 26.8%). Serious adverse events (SAEs) were low (<2%) in the study participants and generally comparable in the V116 and PPSV23 groups (1.6% vs 1.2%). No SAEs were considered to be vaccine related. Only one death was reported (in the V116 group) and was not considered to be vaccine related. See Table 7.

Table 7. Summary of Adverse Events in All Treated Participants in Phase 2 Study

	<u>V116</u> n (%)	<u>PPSV23</u> n (%)
# Participants	254	254
w/ ≥ 1 AEs	169 (66.5)	151 (59.4)
injection site	131 (51.6)	104 (40.9)
systemic	113 (44.5)	111 (43.7)

Vaccine related ^a AEs	157 (61.8)	129 (50.8)
injection site	131 (51.6)	104 (40.9)
systemic	87 (34.3)	68 (26.8)
Serious AEs (up to 6 mo.)	4 (1.6)	3 (1.2)
Serious vaccine related AEs	0 (0.0)	0 (0.0)
Deaths	1 (0.4)	0 (0.0)

* Adapted from Sponsor Table 12-1 (Clinical Study Report P001V116; page 53, STN 125814/0).

^a Determined by investigator to be related to the vaccine. Reported adverse events include nonserious adverse events from Day 1 through Day 30 following vaccination and serious adverse events that occurred from Day 1 through the duration of an individual's study participation.

PPSV23 = Pneumovax 23.

Most common AEs:

The most common AEs (experienced by more than 5% of participants) following administration of V116 or PPSV23 were the solicited injection site and systemic AEs, which were comparable between the V116 and PPSV23 groups and included injection site pain (46.5% vs 37.8%), fatigue (19.7% vs 13.4%), headache (20.1% vs 18.9%), injection site swelling (11.8% vs 7.9%) and myalgia (13.4% vs 11.0%).

Solicited Adverse Events (See Table 84)

Injection-site AEs

Overall solicited injection-site AEs following pneumococcal conjugated vaccine (PCV) were more common following V116 than PPSV23 (51.2 % vs 40.9%). For specific injection-site AEs following PCV, V116 participants more often reported injection site pain (46.5% vs. 37.8%). The frequency of other injection site AEs were comparable between the V116 and PPSV23 groups, including injection site swelling (11.0% vs 7.9%), and injection site erythema (8.7% vs 6.7%). Most solicited injection-site AEs following PCV were mild or moderate in intensity and of short duration (\leq 3 days).

Systemic AEs

Overall, solicited systemic AEs following PCV were comparable between the V116 and PPSV23 groups (34.6% vs 29.5%), including specific systemic AEs of fatigue (19.3 % vs 12.2%), headache (16.9% vs 13.4%) and myalgia (11.0% vs 9.4%). Most solicited systemic AEs following PCV were mild or moderate in intensity and of short duration (\leq 3 days).

Table 8 Treated Participants with Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups) Phase 2- Day 1 to Day 5 Postvaccination

	V116	PPSV23
	n (%)	n (%)
# participants in population	254	254

w/ \geq 1 Solicited injection site AE	130 (51.2)	104 (40.9)
Injection site erythema	22 (8.7)	17 (6.7)
Injection site pain	118 (46.5)	96 (37.8)
Injection site swelling	28 (11.0)	20 (7.9)
w/ \geq 1 Solicited systemic AE	88 (34.6)	75 (29.5)
Fatigue	49 (19.3)	31 (12.2)
Headache	43 (16.9)	34 (13.4)
Myalgia	28 (11.0)	24 (9.4)

* Adapted from Sponsor Table 12-2 and Table 12-3 (Clinical Study Report P001V116; page 54 and 55, STN 125814/0).

PPSV23= Pneumovax 23

SAEs:

Less than 2% of participants in this study experienced a SAE. A total of 7 SAEs, 4 (1.6%) in V116 group and 3 (1.2%) in PPSV23 group occurred, with none assessed to be vaccine related.

PPSV23 SAEs:

- 1) 69-year-old female with history of hypertension, depression, drug hypersensitivity, myocardial infarction, Type 2 diabetes mellitus, GERD, gastritis, Barrett's esophagus, hyperlipidemia, goiter, amnesia, osteoarthritis, vitamin D deficiency, hospitalized on Day 162 due to complaint of neck pain x 2 months duration and associated SOB with exertion, episodes of diaphoresis, and palpitations and elevated troponin in the ED. ECG showed nonspecific intraventricular block, possibly left bundle branch block, ST depression diffuse, and nonspecific T wave changes. Chest x-ray was normal. She was diagnosed with acute coronary syndrome. Subsequent lab testing showed no myocardial infarction. Participant discharged on Day 164 in stable condition. On Day 165 participant returned to ED with fever and weakness. On Day 166 blood cultures showed staphylococcal bacteremia and participant started on antibiotics. On Day 170 SAE of staphylococcal bacteremia was considered resolved and participant discharged to complete remaining 2-week course of antibiotics at home. This reviewer agrees with the study investigator that the SAEs of acute coronary syndrome and staphylococcal bacteremia were not related to the study vaccination.
- 2) 52-year-old male with history of Hepatitis C, insomnia, depression anxiety, hemorrhoids, allergic rhinitis, presbyopia, hypertension, obesity, BPH, hypothyroidism, hypercholesterolemia, was hospitalized on Day 114 for severe UTI, which resolved on Day 121. No further information available. This reviewer agrees with the study investigator that the SAE of UTI was not related to the study vaccination.

- 3) 67-year-old male hospitalized on Day 104 for acute kidney injury (severe) possibly caused by excess ibuprofen self-administration. Also diagnosed with prostatomegaly and splenomegaly. On Day 106 the SAE of acute kidney injury was considered resolved and participant discharged to home. This reviewer agrees with the study investigator that the SAE of acute kidney injury was not related to the study vaccination.

V116 SAEs:

- 1) 62- year- old female admitted to the hospital on Day 15 with right sided chest and neck pain that began weeks prior to admission. The participant was diagnosed with severe rotator cuff syndrome and severe cervical radiculopathy. The participant showed improved range of motion following medical therapy and was discharged on Day 18. The SAE of cervical radiculopathy resolved on Day 68 and the SAE of rotator cuff syndrome resolved on Day 79. This reviewer agrees with the study investigator that these SAEs were not related to the study vaccination.
- 2) 63-year-old male hospitalized on Day 146 for atrial fibrillation and subsequent to medical therapy reverted to sinus rhythm. Participant also diagnosed with pneumonia and gastroenteritis (neither reported as an AE). On Day 147 SAE of atrial fibrillation was considered resolved and participant discharged to home. This reviewer agrees with the study investigator that the SAE of atrial fibrillation was not related to the study vaccination.
- 3) 67-year-old male hospitalized on Day 99 and diagnosed with gastrointestinal hemorrhage (severe) requiring transfusion. EGD showed hiatal hernia, possible eosinophilic esophagitis, antral ulcer, duodenitis, and gastritis. Appropriate medical intervention initiated and on Day 102 the SAE of gastrointestinal hemorrhage was considered resolved and participant discharged. This reviewer agrees with the study investigator that the SAE of gastrointestinal hemorrhage was not related to the study vaccination.
- 4) Death due to COVID-19. See discussion under Deaths.

Deaths

One death occurred in the V116 group: A 70 -year -old female with history of insomnia, allergic rhinitis, osteoporosis, osteoarthritis, GERD, hypercholesterolemia, cataract and s/p appendectomy was admitted to the hospital on Day 25 with severe COVID-19. The participant decompensated despite medical therapy and on Day 26 required intubation for mechanical ventilation due to hypoxic respiratory failure. The participant was diagnosed with sepsis secondary to COVID-19 and died on Day 29. No autopsy was performed. This reviewer agrees with the study investigator that this death was not related to the study vaccination.

Reviewer comments: The overall safety profile for V116 is comparable to PPSV23 in this study, although V116 participants experienced more injection site pain. This study suggests V116 has an acceptable safety profile in adults ≥ 50 years of age who are pneumococcal vaccine naïve. Important limitations of this Phase 2 study include the lack of invasive pneumococcal disease risk factors in this healthy study population.

5.2.3 Clinical study (V116-004)

Study Description:

V116-004 was a Phase 3, randomized, double-blind, active comparator-controlled, Lot-to-Lot consistency study conducted at 72 centers in 8 countries to assess the safety, tolerability and immunogenicity of V116 compared to PPSV23 in pneumococcal vaccine naïve adults 18 to 49 years of age. Participants with underlying chronic medical conditions were eligible if the conditions were assessed to be stable per the investigator's judgement. Participants with prespecified medical history conditions (e.g., alcoholism, diabetes, current smoker, chronic heart, kidney, liver and lung disease) associated with ≥ 1 risk factor for increased risk of pneumococcal disease were included in the V116 (combined lots) and PPSV23 groups (25.1% vs 23.2%).

Participants (2,162) were randomized in a 1:1 ratio to receive a single dose of either V116 Lot 1, V116 Lot 2, V116 Lot 3, or PPSV23.

For V116 Lot 1 group: 541 randomized, 539 vaccinated, 521 completed the study, 20 discontinued the study. Discontinuations were due to: lost to follow-up (16 [3.0%]), withdrawal by subject (4 [0.7%]).

For V116 Lot 2 group: 540 randomized, 538 vaccinated, 520 completed the study, 20 discontinued the study. Discontinuations were due to: lost to follow-up (11 [2.0%]), randomized by mistake without study treatment (1 [0.2%]), withdrawal by subject (8 [1.5%]).

For V116 Lot 3 group: 541 randomized, 540 vaccinated, 525 completed the study, 16 discontinued the study. Discontinuations were due to: lost to follow-up (11 [2.0%]), withdrawal by subject (3 [0.6%]), and "other" (2 [0.4%]).

For PPSV23 group: 540 randomized, 540 vaccinated, 526 completed the study, 14 discontinued the study. Discontinuations were due to: death (1[0.2%]), lost to follow-up (11 [2.0%]), withdrawal by subject (1 [0.2%]), and "other" (1 [0.2%]).

Summary of Adverse Events Across V116 Lots

The majority ($\geq 80\%$) of participants across the three lots of V116 had ≥ 1 AEs.

The proportion of participants with AEs, including injection site, systemic and vaccine related AEs were comparable across the 3 lots of V116. Few participants (≤ 1.5) experienced SAEs across the 3 lots of V116 and none were considered vaccine related. No deaths were reported across the 3 lots of V116. See Table 98

Table 9. Summary of Adverse Events by V116 Lots in all Treated Participants*.

	V116 Lot 1 n (%)	V116 Lot 2 n (%)	V116 Lot 3 n (%)
# Participants	539	536	541
w/ ≥ 1 AEs	438 (81.3)	429 (80.0)	433 (80.0)
Injection site AE	400 (74.2)	393 (73.3)	407 (75.2)
Systemic AE	326 (60.5)	310 (57.8)	292 (54.0)
Vaccine related ^a AE	426 (79.0)	416 (77.6)	426 (78.7)
Injection site AE	400 (74.2)	393 (73.3)	407 (75.2)
Systemic AE	279 (51.8)	259 (48.3)	254 (47.0)
Serious AE	8 (1.5)	5 (0.9)	1 (0.2)
Serious vaccine- related ^a AEs	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

*Adapted from Sponsor Table 12-1 (Clinical Study Report P004V116; page 51, STN 125814/0).

^a Determined by investigator to be related to the vaccine. All injection site adverse events and pyrexia (defined as maximum temperature > 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination) are considered to be vaccine-related.

Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration of participation in the study.

Summary of Adverse Events in V116 (combined Lots) and PPSV23 Groups

The majority of V116 (combined lots) and PPSV23 participants (80.4% vs 74.9%) had ≥ 1 AEs. The proportions of participants with AEs, including systemic and vaccine-related AEs and SAEs, were generally comparable in the V116 (combined lots) and PPSV23 groups. The proportion of participants with injection-site AEs (including vaccine-related injection site AEs) were higher in the V116 (combined lots) group compared to the PPSV23 group (74.35% vs 61.9%). Few participants ($\leq 1.1\%$) experienced SAEs in either the V116 (combined lots) or PPSV23 group, and none of the SAEs were considered to be vaccine related. One death occurred in the PPSV23 group, which was not considered to be vaccine related. See Table 10 9

Table 10. Summary of AEs in V116 (combined Lots) and PPSV23 Treated Participants*

	V116 (combined lots) n (%)	PPSV23 n (%)
# Participants	1,616	541
w/ ≥ 1 AEs	1,300 (80.4)	405 (74.9)
injection site	1,200 (74.3)	335 (61.9)

systemic	928 (57.4)	281 (51.9)
Vaccine ^a related AEs	1,268 (78.5)	386 (71.3)
injection site	1,200 (74.3)	334 (61.7)
systemic	792 (49.0)	237 (43.8)
Serious AEs	14 (0.9)	6 (1.1)
Serious vaccine-related AEs	0 (0.0)	0 (0.0)
Death	0 (0.0)	1 (0.2)

*Adapted from Sponsor Table 12-2 (Clinical Study Report P004V116; page 52, STN 125814/0).

^a Determined by investigator to be related to the vaccine. All injection site adverse events and pyrexia (defined as maximum temperature > 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination) are considered to be vaccine-related.

Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration of participation in the study.

Most common AEs

The most frequently reported AEs (including vaccine related AEs) experienced by $\geq 5\%$ of participants in the V116 (combined lots) and the PPSV23 groups were solicited injection-site and systemic AEs. With the exception of injection site pain, which was higher in the V116 (combined lots) group (73.3% vs 60.6%) compared to the PPSV23 group, the proportions of participants with fatigue, headache, myalgia, injection site erythema and injection site swelling were comparable between V116 and PPSV23 groups.

Table11. Participants with AEs in V116 Group (Incidence $\geq 5\%$ in One of More Vaccination Groups) in All Treated Participants*

	V116 (combined lots) n (%)	PPSV23 n (%)
# Participants	1,616	541
w/ ≥ 1 AEs	1,300 (80.4)	405 (74.9)
Injection site pain ^a	1,184 (73.3)	328 (60.6)
Fatigue ^a	577 (35.7)	184 (34.0)
Headache ^a	473 (29.3)	131 (24.2)
Myalgia ^a	268 (16.6)	49 (9.1)
Injection site erythema ^a	224 (13.9)	41 (7.6)
Injection site swelling ^a	214 (13.2)	41 (7.6)

* Adapted from Sponsor Table 14.3-4 (Clinical Study Report P004V116; page 371, STN 125814/0).

Reported adverse events include non-serious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration participation in the study.

^a Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through 5 post vaccination but may have been reported spontaneously after Day 5. Pyrexia was defined as maximum temperature ≥ 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination but may have been reported spontaneously after Day 5 with or without reported temperature.

Solicited Adverse Events

Overall, the proportions of participants reporting one or more solicited adverse events was comparable between the V116 (combined lots) and PPSV23 groups (78.25 vs

71.5%). Generally, the proportions of participants reporting solicited injection site AEs was higher compared to the PPSV23 group (74.2% vs 61.7%). The proportions of participants reporting solicited systemic AEs were generally comparable between the V1116 (combined lots) group and the PPSV23 group (48.1% vs 43.3%). See Table 12.

Injection-site AEs

For specific solicited injection site AEs following PCV, V116 participants reported more injection site pain (73.3% vs 60.6%) than the PPSV23 group. Other solicited injection site AEs were comparable between the V116 and PPSV23 participants, including injection site erythema (13.9% vs 7.6%) and injection site swelling (13.3 % vs 7.6%). Most solicited injection site AEs following PCV were mild or moderate in intensity and of short duration (≤ 3 days). See Table 12.

Systemic AEs

For specific solicited systemic AEs following PCV, the proportions of V116 participants reporting such events were generally comparable to the PPSV23 group, including fatigue (35.5% vs 34.0%), headache (27.2% vs 21.4%), myalgia (16.3 % vs 8.7%) and pyrexia (3.0% vs 2.2%). Most solicited systemic AEs following PCV were mild or moderate in intensity and of short duration (≤ 3 days). See Table 12.

SAEs

The proportion of participants with SAEs was low ($\leq 1.1\%$) and comparable between the V116 (combined lots) group and the PPSV 23 group (0.9% vs 1.1%). No vaccine related SAEs were reported. See Table 10 .

Listing of SAEs for V116 and PPSV23 (Reference: Sponsor Table 14.3-25, pg. 436, in Clinical Study Report P004V116):

For the V116 (combined lots) group there were 14 (0.9%) SAEs, with most events reported as psychiatric disorders (6 [0.4%]) consisting of 2 bipolar disorder events (0.1%), and 1 event (0.1%) for each of the following: alcohol withdrawal syndrome, depression, major depression, and psychotic disorder. There were 4 SAEs related to neoplasms benign, malignant and unspecified which included 1 case (0.1%) each of breast cancer, clear cell renal cell carcinoma, endometrial cancer and oligodendroglioma. The remaining 4 SAEs, consisted of 1 case (0.1%) each of intestinal perforation, chest discomfort, abdominal abscess, and concussion. None of these SAEs were considered to be related to administration of V116.

For the PPSV23 group there were 6 (1.1%) SAEs, with 5 (0.9%) reported as infections and infestations consisting of 1 case (0.1%) for each of the following: gastroenteritis, infectious mononucleosis, pelvic abscess, pneumonia, and sepsis. There was one fatal SAE (see below under Deaths). None of these SAEs were considered to be related to administration of PPSV23.

Deaths

There was 1 death reported in the PPSV 23 group due to road traffic accident, which the study investigator did not consider related to administration of PPSV23. The participant was a 27- year- old male that was hospitalized on Day 58 following a road traffic accident on a motorcycle. No treatment was reported and no further information was available. On Day 60 the participant died due to his injuries. This reviewer agrees with the study investigator that the event of road traffic accident was not related to the study vaccination.

Table 12. Treated Participants with Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups*

	V116 (combined lots) n (%)	PPSV23 n (%)
# participants in population	1,616	541
w/ ≥ 1 solicited AE	1,263 (78.2)	387 (71.5)
Solicited injection site AEs	1,199 (74.2)	334 (61.7)
Injection site erythema	219 (13.6)	41 (7.6)
Injection site pain	1,184 (73.3)	328 (60.6)
Injection site swelling	213 (13.3)	41 (7.6)
Solicited systemic AEs	778 (48.1)	234 (43.3)
Fatigue	573 (35.5)	184 (34.0)
Headache	440 (27.2)	116 (21.4)
Myalgia	264 (16.3)	47 (8.7)
Pyrexia	48 (3.0)	12 (2.2)

*Adapted from Sponsor Table 12-3 (Clinical Study Report P004V116; page 53, STN 125814/0).

Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through 5 post vaccination. Pyrexia was defined as maximum temperature ≥ 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination.

Reviewer Comment: *The overall safety of V116 is consistent across manufacturing lots and comparable to PPSV23 in this study. This suggests V116 has an acceptable safety profile in adults aged 18 to 49 years of age who are pneumococcal vaccine naïve. Strengths of this study include the large number of participants who received V116 across the three lots (Lot 1: n=539; Lot 2: n=536; Lot 3: n=541), and the inclusion of V116 vaccinated participants (n= 406 [25.1%] in the combined lots) with ≥ 1 prespecified medical history condition (chronic heart, kidney, liver and lung disease, diabetes mellitus, alcoholism or current smoker) associated with an increased risk of pneumococcal disease. A limitation of this study is the exclusion of immunocompromised participants.*

5.2.4 Clinical study (V116-005)

Study Description:

V116-005 was a Phase 3 randomized, double-blind placebo-controlled study conducted at 56 centers in the U.S. to assess the safety, tolerability, and immunogenicity of V116

administered concomitantly with inactivated Quadrivalent Influenza vaccine (QIV), in adults ≥ 50 years of age with or without a history of prior vaccination.

Participants with underlying chronic medical conditions were eligible if the conditions were assessed to be stable by the study investigator. The reported medical history conditions were comparable between the concomitant and sequential groups with the five most frequently reported conditions listed as hypertension (38.8%), osteoarthritis (21.0%), diabetes mellitus (20.4%), gastroesophageal reflux disease (18.3%) and seasonal allergy (17.4%).

1,080 participants were randomly assigned in a 1:1 ratio to either the concomitant group (Day 1: V116 + QIV administered; Day 30: placebo administered) or the sequential group (Day 1: QIV + placebo administered; Day 30: V116 administered). Randomization was stratified by age at enrollment: 50 to 64 years, 65 to 74 years, 75 to 84 years and ≥ 85 years (with at least 50% of participants ≥ 65 years of age); and by prior pneumococcal vaccination status (PCV13 and PPSV23 naïve, prior receipt of PCV 13 only, prior receipt of PPSV23 only, and prior receipt of both PCV13 and PPSV23) with at least 50% of participants PCV13 and PPSV23 naïve.

In the Concomitant Group: 540 randomized, 536 vaccinated, 510 completed the study, 30 (5.6%) discontinued the study. Discontinuations were due to death (1 [0.2%]); lost to follow up (17 [3.1%]); withdrawal by subject (12 [2.2%])

In the Sequential Group: 540 randomized, 536 vaccinated, 507 completed the study, 33 (6.1%) discontinued the study. Discontinuations were due to death (2 [0.4%]), lost to follow up (15 [2.8%]), physician decision (1 [0.2%]), randomized by mistake without study treatment (1 [0.2%]); withdrawal by subject (12 [2.2%]) and “other” (2 [0.4%]).

Summary of Adverse Events

The majority of participants had ≥ 1 AE in the concomitant and sequential group (74.0% vs 70.1%). The proportion of participants with injection site and systemic AEs (including vaccine related AEs) were generally comparable between the concomitant group and sequential group. The occurrence of serious adverse events (SAEs) was low ($\leq 4\%$) and generally comparable between the concomitant and sequential groups. A total of 3 deaths occurred in the study, none were considered to be related to study vaccine (See Table 13).

Participants in the concomitant group versus the sequential group reported comparable occurrences of ≥ 1 unsolicited AE (27% vs 31.4%), most commonly for general disorders and administration site conditions (65.9% in concomitant group and 63.6% in sequential group).

Table 13. Summary of Adverse Events in Concomitant and Sequential Group in Treated Participants*

	Concomitant Group n (%)	Sequential Group n (%)
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# Participants	534	535
w/ > 1 AEs	395 (74.0)	375 (70.1)
injection site	319 (59.7)	315 (58.9)
systemic	279 (52.2)	298 (55.7)
Vaccine related ^a AEs	362 (67.8)	343 (64.1)
injection site	319 (59.7)	314 (58.7)
systemic	206 (38.6)	217 (40.6)
Serious AEs	10 (1.9)	17 (3.2)
Serious vaccine related AEs	0 (0.0)	1 (0.2)
Deaths	1 (0.2)	2 (0.4)

*Adapted from Sponsor Table 12-1 (Clinical Study Report P005V116; page 55, STN 125814/0).

^a Determined by investigator to be related to the vaccine. All injection site adverse events and pyrexia (defined as maximum temperature > 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination) are considered to be vaccine-related.

Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration of participation in the study.

Most common AEs

The most frequently reported AEs (including vaccine related AEs) experienced by $\geq 5\%$ of participants in the concomitant and sequential groups, were the solicited injection site and systemic AEs injection-site pain (58.1% vs 56.6%), fatigue (30.3% vs 32.75%), headache (20.4% vs 22.4%), myalgia (13.9% vs 15.0%), injection site swelling (12.75% vs 12.3%), and injection site erythema (11.8% vs 11.2%).

Solicited Adverse Events

Overall, most ($\geq 65\%$) participants in the concomitant and sequential groups reported ≥ 1 solicited AE. Participants reporting injection-site AEs in the concomitant vs sequential group were generally comparable (59.4% vs 58.7%). Participants reporting systemic AEs in the concomitant vs sequential group were also generally comparable (41.0% vs 41.9%). See Table 14

Injection-site AEs

Overall, solicited injection-site AEs were comparable for participants in the concomitant and sequential groups including injection site pain (57.9% vs 56.6%), injection site swelling (12.5% vs 11.8%) and injection site erythema (11.4% vs 11.0%). Most solicited injection site AEs following any vaccination in the concomitant and sequential group were mild or moderate in intensity and of short duration (≤ 3 days). See Table 14

Systemic AEs

Overall, systemic AEs were comparable for participants in the concomitant and sequential groups including fatigue (30.0% vs 32.7%), headache (20.0% vs 22.1%), myalgia (13.9% vs 15.0%), and pyrexia (1.9% vs 2.4%). Most systemic AEs following any vaccination in the concomitant and sequential group were mild or moderate in intensity and of short duration (≤ 3 days). See Table 14.

SAEs

As summarized in Table 12, the proportion of participants with SAEs was low ($\leq 4\%$) and generally comparable between the concomitant and sequential groups (1.9% vs 3.2%). Similar results were seen for SAEs following each vaccination visit.

Only one SAE of bronchospasm was considered to be vaccine related by the study investigator. The SAE occurred in a 50-year-old female participant (# (b) (6)), in the sequential group, with a history of seasonal allergy, drug hypersensitivity, flank pain, intervertebral disc degeneration, migraine, hypertension, cervical radiculopathy, GERD, vitamin D deficiency, ligament rupture, osteopenia and COVID-19, who, on Day 30 (post vaccination 1) received Vaccination 2 (V116). Ten minutes after V116 administration, the participant reported acute onset of chest tightness, cough and wheezing. Blood pressure and oxygen saturation were WNL. No rash or urticaria experienced by the participant but she did complain of injection site pain and headache. The participant was diagnosed with allergic reaction with acute severe bronchospasm and was treated with diphenhydramine, salbutamol, and paracetamol. The participant reported all signs and symptoms had resolved and returned to baseline in the afternoon. Later in the evening the participant reported reoccurrence of consistent chest tightness with bronchospasm. During this episode the participant was treated with diphenhydramine and albuterol. bronchospasm was considered resolved within 24 hours.

The participant did not have a prior history of asthma, instead had reactive airways in the setting of respiratory infections in the past. Participant was previously treated with albuterol MDI for respiratory symptoms of chest tightness and wheezing associated with COVID-19 infection and had not used albuterol since then. Participant also had prior history of bee sting allergy resulting in bronchospasm and angioedema. Bronchospasm was confirmed by skin allergy testing with an allergist. Participant received an epinephrine pen for bee sting allergy at that time, but no further allergy consultation was done. On Day 68 (Postvaccination 1 and Day 39 Post vaccination 2) the participant reported that respiratory symptoms from prior COVID-19 had fully resolved, with no residual respiratory conditions. The study investigator opined that bronchospasm was related to V116/saline placebo and not related to influenza vaccine. On Day 208 (Postvaccination 1 and Day 179 Postvaccination 2) the participant had completed the study. This reviewer agrees with the study investigator's assessment that the bronchospasm was related to administration of V116/saline placebo and not related to influenza vaccine.

Discontinuations of study vaccine due to AEs

Overall, 3 participants discontinued the study vaccine due to an adverse event:

- 1 (0.2%) participant in the Sequential Group:
 - 53 -year -old female (participant # (b) (6)) with history of seasonal allergy, drug hypersensitivity, myopia, menopause, arthralgia, arthritis, experienced nonserious AE of mild dizziness (Day 6) following

Vaccination 1 (Placebo +QIV) which resolved on Day 7 without medical intervention; no further information was reported. Study vaccination was permanently discontinued due to this event. The last dose of study vaccination was given on Day 1 (Postvaccination1).

Reviewer Comment: Given the paucity of information regarding this AE it is difficult to ascribe causality of the AE to the study vaccination.

- 2 (0.4%) participants in the Concomitant Group:
 - 73- year -old female (participant # (b) (6)) with history of hypertension, gout, atrial fibrillation and diabetes mellitus, experienced nonserious, vaccine related AEs of injection-site pain (Day 6), malaise (Day 6), injection-site swelling (Day 7), and injection-site erythema (Day 8) following Vaccination 1 (V116+ QIV). All the adverse events resolved. Study vaccination was permanently discontinued due to these events (last dose of study vaccination given on Day 1 [Postvaccination 1]). On Day 203 (Postvaccination 1) the participant had completed the study. This reviewer agrees with the study investigator's assessment that the AEs of injection site pain, malaise, injection site swelling, and injection site erythema are vaccine related.
 - One participant following Vaccination 1 (V116 +QIV) due to a serious non-vaccine related AE of blood loss anemia (Day 8), which resolved. No further information (i.e., narrative) was available from the sponsor.

Reviewer Comment: Given the paucity of information regarding this AE it is difficult to ascribe causality of the AE to the study vaccination.

Deaths:

As summarized in Table 12, there was 1 death (0.2%) reported in the concomitant group (due to metastatic malignant melanoma) and 2 deaths (0.4%) reported in the sequential group (one due to septic shock and one due to homicide). None of the deaths were considered to be related to study vaccine by the study investigator.

Death in Concomitant Group:

- 1) 80-year-old- female (participant # (b) (6)) with history of malignant melanoma and pulmonary hypertension was hospitalized on Day 18 (Postvaccination1) with diagnosis of gastric ulcer hemorrhage, acute blood loss anemia, hypokalemia, hyponatremia, hypomagnesemia, worsening pulmonary hypertension and worsening *Helicobacter* infection. After receiving appropriate medical treatment, the participant was discharged in stable condition from the hospital on Day 30. No action taken with study vaccination due to gastric ulcer hemorrhage and hypokalemia and study vaccination was permanently

discontinued due to blood loss anemia. Last dose of study vaccination given on Day 1 (Postvaccination1). On Day 212 participant died in hospice due to metastatic malignant melanoma. On the same day, gastric ulcer, blood loss anemia, hypokalemia, and hyponatremia were considered resolved. On Day 219 the pathology report of the brain showed worsening of metastatic malignant melanoma (onset on Day 148). This condition thought to have originated from previous melanoma excised from arm, thought to be curative at that time, and there was no subsequent treatment received and no evidence of ongoing malignancy. This reviewer agrees with the study investigator that the gastric ulcer hemorrhage, blood loss anemia, hypokalemia, and metastatic malignant melanoma were not related to the study vaccination.

Deaths in Sequential Group:

- 1) 65- year-old male (participant # (b) (6)) received Vaccination 2 and completed the study vaccination. After the site tried unsuccessfully to contact the participant to complete Visit 7, the participant's emergency contact was notified by the site on Day 195 (Postvaccination 1 and Day 164 Postvaccination 2) and informed that the participant was murdered at home, no further information available. On the same day the participant was reported as a victim of homicide. This reviewer agrees with the study investigator that victim of homicide was not related to the study vaccination.
- 2) 64 -year -old male (participant # (b) (6)) received Vaccination 2 on Day 32 and completed the study. On Day 57 (Postvaccination 1 and Day 26 Postvaccination 2) the participant presented to ED appearing critically ill and was admitted to the hospital. The participant developed multiorgan failure with infectious etiology and was diagnosed with septic shock on Day 57. On Day 58 (Postvaccination 1 and Day 27 Postvaccination 2) the participant died due to septic shock. No autopsy report was available (site assumed autopsy not completed since death certificate did not note that an autopsy was performed). This reviewer agrees with the study investigator that septic shock was not related to the study vaccination.

Table 14. Treated Participants with Solicited Adverse Events (Incidence > 0% in One or More Vaccination Groups)

	Concomitant Group	Sequential Group
	n (%)	n (%)
# participants	534	535
w/ ≥ 1 solicited AE	361 (67.6)	348 (65.0)
Solicited injection site AEs	317 (59.4)	314 (58.7)
Injection site erythema	61 (11.4)	59 (11.0)
Injection site pain	309 (57.9)	303 (56.6)
Injection site swelling	67 (12.5)	63 (11.8)

Solicited systemic AEs	219 (41.0)	224 (41.9)
Fatigue	160 (30.0)	175 (32.7)
Headache	107 (20.0)	118 (22.1)
Myalgia	74 (13.9)	80 (15.0)
Pyrexia	10 (1.9)	13 (2.4)

* Adapted from Sponsor Table 12-2 (Clinical Study Report P005V116; page 57, STN 125814/0).

Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through 5 post vaccination. Pyrexia was defined as maximum temperature ≥ 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination.

Reviewer Comment: *The overall safety for V116 concomitantly administered with inactivated Quadrivalent influenza vaccine (QIV) is comparable to V116 and QIV administered sequentially. This study suggests V116 administered concomitantly with inactivated Quadrivalent Influenza vaccine (QIV) in adults ≥ 50 years of age with or without a history of prior vaccination with PCV13 and/or PPSV23 is well tolerated with a safety profile comparable to V116 alone. Strengths of this study include the large number of participants who received V116 in this study and the high proportion of vaccinated participants with ≥ 1 prespecified medical history condition (chronic heart, kidney, liver and lung disease, diabetes mellitus, alcoholism or current smoker) associated with an increased risk of pneumococcal disease (40.6% in concomitant group and 41.1 % in sequential group). A limitation of this study is the exclusion of immunocompromised participants.*

5.2.5 Clinical study (V116-006)

Study Description:

V116-006 was a Phase 3 randomized, double-blind (Cohorts 1 and 2), open label (Cohort 3) active comparator study conducted at 51 centers in 9 countries to assess the safety, tolerability and immunogenicity of V116 in pneumococcal vaccine-experienced adults ≥ 50 years of age (participants with underlying chronic conditions were eligible if the conditions were assessed to be stable per investigator's judgment). 717 participants were enrolled into 1 of 3 parallel cohorts based on the participant's prior pneumococcal vaccination history and 712 participants were vaccinated, 710 participants completed the study, and 7 participants discontinued the study (see Table 15).

Cohort 1: Participants vaccinated with PPSV23 ≥ 1 year prior to enrollment were randomized in a 2:1 ratio to receive V116 or PCV15 on Day 1. This cohort was double-blind, parallel group, and active comparator controlled.

Cohort 2: Participants vaccinated with PCV13 ≥ 1 year prior to enrollment were randomized in 2:1 ratio to receive V116 or PPSV23 on Day 1. This cohort was double-blind, parallel group, and active comparator controlled.

Cohort 3: Participants vaccinated with PCV13+PPSV23, PCV15+PPSV23, PPSV23+PCV13, PCV15 or PCV20 > 1 year prior to enrollment received V116 on Day 1. This cohort was open-label and single group.

Table 15. Participant Disposition into Cohorts 1, 2 and 3 in Study V116-006*

Cohort (# randomized)	Cohort 1 (n=350)		Cohort 2 (n= 261)		Cohort 3 (n= 106)
Prior pneumococcal vaccination history \geq 1 yr. prior enrollment	PPSV23		PCV 13		PCV13+PPSV23, PCV15+PPSV23, PPSV23+PCV13, PCV15 or PCV20
Vaccination group	V116 n (%)	PCV 15 n (%)	V116 n (%)	PPSV23 n (%)	V116 n (%)
# randomized	231	119	176	85	106
# vaccinated	229(99.1)	119(100.0)	174(98.9)	85(100.0)	105 (99.1)
# completed study	229(99.1)	118 (99.2)	173(98.3)	85(100.0)	105(99.1)
# discontinued study	2(0.9)	1(0.8)	3(1.7)	0(0.0)	1(0.9)
Lost to follow up	0(0.0)	0(0.0)	1 (0.6)	0(0.0)	0(0.0)
Subject withdrew	2(0.9)	1(0.8)	1(0.6)	0(0.0)	0(0.0)
Randomized by Mistake w/o study treatment	0(0.0)	0(0.0)	1(0.6)	0(0.0)	1(0.9)

* Adapted from Sponsor Table 10-1 (Clinical Study Report P006V116; page 46, STN 125814/0).

PCV15= pneumococcal 15-valent conjugate vaccine; PPSV23= pneumococcal vaccine, polyvalent (23-valent).

Summary of Adverse Events

Overall, for all three cohorts, the majority of participants with \geq 1 AEs were generally comparable in each intervention group: Cohort 1 (51.3% vs 64.1%), Cohort 2 (52.9% vs 65.9%), and Cohort 3 (52.4%) regardless of pneumococcal vaccination history (see Table 16). Participants in Cohorts 1 and 2 with specific AEs by SOC and PT were generally comparable across vaccine groups (see Table A3 in appendix).

Table 16. Summary of Adverse Events by Cohort in All Treated Participants*

	Cohort 1		Cohort 2		Cohort 3
	V116	PCV 15	V116	PPSV23	V116

	n (%)	n (%)	n (%)	n (%)	n (%)
#Participants	230	117	174	85	105
w/ \geq 1 AEs	118 (51.3)	75 (64.1)	92 (52.9)	56 (65.9)	55 (52.4)
injection site	93 (40.4)	56 (47.9)	75 (43.1)	46 (54.1)	46 (43.8)
systemic	69 (30.0)	44 (37.6)	56 (32.2)	33 (38.8)	33 (31.4)
Vaccine related ^a AEs	107 (46.5)	66 (56.4)	87 (50.0)	52 (61.2)	51 (48.6)
injection site	93 (40.4)	56 (47.9)	75 (43.1)	46 (54.1)	46 (43.8)
systemic	50 (21.7)	27 (23.1)	46 (26.4)	21 (24.7)	26 (24.8)
Serious AEs	2 (0.9)	4 (3.4)	2 (1.1)	3 (3.5)	2 (1.9)
Serious vaccine related AEs	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Adapted from Sponsor Table 12-1 (Clinical Study Report P006V116; page 57, STN 125814/0).

^a Determined by the investigator to be related to the vaccine. All injection site adverse events and pyrexia (defined as maximum temperature \geq 100.4 F (38.0 C) solicited from Day 1 through Day 5 postvaccination) are considered to be vaccine-related.

Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration of participation in the study.

PCV15= pneumococcal 15-valent conjugate vaccine; PPSV23= pneumococcal vaccine, polyvalent (23-valent).

Most common AEs

The most frequently reported AEs (including vaccine related AEs) experienced by \geq 5% of participants across all 3 cohorts in both intervention groups were the solicited injection site (I.S.) and systemic AEs of injection-site pain, fatigue, injection-site swelling (except for V116 group in Cohort 2 [4.6%]), injection-site erythema, headache, and myalgia (except for PCV15 group in Cohort 1[4.3%]). See Table 17.

Table 17. Treated Participants with Adverse Events by Descending Frequency in V116 Group (Incidence \geq 5% in One or More Vaccination Groups) in Cohorts 1,2, and 3*

	Cohort 1			Cohort 2			Cohort 3
	V116 n (%)	PCV 15 n (%)		V116 n (%)	PPSV23 n (%)		V116 n (%)
#Participants	230	117		174	85		105
w/ \geq 1 AEs	118 (51.3)	75 (64.1)		92(52.9)	56 (65.9)		55 (52.4)
I.S. pain ^a	82 (35.7)	51 (43.6)	I.S. pain	72(41.4)	40 (47.1)	I.S. pain	46 (43.8)
Fatigue ^a	33 (14.3)	20 (17.1)	Fatigue	33(19.0)	12 (14.1)	Fatigue	23 (21.9)
I.S. swelling ^a	20 (8.7)	10 (8.5)	Headache	18(10.3)	10 (11.8)	I.S. swelling	11 (10.5)
I.S. erythema ^a	19 (8.3)	9 (7.7)	Myalgia	17 (9.8)	9 (10.6)	Headache	9 (8.6)

Headache ^a	17 (7.4)	11 (9.4)	I.S. erythema	14 (8.0)	8 (9.4)	Myalgia	9 (8.6)
Myalgia ^a	17 (7.4)	5 (4.3)	I.S. swelling	8 (4.6)	14 (16.5)	I.S. erythema	8 (7.6)

*Adapted from Sponsor Table 14.3-5, Table 14.3-7 and Table 14.3-9 (Clinical Study Report P006V116; page 495-501 STN 125814/0).

Reported adverse events include nonserious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through duration of participation in the study.

^a Injection site (I.S.) erythema, injection site (I.S.) pain, injection site (I.S.) swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 post vaccination but may have been reported spontaneously after Day 5. All injection site adverse events and pyrexia (defined as maximum temperature > 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination) are considered to be vaccine related.

PCV15=pneumococcal 15-valent conjugate vaccine. PPSV23= pneumococcal vaccine, polyvalent (23-valent).

Solicited Adverse Events Overall, more than 46% of participants across all 3 cohorts reported experiencing ≥ 1 solicited adverse event (see Table 18).

Injection-site AEs

Generally, solicited injection site AEs were comparable in participants receiving V116 versus PCV 15 or PPSV23, regardless of pneumococcal vaccination history: Cohort 1 (40.0% vs 47.9%) and Cohort 2 (43.1% vs 54.1%). Across Cohorts 1 and 2 the occurrence of injection site pain, erythema and swelling was comparable between V116 and its comparator, except for injection site swelling, which was reported more frequently in the PPSV23 vaccine group of Cohort 2 (16.5%). Across all 3 cohorts, most solicited injection site AEs following any vaccination were mild or moderate in intensity and of short duration (≤ 3 days). See Table 18. Of note, one participant (PCV15 group in Cohort 1) had injection site pain with a duration of > 10 days.

Systemic AEs

Generally, solicited systemic AEs were comparable for participants receiving V116 versus PCV 15 or PPSV23 regardless of pneumococcal vaccination history: Cohort 1 (20.9% vs 21.4%) and Cohort 2 (25.9% vs 23.5%). Across Cohorts 1 and 2 the occurrence of fatigue, headache, myalgia and pyrexia was comparable between V116 and its comparator, except for myalgia which was reported less frequently in the PCV vaccine group (Cohort 1). Across all 3 cohorts, most solicited systemic AEs were mild or moderate in intensity and of short duration (≤ 3 days). See Table 18.

Table 18. Treated Participants with Solicited Adverse Events by Cohort (Incidence > 0% in One or More Vaccination Groups)*

	Cohort 1		Cohort 2		Cohort 3
	V116 n (%)	PCV 15 n (%)	V116 n (%)	PPSV23 n (%)	V116 n (%)
#Participants	230	117	174	85	105

w/ ≥ 1 AEs	107 (46.5)	65 (55.6)	86 (49.4)	52 (61.2)	51 (48.6)
Solicited injection site AEs	92 (40.0)	56 (47.9)	75 (43.1)	46 (54.1)	46 (43.8)
Pain	82 (35.7)	51 (43.6)	72 (41.4)	40 (47.1)	46 (43.8)
Erythema	17 (7.4)	9 (7.7)	13 (7.5)	8 (9.4)	8 (7.6)
Swelling	19 (8.3)	10 (8.5)	8 (4.6)	14 (16.5)	11 (10.5)
Solicited systemic AEs	48 (20.9)	25 (21.4)	45 (25.9)	20 (23.5)	26 (24.8)
Fatigue	33 (14.3)	20 (17.1)	33 (19.0)	11 (12.9)	23 (21.9)
Headache	16 (7.0)	11 (9.4)	18 (10.3)	10 (11.8)	9 (8.6)
Myalgia	17 (7.4)	3 (2.6)	17 (9.8)	8 (9.4)	9 (8.6)
Pyrexia	4 (1.7)	3 (2.6)	5 (2.9)	1 (1.2)	0 (0.0)

*Adapted from Sponsor Table 12-2 (Clinical Study Report P006V116; page 59, STN 125814/0).

Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through 5 post vaccination. Pyrexia was defined as maximum temperature ≥ 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination but may have been reported spontaneously after Day 5 with or without reported temperature.

PCV15= pneumococcal 15-valent conjugate vaccine; PPSV23= pneumococcal vaccine, polyvalent (23-valent).

Unsolicited Adverse Events

Less than 18% of participants in each vaccination group, in all 3 cohorts, reported \geq unsolicited AEs from Day 1 through Day 30 postvaccination (excluding solicited AEs reported Day 1 through Day 5). For Cohorts 1 and 2, the proportion of participants with unsolicited AEs (excluding solicited AEs reported Day 1 through Day 5) were generally comparable in between V116 and the comparator in Cohort 1 (13.9% vs 17.9%) and Cohort 2 (12.6% vs 16.5%). In Cohort 3, the proportion of participants with one or more unsolicited adverse events was 10.5%.

SAEs

Overall, the proportions of participants with SAEs were low (< 4%) within each cohort with participants administered V116 reporting fewer SAEs than those receiving PCV 15 (0.9% vs 3.4%, Cohort 1) and PPSV23 (1.1 % vs 3.5%, Cohort 2).

One vaccine related SAE of injection site cellulitis was reported for a 67-year-old - female participant in Cohort 1 who received V116. The cellulitis developed on Day 5 post vaccination with the participant requiring hospital admission on Day 8. The cellulitis resolved on Day 16 after initiation of appropriate antimicrobial treatment (blood culture showed no bacterial growth) and the participant was able to complete the study.

Reviewer Comment: This reviewer agrees with the study investigator's assessment that the SAE of cellulitis was vaccine related.

There were no vaccine related SAEs for participants in Cohort 2 or Cohort 3. .

Deaths: There were no deaths reported in this study.

Reviewer Comment: The overall safety for V116 is comparable to PCV15 and PPSV23 in this study. This study suggests that V116 has an acceptable safety profile in immunocompetent, pneumococcal vaccine-experienced adults ≥ 50 years of age (some) with risk factors for pneumococcal disease. Strengths of this study include the large number of participants who received V116 across three cohorts (n= 508) and the high proportion of V116 participants with ≥ 1 prespecified medical history condition (chronic heart, kidney, liver and lung disease, diabetes mellitus, alcoholism or current smoker) associated with an increased risk of pneumococcal disease (44.1% in Cohort 1; 42.0% in Cohort 2 and 48.0 % in Cohort 3). A limitation of this study is the exclusion of immunocompromised participants.

5.2.6 Integrated Population (Studies V116-003, V116-004, V116-005 and V116-006)

Description of pooled studies

For the integrated safety analysis, the sponsor created an “integrated population” (n=6,038) by pooling safety data from the four Phase 3 studies of participants who received V116 into one group (V116-003, V116-004, V116-006 and the sequential group in V116-005) and by pooling the participants who received an active comparator (PCV 15, PCV 20, or PPSV 23) into one combined control group. Therefore, the number of V116 participants in the integrated population was 4,020 and the number of control participants was 2,018.

AEs in the Integrated Safety Population

67% or more participants in the V116 and combined control groups (67% vs 68.7%) reported one or more adverse events from Day 1 through Day 30 postvaccination. Participants in the V116 group and the combined control group experienced comparable solicited AEs (63.3% vs 63.9%), unsolicited AEs (22.3% vs 22.2%), and vaccine related solicited AEs (62.6% vs 63.4%) and vaccine related unsolicited AEs (7.8% vs 6.1%) from Day1 through Day 30 postvaccination.

Most common AEs

The most common vaccine related AEs (experienced by more than 5% of participants) in the integrated safety population were the solicited AEs of injection-site pain, fatigue, headache, myalgia, injection-site erythema, and injection- site swelling.

Solicited Adverse Events

Overall, the number of participants with one or more solicited AE were generally comparable between the V116 group and the combined control group (63.3% vs 63.9%). Generally, solicited injection site adverse events were comparable between V116 group and the combined control group (57.1% vs 56.5%) and likewise comparable between V116 group and combined control group for solicited systemic AEs (36.8% vs 32.0%)

Injection-site AEs:

For specific solicited injection AEs, the proportions of participants in the V116 group versus the combined control group was generally comparable for injection site pain (55.6% vs 54.5%); injection site erythema (9.9% vs 7.2%); and injection site swelling (9.8% vs 8.8 %). Most solicited injection site AEs were mild or moderate in intensity and of short duration (≤ 3 days).

Systemic AEs

For specific solicited systemic AEs, the proportions of participants in the V116 group versus the combined control group was generally comparable for fatigue (27.1% vs 23.7%); headache (18.4% vs 15.5%); myalgia (11.3% vs 7.5%); and pyrexia (2.2% vs 1.6%). Most solicited systemic AEs were mild or moderate in intensity and of short duration (≤ 3 days).

Unsolicited Adverse Events

In the integrated safety population, the proportion of participants with unsolicited AEs reported Day 1 through Day 30 (excluding solicited events reported Day 1 to Day 5 post vaccination) were generally comparable between V116 group and the combined control group. Most unsolicited AEs were mild or moderate in intensity and of short duration (< 3 days).

SAEs

Overall, the proportion of participants with SAEs was low ($\leq 2\%$) and comparable between the V116 group and the combined control group in SAEs from Day 1 through Day 30 postvaccination (0.3% vs 0.3%), in SAEs from Day 1 through month 6 post vaccination (1.4% vs 2.0%). Two participants in the V116 group reported vaccine related SAEs from Day 1 through Day 30 post vaccination and vaccine related SAEs from Day 1 through month 6 post vaccination, that were considered to be vaccine related by the study investigator*. There were no such reports for the combined control group. Lastly, one participant in the V116 group reported a SAE within 30 minutes post vaccination*.

**Reviewer comment: The two vaccine related SAEs were previously discussed in this review and consist of bronchospasm in the sequential group of V116-005 (which occurred within 30 minutes of V116 administration) and injection site cellulitis in the V116 group in V116-006 study.*

Deaths

There were 9 (0.1%) deaths reported in the integrated population, six in the V116 group (due to MI, sepsis, septic shock, CVA, hepatic cirrhosis/hepatic encephalopathy, and homicide victim) and 3 (0.1%) in the combined control group (due to cardiac arrest, abdominal abscess and motorcycle road traffic accident). See previous discussion of these death events in this review. None of the deaths were considered to be vaccine related.

One additional death (metastatic malignant melanoma) occurred in the V116-005 concomitant group and was not included in the integrated safety population. The death was not considered by the investigator to be related to study vaccine and this reviewer agrees with this assessment.

None of these deaths were considered by this reviewer to be related to study vaccine.

Body Temperature Measurements

Within each of the Phase 3 clinical studies, the majority (> 96%) of participants reported a maximum body temperature < 100.4 degrees Fahrenheit in each intervention group between Day 1 and Day 5 postvaccination.

5.2.7 Summary of Adverse Events

The safety data from 5 clinical studies reviewed here shows an acceptable safety profile for V116, which was generally well tolerated when administered as a single dose in adults ≥ 18 years of age, including pneumococcal vaccine-naïve and pneumococcal vaccine-experienced participants. V116 was well tolerated in participants (V116-003 and V116-004) with 1 or more risk factors for pneumococcal disease and when administered concomitantly with inactivated influenza vaccine (V116-005).

The most frequently reported AEs (experienced by $\geq 5\%$ of participants) were the solicited AEs of injection-site pain, injection site swelling, injection site erythema, myalgia, fatigue, and headache. Most of the solicited AEs were considered mild or moderate and were of short duration (≤ 3 days).

There were no consistent trends in unsolicited AEs across the studies, with rates of unsolicited AEs through day 30 post vaccination similar between V116 (22.3%) and the control groups (22.2%). The most common MedDRA terms consisted of Infections and infestations (7.5% vs 7.9%), General disorders and administrative site conditions (4.8% vs 5.0%), GI disorders (3.7% vs 3.4%), Nervous system disorders (3.9% vs 4.1%), Respiratory, thoracic and mediastinal disorders (3.7% vs 3.2%), and musculoskeletal and connective tissue disorders (3.2% vs 3.3%).

Discontinuation of Study Intervention Due to AEs

In V116-005, 2/534 (0.4%) participants in the concomitant group and 1/535 (0.2%) participants in the sequential group had AEs leading to study vaccine discontinuation.

Participants in V116-003, V116-004, and V116-006 received a single dose of V116 or control and could therefore not discontinue study intervention.

The proportion of participants who experienced 1 or more SAEs within 6 months post vaccination was low and generally comparable between participants vaccinated with V116 or an active comparator (1.4% vs 2.0%). There were no notable imbalances between vaccine groups for SAEs and the events were consistent with the population studied. Two SAEs were considered to be related to V116 administration by the study investigator (0.05%; bronchospasm and cellulitis) and there were few discontinuations due to AEs.

Finally, there were a total of 9 deaths: 6 deaths in V116 recipients and 3 deaths in active control recipients, none of which were considered to be related to vaccination with V116.

Overall, there were no new safety signals identified by this reviewer in the five clinical studies submitted in support of V116 for licensure.

6 SUMMARY OF POSTMARKETING EXPERIENCE

6.1 Sponsor's Analysis

No post-marketing data available as V116 has not been licensed in any country.

7 SPONSOR'S PHARMACOVIGILANCE PLAN

A summary of the sponsor's pharmacovigilance plan (PVP) is provided in the table below.

Table 19 Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Important identified risks	None	N/A
Important potential risks	None	N/A
Missing Information	None	N/A

*Adapted from Table SVIII.1: Summary of Safety Concerns of the sponsor's Risk Management (Non-REMS) document (pg 23), STN 125814/0, Module SVIII.

7.1 Postmarketing Safety Studies and Risk Evaluation and Mitigation Strategies

There are no planned postmarketing safety studies or risk evaluation and mitigation strategies for this product.

8 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

A summary of the sponsor's pharmacovigilance plan (PVP) is provided in Table 19 above.

The sponsor proposes routine pharmacovigilance (adverse reaction reporting and signal detection) for all AEs.

8.1 Important Identified Risks

The sponsor did not list any important identified risks for V116.

Reviewer comment: This reviewer agrees with the sponsors assessment regarding important identified risks.

8.2 Important Potential Risks

The sponsor did not list any important potential risks for V116.

Reviewer comment: This reviewer agrees with the sponsor's assessment regarding important potential risks.

8.3 Important Missing Information

The sponsor did not list any important missing information for V116.

Reviewer Comment:

This reviewer considered if other excluded population, specifically immunocompromised individuals or pregnant/lactating women, should be considered as missing information.

Although Phase 3 studies (V116-003; V116-004; V116-005) enrolled adults ≥ 18 years of age with increased risk of pneumococcal disease due to stable chronic medical conditions (e.g., chronic heart, kidney, lung or liver disease; diabetes mellitus, alcoholism, or smoking) patients immunocompromised due to congenital or acquired immunodeficiencies, functional or anatomic asplenia, autoimmune disease, and those receiving immunosuppressive therapy were not represented in the studies. This reviewer does not believe that the safety profile of V116 would be different in immunocompromised individuals based upon post-marketing experience with other previously licensed pneumococcal vaccines, such as Prevnar 13. A 2016 review of almost 3000 post-marketing reports to VAERS for Prevnar 13 did not detect any unexpected AEs for immunocompromised individuals ³, and similar to the Prevnar 13 Package insert ⁴, the sponsor's proposed Package insert for V116 includes a warning about the potential for reduced immune response to V116 in immunocompromised individuals. Therefore, it is appropriate for the sponsor to not include immunocompromised population in missing information.

Also excluded from all clinical studies were pregnant and lactating women; participants of childbearing potential were instructed to use effective birth control methods for 6

weeks postvaccination. Across the four Phase 3 clinical studies, 1 participant in the V116 group reported 1 pregnancy during Study V116-004 [Ref. 5.3.5.1: P004V116: 16.2.7.1]. The participant was vaccinated 21 days prior to last menstrual period reported, and the outcome was ruptured ectopic pregnancy. The effect of V116 on the breastfed infant or on milk production/excretion was not evaluated in the studies; no data regarding exposure during breastfeeding are available. The Pregnancy section of V116 package insert states *there are no adequate and well-controlled studies done in pregnant women and data on V116 administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.*⁵ The label also states *that a developmental toxicity study was performed in female rats administered one-half the full human dose of V116, providing a margin of approximately 100-fold on a per kg basis, on four occasions: twice prior to mating, once during gestation and once during lactation. Reportedly, the study did not show adverse effects on fetal or preweaning development due to V116.*⁵

The sponsor of the previously FDA licensed pneumococcal vaccine, VAXNEUVANCE, also did not include pregnant/lactating women in missing information, and when an information request to the sponsor requesting further explanation as to why this group was not included in missing information, the sponsor responded (on February 11, 2021 (125741/0.9), that based on VAXNEUVANCE preclinical animal studies and the experience with currently licensed pneumococcal vaccines, they did not expect the safety profile for VAXNEUVANCE administered to pregnant/lactating women to differ from the known safety profile for VAXNEUVANCE in nonpregnant/nonlactating adults. The sponsor also stated they planned to monitor reports of VAXNEUVANCE exposure in pregnant/lactating women via routine pharmacovigilance (with “targeted follow-up questionnaires specific to pregnancy/lactation per standard process”). The Pregnancy section of the VAXNEUVANCE Package Insert states that “*Available data on VAXNEUVANCE administered to pregnant women are insufficient to inform vaccine associated risks in pregnancy.*”⁶

Comparison to the other currently licensed pneumococcal vaccines, to evaluate how this issue was addressed in the Package Insert and the Risk Management Plan for both Prevnar 13 and Pneumovax 23, showed that the Package Inserts for both Prevnar 13 and Pneumovax 23 comment on the lack of adequate data regarding vaccine-associated risks in pregnancy.^{4,7} For the Risk Management Plans, the Prevnar 13 Risk Management Plan (version 6.1, 2015) includes “Vaccine exposure during pregnancy and lactation” as missing information but addresses this with routine pharmacovigilance only.

The Pneumovax 23 Risk Management Plan (version 2, 2018) previously had “exposure during pregnancy” and “exposure during lactation” listed as missing information but they were “...removed in accordance with the revised guidance since patients who are pregnant or who are lactating are not in the indicated population.”

Therefore, for the reasons stated above, this reviewer agrees with the sponsor’s rationale for not including pregnant/lactating women in the missing information section

of the PVP. In addition, the lack of a clear precedent for including pregnant/lactating women in the PVP for other pneumococcal vaccines further supports this decision.

9 DPV ASSESSMENT

The sponsor's PVP adequately reflects the safety concerns based on the clinical trial experience. There are no important identified or potential risks in the sponsor's proposed PVP. This risk assessment is consistent with the safety profile observed in the clinical trials, for which there were no concerning differences in rates of SAEs, very few SAEs (one event each of bronchospasm and injection site cellulitis) and no deaths that this reviewer attributed to vaccination with V116.

Other populations discussed (other immunocompromised, pregnancy/lactating, women) do not warrant inclusion in the PVP at this time.

The reviewed data do not indicate a safety signal which would require either a Risk Evaluation and Mitigation Strategy (REMS), or a post marketing commitment (PMC) or post marketing requirement (PMR) study that is specifically designed to evaluate safety as a primary endpoint.

10 DPV RECOMMENDATIONS

No additional actions recommended prior to approval. The sponsor's proposed pharmacovigilance plan is adequate. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related post marketing requirement of commitment (PMR/PMC) study.

Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

REFERENCES

1. UpToDate. Invasive pneumococcal (*Streptococcus pneumoniae*) infections and bacteremia in adults. Accessed on January 26, 2024.
2. Centers for Disease Control and Prevention. *Streptococcus pneumoniae*. Available at: *Streptococcus pneumoniae* (CDC). Accessed January 26, 2024.
3. Haber P, Arana J, Pilishvili T, Lewis P, Moro PL, Cano M. Post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged >19years old in the United States, Vaccine Adverse Event Reporting System (VAERS), June 1, 2012-December 31, 2015. *Vaccine*. 2016 Dec 7;34(50):6330-6334. doi: 10.1016/j.vaccine.2016.10.052. Epub 2016 Nov 9. PMID: 27836437.
4. Prevnar 13- Package Insert. Accessed March 18, 2024
5. V116 Package Insert. Accessed March 18, 2024
6. Vaxneuvance-Package Insert. Accessed March 18, 2024
7. Pneumovax 23 Package Insert. Accessed March 18, 2024

APPENDIX 1

Materials Reviewed

Reviewer instruction: Only include documents relevant to this review.

Table A1: Materials reviewed in support of this assessment.

[illegible]

*Include FDA documents reviewed if applicable

Table A2. Overview of Clinical Trials*

Study Number	Design	Purpose	Population	Randomization/Exposure
V116-001	Phase 2 multicenter randomized double-blind active-comparator controlled study	Safety, tolerability, and immunogenicity of V116 compared to PPSV23	Healthy adults ≥ 50 year of age who were pneumococcal vaccine-naïve.	Randomization ratio V116:PPSV23 = 1:1 Number randomized/PCV vaccinated. V116 (n= 254/254) PPSV23 (n= 256/254)
V116-003	Phase 3 multicenter randomized double-blind active comparator controlled study	Safety, tolerability, and immunogenicity of V116 compared to PCV 20	Healthy adults ≥ 18 years of age who were pneumococcal vaccine-naïve <u>Cohort 1 (N=2300)</u> Age ≥ 50 years <u>Cohort 2 (N= 300)</u> Age: 18-49 years	<u>Cohort 1</u> Randomization ratio V116: PCV20= 1:1 Number randomized/PCV vaccinated V116 (n= 1181/1179) PCV 20 (n= 1181/1177) <u>Cohort 2</u> Randomization ratio V116:PCV20= 2:1 Number randomized/PCV vaccinated V116 (n=201/200) PCV 20 (n= 100/100)
V116-004	Phase 3 multicenter randomized double-blind active comparator controlled lot consistency study	Safety, tolerability, and immunogenicity of three manufacturing lots of V116	Adults 18-49 years of age who were pneumococcal vaccine-naïve	V116 Lot 1: 539 V116 Lot 2: 538 V116 Lot 3: 540 PPSV23: 540 Randomization ratio V116 Lot 1: V116 Lot 2: V116 Lot 3: PPSV23= 3:3:3:1 Number randomized/PCV vaccinated V116 Lot 1 (n= 541/539) V116 Lot 2 (n= 540/538) V116 Lot 3 (n= 541/540) PPSV23 (n=540/540)
V116-005	Phase 3 multicenter randomized double-blind	Safety, tolerability, and immunogenicity of V116 when	Adults ≥ 50 years of age with or without prior administration of any	Randomization ratio Concomitant:Sequential =1:1

	placebo-controlled study	administered concomitantly with inactivated quadrivalent influenza vaccine (QIV)	pneumococcal vaccine <u>Concomitant Grp (n=536)</u> Day 1: V116 +QIV Day 30: Placebo <u>Sequential Grp (n=536)</u> Day 1: Placebo+ QIV Day 30: V116	Number randomized/PCV vaccinated Concomitant (n= 540/536) Sequential (n=540/536)
V116-006	Phase 3 multicenter randomized double-blind placebo-controlled study	Safety, tolerability, and immunogenicity of V116 compared to PCV 15 or PPSV23	Adults \geq 50 years of age with prior pneumococcal vaccine experience <u>Cohort 1</u> (prior PPSV23): Parallel assignment, double-blind, active comparator V116 or PCV15 on Day 1 <u>Cohort 2</u> (prior PCV13): parallel assignment, double blind, active comparator V116 or PPSV23 on Day 1 <u>Cohort 3</u> (prior PCV13+PPSV23,) PCV15+PPSV23, PPSV23+PCV13, PCV15): single arm, open label V116 on Day 1	<u>Cohort 1</u> Randomization ratio V116: PCV15= 2:1 Number randomized/PVC vaccinated V116 (n=231/229) PCV15 (n= 119/119) <u>Cohort 2</u> Randomization ratio V116: PPSV23= 2:1 Number randomized/PVC vaccinated V116 (n=176/174) PPSV23 (n= 85/85) <u>Cohort 3</u> V116: 106/105

*Adapted from: Table 2.7.4 Summary of Clinical Safety Studies with V116 (2.7.4 Summary of Clinical Safety) and Table of all Clinical Trials (5.2 Tabular Listing of All Clinical Trials) and 5.3.5.1

+Risk factors for pneumococcal disease (V116-xxx) included underlying comorbidities (i.e., chronic heart, liver and kidney disease, diabetes mellitus, alcoholism and current smoker)

Abbreviations: pneumococcal conjugate vaccine (PVC), 13-valent pneumococcal conjugate vaccine (PCV 13), 20-valent pneumococcal conjugate vaccine (PCV 20), 23-valent pneumococcal polysaccharide vaccine (PPSV23).

Table A3. Participants with Adverse Events (Incidence > 0%) in One or More Vaccination Groups) in Cohorts 1, 2 and 3* of Study V116-006

	Cohort 1 (n=350)		Cohort 2 (n= 261)		Cohort 3 (n=106)
	V116 n (%)	PCV 15 n (%)	V116 n (%)	PPSV23 n (%)	V116 n (%)
#Participants	230	117	174	85	105
w/ ≥ 1 AEs	118 (51.3)	75 (64.1)	92 (52.9)	56 (65.9)	55 (52.4)
Blood & lymphatic system d/o	0 (0.0)	1 (0.9)			
Cardiac d/o	1 (0.4)	2 (1.7)			
Eye d/o	1 (0.4)	0			
GI d/o	8 (3.5)	5 (4.3)	4 (2.3)	2 (2.4)	1 (1.0)
General d/o & Admin site conditions	106 (46.1)	63 (53.8)	85 (48.9)	51 (60.0)	51 (48.6)
Fatigue^a	33 (14.3)	20 (17.1)	33 (19.0)	12 (14.1)	23 (21.9)
Injection site erythema^a	19 (8.3)	9 (7.7)	14 (8.0)	8 (9.4)	8 (7.6)
Injection site pain^a	82 (35.7)	51 (43.6)	72 (41.4)	40 (47.1)	46 (43.8)
Injection site swelling^a	20 (8.7)	10 (8.5)	8 (4.6)	14 (16.5)	11 (10.5)
Hepatobiliary d/o	1 (0.4)	0	1 (0.6)	1 (1.2)	1 (1.0)
Immune system d/o	0	1 (0.9)			
Infections & infestations	11 (4.8)	10 (8.5)	6 (3.4)	5 (5.9)	
Injury, poisoning & procedural complications	4 (1.7)	1 (0.9)	1 (0.6)	0	4 (3.8)
Metabolism & nutrition d/o			0	1 (1.2)	
Musculoskeletal & connective tissue d/o	19 (8.3)	6 (5.1)	18 (10.3)	11 (12.9)	12 (11.4)
Myalgia^a	17 (7.4)	5 (4.3)	17 (9.8)	9 (10.6)	9 (8.6)

Nervous system d/o	18 (7.8)	12 (10.3)	18 (10.3)	11 (12.9)	9 (8.6)
Headache^a	17 (7.4)	11 (9.4)	18 (10.3)	10 (11.8)	9 (8.6)
Psychiatric d/o	1 (0.4)	0	1 (0.6)	0	1 (1.0)
Reproductive system & breast d/o			2 (1.1)	0	
Respiratory, thoracic, mediastinal d/o	3 (1.3)	3 (2.6)	4 (2.3)	2 (2.4)	
Skin & subcutaneous tissue d/o			1 (0.6)	0	
Social circumstances			1 (0.6)	0	
Vascular d/o	0	1 (0.9)	1 (0.6)	0	

*Adapted from Sponsor Table 14.3-11, Table 14.3-12, and Table 14.3-13 (Clinical Study Report P006V116; page 503-510, STN 125814/0).

Reported adverse events include non-serious adverse events within 30 days of vaccination and serious adverse events occurring Day 1 through the duration participation in the study.

^a Injection site erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through 5 post vaccination but may have been reported spontaneously after Day 5. Pyrexia was defined as maximum temperature ≥ 100.4 F (38.0 C) solicited from Day 1 through Day 5 post vaccination but may have been reported spontaneously after Day 5 with or without reported temperature.