

**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Division of Epidemiology (DE)**

**PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

**From:** Phillip Blanc, MD, MPH  
Medical Officer, Analytic Epidemiology Branch (AEB)  
Division of Epidemiology (DE)  
Office of Biostatistics and Epidemiology (OBE)  
CBER, FDA

**To:** Christina Houck  
Chair of the Review Committee

**Through:** Ravi Goud, MD, MPH  
Acting Branch Chief, AEB/DE

Narayan Nair, MD  
Director, DE  
OBE, CBER, FDA

**Subject:** Pharmacovigilance Plan Review

**Sponsor:** Wyeth Pharmaceuticals LLC

**Product:** PREVNAR 20 (20-valent  
Pneumococcal Conjugate Vaccine)

**Application Type/Number:** BLA/STN 125731

**Proposed Indication:** *Active immunization for prevention of pneumonia and invasive disease caused by S pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older.<sup>1</sup>*

**Submission Date:** 10/8/2020

**Action Due Date:** 06/08/2021

---

<sup>1</sup> Italicized text in this memorandum is quoted directly from the source document. An exception to this is text pertaining to Reviewer's Comments.

## 1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) for PREVNAR 20.

## 2 PRODUCT INFORMATION

### 2.1 Product Description

20-valent Pneumococcal Conjugate Vaccine (20vPnC) consists of the currently marketed 13vPnC (PREVNAR 13) capsular polysaccharide antigens of *S pneumoniae* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and seven additional polysaccharide antigens of pneumococcal serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F. All saccharides are individually conjugated to plasmid-derived diphtheria cross-reactive material 197 (CRM197).

### 2.2 Proposed dosing regimen(s) and formulation(s)

20vPnC is a sterile liquid suspension available in a 0.5 mL pre-filled syringe for intramuscular injection as a single dose in adults aged  $\geq 18$  years.

## 3 MATERIALS REVIEWED

The materials reviewed in support of BLA 125731/0 are included in **Table 1**.

**Table 1.** Materials reviewed in support of this assessment (BLA 125731)

Source; Received/ Issued Date	Document Information	Document(s) Reviewed
Sponsor; 03/31/2009	BLA 125324/0.4 Sequence 0004	<a href="#">Module 1.16</a> PREVNAR 13 Risk Management Plan (RMP) (Version 1.0)
Sponsor; 07/22/2014	BLA 125324/1196.0 Sequence 0580	<a href="#">Module 1.16</a> PREVNAR 13 Risk Management Plan (RMP) (Version 5.0)
Sponsor; 08/29/2017	BLA 125324/1670.2 Sequence 1158	<a href="#">Module 1.14.1.3</a> PREVNAR 13 U.S. Package Insert (USPI)

Source; Received/ Issued Date	Document Information	Document(s) Reviewed
Sponsor;  04/30/2020	IND 017039/0.104  Sequence 0105	<a href="#">Module 1.11.3</a> 11/8/2019 Information Request (IR) Response Letter
Sponsor;  09/23/2020	BLA 101094/6617.5008  Sequence 0533	<a href="#">Module 1.14.1.3</a> PNEUMOVAX 23 U.S. Package Insert (USPI)
Sponsor;  10/08/2020	BLA 125731/0.1  Sequence 0002	<a href="#">Module 1.16.1</a> Risk Management Plan (RMP)
		<a href="#">Module 2.7.4</a> Summary of Clinical Safety (SCS)
		<a href="#">Module 5.3.5.3</a> Integrated Summary of Safety (ISS)
		<a href="#">Module 5.3.5.1</a> Phase 3 Clinical Study Report Materials (Trial B7471006 – A Phase 3, Randomized, Open-Label Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine in Adults ≥65 Years of Age with Prior Pneumococcal Vaccination)
		<a href="#">Module 5.3.5.1</a> Phase 3 Clinical Study Report Materials (Trial B7471007 – A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine in Pneumococcal Vaccine-Naïve Adults 18 Years of Age and Older)

Source; Received/ Issued Date	Document Information	Document(s) Reviewed
		<a href="#">Module 5.3.5.1</a> Phase 3 Clinical Study Report Materials (Trial B7471008 – A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of 3 Lots of 20-Valent Pneumococcal Conjugate Vaccine in Pneumococcal Vaccine-Naïve Adults 18 through 49 Years of Age)
Sponsor; 11/13/2020	IND 017039/0.128 Sequence 0129	<a href="#">Module 16.1.9</a> Statistical Analysis Plan (SAP) (Trial B7471004 – A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine (20vPnC) when Co-Administered with Seasonal Inactivated Influenza Vaccine (SIIV) in Adults $\geq 65$ Years of Age)
Sponsor; 01/05/2021	BLA 125731/0.6 Sequence 0007	<a href="#">Module 1.11.13</a> 12/21/2020 Information Request (IR) Response Letter
Sponsor; 01/08/2021	BLA 125731/0.7 Sequence 0008	<a href="#">Module 1.14.1.3</a> U.S. Package Insert (USPI) (Draft)

Source; Received/ Issued Date	Document Information	Document(s) Reviewed
Sponsor;  01/15/2021	BLA 125731/0.8  Sequence 0009	<a href="#">Module 1.17.2</a> Study Protocol (Study B7471015 – A Phase 4 Study Using a Test-Negative Design to Evaluate the Effectiveness of a 20-Valent Pneumococcal Conjugate Vaccine Against Vaccine-Type Radiologically-Confirmed Community-Acquired Pneumonia in Adults ≥65 Years of Age)
Sponsor;  02/05/2021	BLA 125731/0.13  Sequence 0014	<a href="#">Module 1.11.3</a> 1/19/2021 Information Request (IR) Response Letter
		<a href="#">Module 1.11.3</a> PREVNAR 13 Postmarketing Safety Analysis
		<a href="#">Module 5.3.5.4</a> PMC Study Report Materials (Trial B1851138 – A Phase 4, Randomized, Double-Blind Trial to Evaluate the Immunogenicity and Safety of a 13-Valent Pneumococcal Conjugate Vaccine when Administered Concomitantly with Seasonal Inactivated Influenza Vaccine in Adults 50 Years and Older Who Received 1 or More Doses of 23-Valent Pneumococcal Polysaccharide Vaccine Prior to Study Enrollment)

Source; Received/ Issued Date	Document Information	Document(s) Reviewed
		<a href="#">Module 5.3.5.4</a> PMC Study Report Materials (Trial B1851025 [CAPiTA] – A Phase 4, Randomized, Placebo-Controlled Clinical Trial of 13-Valent Pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-Serotype Pneumococcal Community-Acquired Pneumonia and Invasive Pneumococcal Disease)
Sponsor;  05/04/2021	BLA 125731/0.32  Sequence 0035	<a href="#">Module 1.14.1.3</a> U.S. Package Insert (USPI) (Draft)
		<a href="#">Module 1.16.1</a> Risk Management Plan (RMP) (Revised)
FDA;  04/20/2015	BLA 125324/1196	PREVNAR 13 Pharmacovigilance Plan (PVP) Review Memorandum
FDA;  08/02/2016	IND 017039	Intercenter Consult Memorandum (Division of Cardiovascular and Renal Products [DCaRP], CDER)
FDA;  04/24/2017	BLA 125324/1561	PREVNAR 13 Approval Letter
FDA;  09/04/2018	IND 017039/0.33	PREVNAR 20 Adult Clinical Program Type B EOP2 Meeting Presentation Slides
FDA;  02/03/2021	BLA 125731/0	PREVNAR 20 Non-Clinical Cardiac Toxicity Findings Presentation Slides

## 4 SUMMARY OF PRIOR MARKETED EXPERIENCE

PREVNAR 20 is not marketed for use in adults in any region; therefore, no prior marketed experience for PREVNAR 20 exists. However, PREVNAR 13 postmarketing data are available and were submitted by the sponsor in response to an information request (IR) by DE.

As requested, the sponsor analyzed PREVNAR 13 adult (aged  $\geq 18$  years) postmarketing data from 10/2015 to 10/2020. Generally, the sponsor indicated that data in its safety database are derived from multiple sources, including from passive surveillance and studies. During this interval, 9,446 cases from several countries were reported, including 1,777 (18.8%) serious cases. Among the 9,446 cases, 26,234 adverse events (AEs) were reported, mostly belonging to the following System Organ Classes (SOCs): General disorders and administration site conditions (n=12,619 [48.1%]), Injury, poisoning and procedural complications (n=3,617 [13.8%]), and Musculoskeletal and connective tissue disorders (n=2,011 [7.7%]).

Overall, the most commonly reported preferred terms (PTs) included Vaccination site erythema (n=1,869 [19.8%]), Vaccination site pain (n=1,532 [16.2%]), Vaccination site swelling (n=1,380 [14.6%]), Pyrexia (n=1,119 [11.8%]), and Incorrect dose administered (n=1,019 [10.8%]). The most commonly reported AEs from serious non-fatal cases included Pyrexia (n=290 [16.9%]), Drug ineffective (n=255 [14.8%]), Vaccination site erythema (n=221 [12.9%]), Vaccination site pain (n=208 [12.1%]), and Pneumonia (n=204 [11.9%]).

Fifty-eight (58/9446; 0.6%) deaths were reported during the reporting interval. The sponsor categorized death cases into deaths caused by Lack of Efficacy (LOE)<sup>2</sup> (n=11 [19.0%]), Pneumococcal Infections (Not LOE) (n=4 [6.9%]), Other Infections (n=4 [6.9%]), Cardiac Disorders (n=14 [24.1%]), Respiratory Disorders, COPD (n=5 [8.6%]), Other Causes (n=4 [6.9%]), and Unknown (n=16 [27.6%]). Medical history for most decedents (n=44 [75.9%]) included at least one illness and/or medical condition. The sponsor did not identify any new safety concerns.

In addition to providing postmarketing analyses, the sponsor also submitted summaries of two adult postmarketing commitment (PMC) studies for PREVNAR 13 (13vPnC). One of the PMCs was a randomized, placebo-controlled, double-blind Phase 4 trial (CAPiTA [Community-Acquired Pneumonia Immunization Trial in Adults]), assessing the safety and efficacy of PREVNAR 13 (13vPnC) among older adults (aged  $\geq 65$  years) by randomizing 84,496 subjects to either 12vPnC (n=42,240

---

<sup>2</sup> The sponsor differentiated Lack of Efficacy (LOE) deaths from Pneumococcal Infection deaths based on strains protected against or death latency in relation to vaccine administration.

[50.0%]) or placebo (n=42,256 [50.0%]). Another PMC was a Phase 4 randomized, double-blind trial assessing the safety and immunogenicity of PREVNAR 13 (13vPnC) when administered in conjunction with a quadrivalent influenza vaccine (QIV) in adults aged  $\geq 50$  years who had been previously exposed to pneumococcal vaccine. Subjects (n=882 [100.0%]) were randomized to receive either 13vPnC with QIV (followed by placebo approximately one month later) (n=441 [50.0%]) or placebo with QIV (followed by 13vPnC approximately one month later) (n=441 [50.0%]).

In the CAPiTA trial, statistically significant differences in SAE reporting were noted between 13vPnC and control arms in the General disorders and administration site conditions SOC (including the PT Noncardiac chest pain), as well as with the PT Chest pain. Nearly all subjects reporting these PTs had a history of cardiovascular disease or risk factors.

The sponsor considered the safety profile of 13vPnC to be acceptable for each of the PMC's respective study populations when administered independently or concomitantly with QIV.

**Reviewer Comment:** *Generally, AEs reported during the reporting interval were consistent with PREVNAR 13's safety profile. AEs, including causes of death, were generally consistent with those reported in adult PREVNAR 13 clinical trials and are labeled in PREVNAR 13's package insert (USPI). Causes of death in AE reports such as Myocardial infarction, Chronic Obstructive Pulmonary Disease (COPD), and Pneumonia were generally consistent with common causes of death in an older adult population (the mean age of patients with death reports was 72.9 years).*

*Generally, AEs and serious AEs (SAEs) observed in the PREVNAR 13 PMC studies were consistent with PREVNAR 13's safety profile, and comparable to 20vPnC Phase 3 trial AEs and SAEs (e.g., no SAEs were assessed as related to trial vaccine in either Phase 3 20vPnC trials, or in the CAPiTA trial).*

## **5 BRIEF DESCRIPTION OF SAFETY DATABASE**

### **5.1 Preclinical Experience**

During this review, the reviewer was made aware by the clinical review team of a potential cardiac-related concern based on 20vPnC preclinical findings. In preclinical trials, cardiac myocyte inflammation and necrosis were observed in rabbits administered 20vPnC. To investigate if this risk applied to humans, the sponsor had performed cardiac monitoring (e.g., ECG and cardiac biomarker testing) in its first-in-human (FIH) Phase 1 trial for 20vPnC. Trial results did not corroborate the preclinical rabbit cardiac findings in human subjects. To further evaluate any clinically significant 20vPnC-related cardiac risk in humans, the reviewer reviewed data for individual



20vPnC subjects who experienced a cardiac-related SAE. As summarized in **Tables 4 and 5** below, across the three Phase 3 trials, the reporting of a given cardiac-related SAE (e.g., Acute myocardial infarction, Atrial fibrillation, Cardiac failure congestive, etc.) by 20vPnC subjects within six months of vaccination was uncommon (i.e.,  $\leq 0.2\%$  of pneumococcal vaccine naïve subjects in any given study arm and  $\leq 0.6\%$  of subjects aged  $\geq 65$  years in any given study arm reported an SAE within six months of vaccination). A similar proportion of subjects in 20vPnC and control arms reported cardiac-related SAEs (i.e., among vaccine-naïve subjects, the proportion of subjects reporting a cardiac-related SAE within six months of vaccination did not differ by more than 0.1% between 20vPnC and control arms in Phase 3 studies; among subjects aged  $\geq 65$  years, the proportion of subjects reporting a cardiac-related SAE within six months of vaccination did not differ by more than 0.4% between 20vPnC and control arms in Phase 3 studies). Most cases in which a 20vPnC subject reported a cardiac-related SAE included a confounding history of cardiovascular disease and/or at least one risk factor.

**Table 4.** Cardiac-Related Serious Adverse Events Reported Within 6 Months After Vaccination—Pneumococcal Vaccine Naïve Subjects by Study and Age Group – Safety Population\*

	<b>B7471007 <math>\geq 60</math> Years</b>		<b>B7471007 50-59 Years</b>		<b>B7471007 B7471008 18-49 Years</b>	
	20vPnC/ Saline (N <sup>a</sup> =1507)	13vPnC/ PPSV23 (N <sup>a</sup> =1490)	20vPnC (N <sup>a</sup> =334)	13vPnC (N <sup>a</sup> =111)	20vPnC (N <sup>a</sup> =1798)	13vPnC (N <sup>a</sup> =357)
	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)
<b>CARDIAC DISORDERS</b>	<b>5 (0.3)</b>	<b>5 (0.3)</b>	<b>0</b>	<b>0</b>	<b>1 (0.1)</b>	<b>0</b>
Acute myocardial infarction	0	1 (0.1)	0	0	1 (0.1)	0
Atrial fibrillation	1 (0.1)	1 (0.1)	0	0	0	0
Cardiac failure congestive	0	2 (0.1)	0	0	0	0

Coronary artery disease	3 (0.2)	1 (0.1)	0	0	0	0
Myocardial infarction	1 (0.1)	0	0	0	0	0
Silent myocardial infarction	0	1 (0.1)	0	0	0	0

*\*Adapted from Table 11 of the sponsor's Integrated Summary of Safety (ISS) (pg. 42).*

- N = number of subjects in the specified group. This value is the denominator for the percentage calculations.*
- n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any serious adverse event.*

**Table 5.** Cardiac-Related Serious Adverse Events Reported Within 6 Months After Vaccination—Subjects ≥65 Years of Age by Study and Prior Pneumococcal Vaccination Status – Safety Population\*

	<b>B7471007 Naïve</b>		<b>B7471006 Prior PPSV23</b>		<b>B7471006 Prior 13vPnC</b>		<b>B7471006 Prior 13vPnC and PPSV23</b>
	20vPnC/ Saline (N <sup>a</sup> =514)	13vPnC/P PSV23 (N <sup>a</sup> =498)	20vPnC (N <sup>a</sup> =253)	13vPnC (N <sup>a</sup> =122)	20vPnC (N <sup>a</sup> =246)	PPSV23 (N <sup>a</sup> =127)	20vPnC
	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)	n <sup>b</sup> (%)
<b>CARDIAC DISORDERS</b>	<b>4 (0.8)</b>	<b>3 (0.6)</b>	<b>1 (0.4)</b>	0	<b>1 (0.4)</b>	0	0
Acute myocardial infarction	0	0	0	0	1 (0.4)	0	0
Atrial fibrillation	0	1 (0.2)	0	0	0	0	0

Cardiac failure congestive	0	0	1 (0.4)	0	0	0	0
Coronary artery disease	3 (0.6)	1 (0.2)	0	0	0	0	0
Myocardial infarction	1 (0.2)	0	0	0	0	0	0
Silent myocardial infarction	0	1 (0.2)	0	0	0	0	0

*\*Adapted from Table 13 of the sponsor's Integrated Summary of Safety (ISS) (pg. 50).*

- c. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.*
- d. n = Number of subjects reporting at least 1 occurrence of the event specified. For "Any event", n = number of subjects reporting at least 1 occurrence of any serious adverse event*

**Reviewer Comment:** *In addition to the above investigation by the reviewer of individual cases in which a cardiac-related SAE was reported, FDA requested the sponsor to analyze 20vPnC Phase 2 and Phase 3 safety data using cardiac-related SMQs. Neither the reviewer's review of individual subject data, nor the sponsor's cardiac SMQ analyses established a cardiac-related safety concern for 20vPnC administration.*

## 5.2 Clinical Development Program Overview

The 20vPnC clinical development program is comprised of three early stage trials (two Phase 1 and one Phase 2 trial) and three Phase 3 trials, which established the safety and tolerability of 20vPnC in adults  $\geq 18$ -years-old. The sponsor indicated that based on these trials—including the early stage trials—20vPnC was “safe and well tolerated.” Safety analyses in the Summary of Clinical Safety (SCS) focused on the Phase 3 trials.

Two of the Phase 3 trials included pneumococcal vaccine-naïve adults ( $\geq 18$ -years-old in trial B7471007 and ages 18 through 49 in trial B7471008), and one trial (B7471006) included previously vaccinated older adults  $\geq 65$  years of age. In all three Phase 3 trials, 13-valent pneumococcal polysaccharide vaccine (13vPnC) was the main comparator used to evaluate 20vPnC's safety. In one trial (B7471007), a 23-valent pneumococcal polysaccharide vaccine (PPSV23) served as an additional comparator.

The two studies that enrolled pneumococcal vaccine-naïve adults were randomized, double-blinded, and consisted of a pivotal, non-inferiority trial (B7471007) and a lot consistency trial (B7471008). Trial B7471007 included three cohorts, stratified by age groups (18 to 49, 50 to 59, and  $\geq 60$  years of age). As summarized in **Table 2**, each cohort included adults randomized to treatment with either 20vPnC or with active comparators (13vPnC and PPSV23). Subjects 60 years or older (Cohort 1) initially received either 20vPnC or 13vPnC, followed one month later by either saline or PPSV23, respectively. Trial B7471008 included four arms that compared three different 20vPnC lots with 13vPnC.

**Table 2.** Number (%) of Subjects Who Received at Least 1 Study Vaccination in the Phase 3 Studies—Pneumococcal Vaccine Naïve Subjects by Study and Age Group\*

	<b>B7471007</b>			<b>B7471008</b>	<b>B7471007 B7471008</b>	
	Cohort 1	Cohort 2**	Cohort 3**			
	$\geq 60$ Years	50-59 Years	18-49 Years	18-49 Years	18-49 Years	
<b>20vPnC</b> n (%)	20vPnC/ Saline	20vPnC	20vPnC	20vPnC Lot 1, 2, & 3 (Combined)	20vPnC	<b>Total Exposure†</b>
	1507 (41.4)	334 (9.2)	335 (9.2)	1463 (40.2)	1798 (49.4)	<b>3639</b> (100.0)
<b>Control</b> n (%)	13vPnC/PPSV23	13vPnC	13vPnC	13vPnC	13vPnC	--
	1490 (76.1)	111 (5.7)	112 (5.7)	245 (12.5)	357 (18.2)	<b>1958</b> (100.0)
<b>Total</b> n (%)	<b>2997</b> (53.5)	<b>445</b> (8.0)	<b>447</b> (8.0)	<b>1708</b> (30.5)	<b>2155</b> (38.5)	<b>5597</b> (100.0)

\*Adapted from Table 2 of the sponsor's Summary of Clinical Safety (SCS) (pg. 12).

\*\*Subjects who were incorrectly enrolled in Cohort 2 (n=1) and Cohort 3 (n=1) were included in data analyses for Cohorts 2 and 3, respectively.

†Per the sponsor, values in this column are the denominators for percentage (%) calculations.

The third Phase 3 trial (B7471006) was a randomized, open-label trial and included three cohorts, with patients assigned according to previous pneumococcal vaccination status, as summarized in **Table 3**. For Cohorts A and B, subjects were randomized to

treatment with either 20vPnC or active comparators (13vPnC or PPSV23). Cohort C did not include an active comparator.

**Table 3.** Number (%) of Subjects Who Received at Least 1 Study Vaccination in the Phase 3 Studies—Subjects  $\geq 65$  Years of Age by Study and Pneumococcal Vaccination Status\*

	<b>B7471006</b>			<b>B7471007</b>	<b>Total Exposure<sup>†</sup></b>
	Cohort A	Cohort B	Cohort C	Cohort 1	
	Prior PPSV23	Prior 13vPnC	Prior 13vPnC & PPSV23	Naïve	
<b>20vPnC</b> n (%)	20vPnC	20vPnC	20vPnC	20vPnC/ Saline	1138 (100.0)
	253 (22.2)	246 (21.6)	125 (11.0)	514 (45.2)	
<b>Control</b> n (%)	13vPnC	PPSV23	--	13vPnC/ PPSV23	747 (100.0)
	122 (16.3)	127 (17.0)	--	498 (66.7)	
<b>Total</b> n (%)	375 (19.9)	373 (19.8)	125 (6.6)	1012 (53.7)	1885 (100.0)

\*Adapted from Table 3 of the sponsor's Summary of Clinical Safety (SCS) (pg. 12).

<sup>†</sup>Per the sponsor, values in this column are the denominators for percentage (%) calculations.

### 5.3 20vPnC Phase 3 Clinical Trial Safety Data Collection

Subjects comprising the safety population received at least one vaccine dose, and were followed for safety, including reporting of SAEs and newly diagnosed chronic medical conditions (NDCMCs) up to approximately six months after receiving 20vPnC or control vaccines. Across Phase 3 trials, the number of subjects vaccinated with any vaccine (20vPnC or control vaccines) totaled 6,470 subjects. Of these subjects, 5,597 (86.5%) were pneumococcal vaccine-naïve and 873 (13.5%) were previously exposed to pneumococcal vaccine (either 13vPnC, PPSV23, or both). Most of the 6,470 subjects (n=4,263; 65.9%) received 20vPnC; the remaining subjects (n=2,207; 34.1%)

received control vaccines. Of the 6,470 subjects, almost one third (n=1,885; 29.1%) were  $\geq 65$  years of age. Almost half (n=873; 46.3%) of these subjects had been previously exposed to pneumococcal vaccine.

Safety data were collected and analyzed in the same manner across all three Phase 3 trials. Safety data endpoints included specific AEs that subjects could report using an electronic diary (e-diary) that solicited subjects' responses by way of prompts. Solicited AEs included local reactions (i.e., "redness, swelling, and pain at the injection site") occurring within 10 days of vaccination, and systemic events (i.e., "fever, headache, fatigue, muscle pain, and joint pain") occurring within seven days of vaccination. Via e-diary, subjects also reported their use of antipyretics or analgesics within seven days of vaccination.

In addition to data received via e-diary, safety data were collected at three time points: at the vaccination visit, at a follow-up visit approximately one month after the vaccination visit, and during a phone call approximately six months after the vaccination visit. At the one-month follow-up visit, subjects were to report any AEs experienced within one month from their vaccination.<sup>3</sup> At the six-month follow-up phone call, subjects could report serious adverse events (SAEs) and/or newly diagnosed chronic medical conditions (NDCMCs) that they may have experienced within six months of being vaccinated.

No clinically relevant laboratory or other evaluations (e.g., vital signs, physical exam findings, etc.) were systematically collected in the Phase 3 trials; however, when apprised of such information, investigators would report concerning findings as AEs if they were experienced within the appropriate safety data collection time window.

## **5.4 20vPnC Phase 3 Clinical Trial Safety Results**

### **5.4.1 Adverse Events**

#### **5.4.1.1 Pneumococcal Vaccine Naïve Subjects**

Among pneumococcal vaccine naïve subjects, the sponsor detected *no clinically important differences* across study arms in solicited local reactions within 10 days of vaccination. Of these reactions, naïve subjects most frequently reported pain at the injection site (55.4% to 79.2% of 20vPnC subjects). Older naïve subjects tended to report this reaction less frequently than younger subjects (55.4% of 20vPnC

---

<sup>3</sup> For B7471007 Cohort 1 subjects (described in Section 5.1), this reporting applied to AEs noted within one month of receiving the first vaccination (after receiving either 20vPnC or 13vPnC) *and* within one month of receiving the second vaccination (after receiving either saline or PPSV23). Of note, the sponsor's primary safety interests pertained to AEs occurring after the *first* vaccination. AE data herein described reflect these AEs (and not those collected after the *second* vaccination).

subjects  $\geq 60$  years of age compared to 79.2% of 20vPnC subjects 18 to 49 years of age). Generally, local reactions tended to begin in naïve subjects within a median period of two-and-a-half days and tended to last a median period of one to two days.

Among naïve subjects, the sponsor detected *no clinically important differences* across study arms in prompted reporting of systemic events within seven days of vaccination. Of these events, naïve subjects most frequently reported Muscle pain (39.1% to 62.9% of 20vPnC subjects and 37.3% to 64.8% of 13vPnC and 13vPnC/PPSV23 subjects), followed by Fatigue, Headache, Joint pain, and Fever. Older naïve subjects tended to report these reactions less frequently than younger subjects (e.g., Muscle pain was reported by 39.1% of 20vPnC subjects aged 60 years or older, compared to 62.9% of 20vPnC subjects aged 18 to 49 years). Generally, most systemic reactions in naïve subjects tended to begin within a median period of two days and tended to last a median period of one to two days.

Up to one month after subjects' first vaccination<sup>3</sup>, naïve subjects most frequently reported AEs from the Infections and infestations SOC. AEs reported by  $\geq 1\%$  of naïve subjects from at least one vaccine group (i.e., randomized to either 20vPnC or 13vPnC for a given study)<sup>4</sup> were Upper respiratory tract infection (0.8% to 1.2% of 20vPnC subjects and 0.3% to 2.7% of control subjects) and Fall (0.2% to 1.2% of 20vPnC subjects and 0.0% to 0.5% of control subjects). AEs considered related to the study vaccine by the investigator were comparable between study arms ( $\leq 0.9\%$  among 20vPnC subjects compared to  $\leq 1.51\%$  among 13vPnC subjects). Among naïve subjects, injection site-related AEs (e.g., Injection site pain, Injection site pruritis, etc.) accounted for the greatest proportion of related AEs.

#### **5.4.1.2 Subjects $\geq 65$ Years of Age**

Among older ( $\geq 65$  years of age) subjects, the sponsor detected *no clinically important differences* across study arms (20vPnC compared to 13vPnC or PPSV23) in solicited reporting of local reactions within 10 days of vaccination. The sponsor also detected no clinically meaningful differences in local reaction reporting frequency among 20vPnC subjects based on prior vaccination (regardless of which vaccine[s] was/were previously received). Of these reactions, older subjects most frequently reported Pain at the injection site (44% to 61% of 20vPnC subjects and 43% to 56% of control subjects). Generally, local reactions tended to begin within a median period of two-and-a-half days and tended to last for one to two days.

Among older subjects, the sponsor detected *no clinically important differences* across study arms in solicited systemic events within seven days of vaccination.

---

<sup>4</sup> Per the sponsor (in reference to SCS tables including AEs from  $\geq 1\%$  of subjects from at least one vaccine arm): *For B7471007  $\geq 60$  years (Cohort 1), only adverse events reported after Vaccination 1 (20vPnC or 13vPnC) are included.*

The sponsor also detected no clinically meaningful differences in systemic adverse event reporting frequency among 20vPnC subjects based on prior vaccination (regardless of which vaccine[s] was/were previously received). Of these events, older subjects most frequently reported Muscle pain (32.0% to 37.6% of 20vPnC subjects and 31.4% to 46.0% of control subjects), followed by Fatigue, Headache, Joint pain, and Fever. Generally, systemic reactions in older subjects tended to begin within a median period of three-and-a-half days and tended to last a median period of one to two days.

Up to one month after vaccination, older subjects ( $\geq 65$  years of age) most frequently reported AEs from the Infections and infestations SOC. AEs reported by  $\geq 1\%$  of older subjects from at least one vaccine arm were Nasopharyngitis (0.0% to 1.2% of 20vPnC subjects and 0.0% to 0.8% of control subjects), Urinary tract infection (0.0% to 0.8% of 20vPnC subjects and 0.0% to 1.6% of control subjects), and Dizziness (0.0% to 0.8% of 20vPnC subjects and 0.0% to 1.6% of control subjects). AEs considered related to the study vaccine by the investigator were reported by older subjects at comparable rates between study arms ( $\leq 1.6\%$  among 20vPnC subjects compared to  $\leq 2.4\%$  among control subjects). Among older subjects, injection site-related AEs accounted for the greatest proportion of AEs that were considered related by the investigator.

**Reviewer Comment:** *Systemic and local eDiary events (reported within seven and 10 days of vaccination, respectively) did not differ substantially across 20vPnC and control arms and between naive and previously exposed subjects (of whom the latter were all aged  $\geq 65$  years). Median duration of local and systemic events also tended to be similar (one to two days' duration) between local and systemic events, for naive and previously exposed subjects. The reporting rates among naive subjects for some local and systemic events tended to be lower for older subjects.*

*When the reviewer compared 20vPnC data trends to PREVNAR 13 (13vPnC) data, the reviewer observed some similarities and differences between 20vPnC and PREVNAR 13 data. For instance, the most frequently reported local reactions and systemic events described for 20vPnC are consistent with PREVNAR 13's safety profile (i.e., listed in the PREVNAR 13 USPI as AEs reported in PREVNAR 13 adult clinical trials). Though 20vPnC subjects most frequently reported one-month AEs from the Infections and infestations SOC, AEs most frequently reported in the adult 13vPnC postmarketing experience (from October 2015 to October 2020) belonged to the General disorders and administration site conditions SOC. Generally, the most commonly reported AEs in Phase 3 20vPnC clinical trials resembled AEs reported in the aforementioned PREVNAR 13 postmarketing and PMC study data obtained via IR, so no new or different safety concerns were observed for 20vPnC.*



## 5.4.2 Serious Adverse Events (SAEs)

### 5.4.2.1 Pneumococcal Vaccine Naïve Subjects

The proportion of pneumococcal vaccine naïve 20vPnC subjects ( $\leq 2.4\%$ ) who reported at least one SAE within six months of vaccination was similar to the proportion of naïve 13vPnC subjects ( $\leq 1.9\%$ ) who reported at least one SAE during this time frame. Naïve subjects  $\geq 60$  years of age tended to report SAEs more frequently (2.4% after 20vPnC, 1.9% after 13vPnC) than younger subjects ( $\leq 0.9\%$  after either vaccine). No (0.0%) SAEs were considered related to trial vaccine. SAEs that were most frequently reported belonged to the Infections and infestations SOC, such as Appendicitis (n=2 among naïve 20vPnC subjects across all Phase 3 trials) and Cellulitis (n=2 among naïve 20vPnC subjects across all Phase 3 trials).

### 5.4.2.2 Subjects $\geq 65$ Years of Age

Among older subjects (aged  $\geq 65$  years) enrolled across the trials, SAEs within six months of vaccination were reported by a similar proportion of 20vPnC subjects ( $\leq 3.7\%$ ) as control subjects ( $\leq 2.8\%$ ). No (0.0%) SAEs were considered related to trial vaccine. SOC with the most reported SAEs included the Cardiac disorders SOC (such as Coronary artery disease, n=3 across all Phase 3 trials among 20vPnC subjects aged  $\geq 65$  years) and the Nervous system disorders SOC (such as Syncope, n=3 across all Phase 3 trials among 20vPnC subjects aged  $\geq 65$  years).

Overall, the sponsor considered Phase 3 SAEs to be consistent with medical conditions observed in the general adult population.

**Reviewer Comment:** Based on data presented in the sponsor's Integrated Summary of Safety (ISS), the reviewer agrees with the sponsor that the proportions of subjects reporting SAEs within six months of vaccination were similar among 20vPnC and 13vPnC subjects. In both 20vPnC and 13vPnC arms, the reporting of a given SAE (e.g., Cerebrovascular accident, Gastritis, Staphylococcal bacteraemia, etc.) by naïve and older (aged  $\geq 65$  years) subjects within six months of vaccination was also uncommon (i.e., generally less than 0.5% of naïve subjects in any given study arm and generally less than 1.0% of older subjects in any given study arm reported an SAE within six months of vaccination). The reviewer also agrees with the sponsor that SAEs reflected conditions expected in the general adult population, such as Gastroesophageal reflux disease, Migraine, and Nephrolithiasis.

## 5.4.3 Deaths

Among the Phase 3 trials, one death occurred in trial B7471007: A 60-year-old male subject received Vaccine 1 (20vPnC) on 03-May-2019 (Day 1) and Vaccine 2

(saline) on 04-Jun-2019 (Day 33) and died by a self-inflicted gunshot wound on (b) (6). The subject's past medical history included depression and multiple suicide attempts. Per the sponsor, the completed suicide was not considered related by the investigator to trial product or procedure.

**Reviewer Comment:** *Across the three Phase 3 trials, death rarely occurred (1/4,263 [0.02%]) among subjects receiving 20vPnC. In agreement with the investigator's assessment, the reviewer considers the death as more likely related to the subject's history of depression and suicide attempts than to 20vPnC administration.*

#### 5.4.4 Subject Disposition

Across the Phase 3 trials, AEs led to withdrawals only in trial B7471007 (Cohort 1). Such withdrawals occurred comparably in the 20vPnC arm (11 subjects; 0.7%) and the 13vPnC arm (8 subjects; 0.5%).

**Reviewer Comment:** *Among pneumococcal vaccine naïve subjects, AEs and death (in one subject) led to withdrawal from the trial in 0.8% of 20vPnC subjects aged  $\geq 60$  years and accounted for 12.5% (12/96) of all withdrawals among subjects administered 20vPnC in this age group. No withdrawals occurred due to an AE or death in any other age group (18-49 and 50-59).*

*These trends were similar for subjects aged  $\geq 65$  years: AEs led to withdrawals from the trial in 1.0% of naïve subjects aged  $\geq 65$  years who received 20vPnC and accounted for 15.2% (5/33) of all withdrawals among subjects administered 20vPnC in this age group. No withdrawals occurred due to an AE among subjects previously exposed to 13vPnC, PPSV23, or both 13vPnC and PPSV23. Withdrawals did not raise significant safety concerns.*

#### 5.4.5 20vPnC Adverse Drug Reactions (ADRs)

The sponsor performed a review to determine which 20vPnC trial AEs should be considered adverse drug reactions (ADRs) for 20vPnC. The sponsor reviewed 20vPnC Phase 3 trial safety data (e.g., local and systemic events collected in e-diaries) and determined which AEs should be considered ADRs based on the AEs' frequency and biological plausibility. Ultimately, the list of 20vPnC ADRs resulted in ADRs that were all previously established as ADRs for 13vPnC, without any additional ADRs added for 20vPnC (conversely, some ADRs that were established for 13vPnC were not reported for 20vPnC). Except for three ADRs (spontaneously reported post-market)—Angioedema, Vaccination-site pruritus, and Vaccination-site urticaria—none of the ADRs determined for 20vPnC were reported more frequently in a 20vPnC trial arm than any of the 13vPnC adult trials.

**Reviewer Comment:** Per the sponsor's SCS, it appears that three ADRs noted among subjects in a given 20vPnC group (Angioedema, Vaccination-site pruritus, and Vaccination-site urticaria) did not appear in adult PREVNAR 13 clinical trials (instead, these were reported in PREVNAR 13 postmarketing data and are identified as AEs within the label). The absence of any new ADRs from 20vPnC trial data compared to 13vPnC trial data suggests a similar safety profile for 20vPnC as 13vPnC, with no clinically apparent safety risks imposed by the seven additional serotype saccharides in 20vPnC, compared to 13vPnC.

## 6 SPONSOR'S PHARMACOVIGILANCE PLAN (PVP)

A summary of the sponsor's Pharmacovigilance Plan (PVP) is provided in **Table 6**.

**Table 6.** Safety Concerns and Planned Actions for PREVNAR 20\*

Safety Concern	Planned Actions
<b>Important Identified Risks</b>	
None	N/A
<b>Important Potential Risks</b>	
None	N/A
<b>Missing Information</b>	
Effectiveness of 20vPnC	Phase 4 Confirmatory Study Routine Pharmacovigilance (PV)

\*Adapted from Table 2 of the sponsor's Risk Management (Non-REMS) document (pg. 3).

## 7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN (PVP)

### 7.1 Important Identified Risks: None

**Reviewer Comment:** After review of the PMC data and postmarketing analyses, PREVNAR 13's safety profile appeared similar to that of 20vPnC. As such, the

reviewer is agreeable to accepting the sponsor's lack of identifying any risks in its PVP.

## **7.2 Important Potential Risks: None**

**Reviewer Comment:** After review of the PMC data and postmarketing analyses, PREVNAR 13's safety profile appeared similar to that of 20vPnC. As such, the reviewer is agreeable to accepting the sponsor's lack of identifying any risks in its PVP.

## **7.3 Missing Information: Effectiveness of 20vPnC**

The sponsor identified 20vPnC's effectiveness as Missing Information. The sponsor indicates that 20vPnC's effectiveness may be inferred according to similar responses in immunity demonstrated among older pivotal trial subjects (aged  $\geq 60$  years) by licensed products that share the same serotypes (PREVNAR 13 and 23-valent pneumococcal polysaccharide vaccine). To formally address 20vPnC's effectiveness as Missing Information, the sponsor plans to conduct a Phase 4 observational study, which would assess the effectiveness of 20vPnC against radiologically-confirmed community-acquired pneumonia caused by the seven additional serotypes covered by 20vPnC (in addition to 15C) among adults aged  $\geq 65$  years.

**Reviewer Comment:** As 20vPnC vaccine's effectiveness has not been assessed, but will be examined through a postmarketing study, the reviewer is agreeable to accepting this as missing information.

## **8 CONCLUSION**

The sponsor does not acknowledge any Important Identified or Important Potential Risks in association with 20vPnC and this is acceptable as the safety profile of 13vPnC is well established, and the trial data for 20vPnC demonstrate a similar profile. The only Missing Information that the sponsor acknowledges is the effectiveness of 20vPnC. In general, the sponsor recommends routine pharmacovigilance (PV) as sufficient for monitoring 20vPnC's safety profile. Review of 20vPnC Phase 3 clinical trial data did not reveal any significant safety issues. The sponsor's PVP is acceptable.

## **9 DE RECOMMENDATIONS**

Should 20vPnC be approved, the proposed PVP is adequate to monitor postmarketing safety with routine PV in accordance with 21 CFR 600.80. The available safety data does not substantiate a need for a Risk Evaluation and

Mitigation Strategy (REMS) or a safety-related postmarketing requirement or commitment (PMR/PMC) study. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon label language.