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Division / Office	DVRPA/OVRR
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Priority Review	Yes
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Applicant	Pfizer Inc.
Established Name	20-valent Pneumococcal Conjugate Vaccine
(Proposed) Trade Name	Prevnar20
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	2.2 µg of each of 20 saccharides, except for 4.4 µg of 6B, (b) (4) succinate buffer, (b) (4) sodium chloride, (b) (4) polysorbate 80, and 0.125 mg aluminum as aluminum phosphate
Dosage Form(s) and Route(s) of Administration	0.5 mL suspension for intramuscular injection, supplied in a single-dose pre-filled syringe
Dosing Regimen	single dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of pneumonia and invasive disease caused by Streptococcus 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

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## 1. Executive Summary

### 1.1 Introduction

Pfizer, the applicant, submitted the rolling original Biologics License Application (BLA) STN 125731/0 for the 20-valent Pneumococcal Conjugate Vaccine (20vPnC); the final module of the application was submitted on October 8, 2020. The proposed indication for the vaccine is for the prevention of pneumonia and invasive disease caused by *Streptococcus 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. Within this proposed indication, the applicant is seeking accelerated approval for the indication of the prevention of pneumonia caused by *Streptococcus pneumoniae* serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F.

20vPnC is a sterile liquid suspension for intramuscular injection, developed to expand protection against the global burden of vaccine-preventable disease caused by *Streptococcus pneumoniae* over that of currently marketed Prevnar 13 (13vPnC). 20vPnC contains the same 13 serotype-specific capsular polysaccharide antigens included in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), plus 7 additional serotype-specific capsular polysaccharides (8, 10A, 11A, 12F, 15B, 22F, and 33F). The 7 additional serotypes not covered by 13vPnC are included in the currently marketed unconjugated polysaccharide vaccine, Pneumovax 23 (PPSV23; Merck Sharp & Dohme Corp).

A randomized placebo-controlled efficacy trial (with clinical endpoints) of 20vPnC is not feasible due to sample size and ethical considerations in settings where 13vPnC is licensed and recommended. Therefore, it was agreed that licensure for the proposed indication could be granted based on demonstration of an adequate safety profile of the vaccine, as well as by establishing an immunobridge between 20vPnC and 13vPnC for the 13vPnC serotypes (the “13 matched” serotypes) and between 20vPnC and PPSV23 for the 7 additional serotypes. As in the 13vPnC development program, opsonophagocytic activity (OPA) assays would be used to assess immune response.

It was agreed between the applicant and the FDA that an indication for IPD and pneumonia for the 13 matched serotypes would be supported if the immunological success criteria for these serotypes were met (with a totality of data approach), since it would establish a bridge between 20vPnC and 13vPnC, which is approved and effective for prevention of IPD and pneumonia in adults.

It was also agreed that an indication for IPD would be supported for the 7 additional serotypes if the immunological success criteria for these serotypes were met (with a totality of data approach), as it would establish a bridge between 20vPnC and PPSV23, which has been shown to be effective against IPD. However, PPSV23 has not been demonstrated to be effective in the prevention of nonbacteremic pneumococcal pneumonia. FDA agreed that OPA assay data for the 7 additional serotypes may be used as the basis to support the accelerated approval for a pneumonia indication in adults for these serotypes. A well-designed real-world observational effectiveness study with pre-

specified endpoints measuring protection against pneumonia caused by the 7 additional serotypes would be required to confirm the clinical benefit as a confirmatory study after licensure.

## 1.2 Brief Overview of BLA Submission

The 20vPnC clinical development program comprised six completed trials: three Phase 1 and 2 and three Phase 3 safety and immunogenicity trials (Table 1).

## 1.3 Summary Results

In the pivotal trial B7471007, the primary objective was to assess noninferiority of immune responses elicited by 20vPnC to those elicited by 13vPnC for each of the 13 matched serotypes and by PPSV23 for each of the 7 additional serotypes, in subjects  $\geq 60$  years of age (Cohort 1). 20vPnC met the primary immunogenicity objective for the 13 matched vaccine serotypes. One month after 20vPnC or 13vPnC, the immune responses to all 13 matched serotypes induced by 20vPnC were noninferior (NI) to those induced by 13vPnC, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA geometric ratios (GMRs) (20vPnC/saline relative to 13vPnC/PPSV23 group)  $>0.5$ . The observed OPA GMRs for the 13 matched serotypes were between 0.76 and 1.00. 20vPnC met the primary immunogenicity objective for 6 of the 7 additional serotypes. One month after 20vPnC or PPSV23, the immune responses to 6 of the 7 additional vaccine serotypes induced by 20vPnC were noninferior to those induced by PPSV23, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (20vPnC/saline relative to 13vPnC/PPSV23 group)  $>0.5$ . Although superiority of 20vPnC to PPSV 23 couldn't be formally evaluated due to a missed NI for serotype 8 as per the statistical analysis plan, the lower bounds of the 2-sided 95% CIs for the GMRs were  $>1$ , with nominal p values for superiority  $<0.001$  for the 6 serotypes. For serotype 8, the model-based GMR (2-sided 95% CI) was 0.55 (0.49, 0.62), narrowly missing the statistical noninferiority criterion. Based on additional analyses that further characterize the immune responses to serotype 8, the immune response is expected to provide protection similar to the other 13vPnC serotypes that met noninferiority:

- A geometric mean fold rise (GMFR) of 22.1 was observed for serotype 8 from before to 1 month after 20vPnC, which is within the range of the observed GMFRs (5.8 for serotype 3 to 42.6 for serotype 6A) for the 13 matched serotypes from before to 1 month after 13vPnC.
- After 20vPnC, 77.8% of subjects achieved a  $\geq 4$ -fold rise in OPA titers from before to 1 month after vaccination for serotype 8, which is within the range of proportions observed (54.0% for serotype 14 to 84.0% for serotype 6A) for the 13 matched serotypes after 13vPnC.
- After 20vPnC, 93% of subjects had OPA titers  $\geq$  LLOQ for serotype 8, which is within the range of proportions observed (76.0% for serotype 5 to 96.6% for serotype 19A) for the 13 matched serotypes after 13vPnC.

In Study B7471007, 20vPnC met the secondary immunogenicity objective for all 20 vaccine serotypes based on comparison of the immune responses in subjects 50 through 59 years of age (Cohort 2) to those in subjects 60 through 64 years of age in Cohort 1,

and comparison of the immune responses in subjects 18 through 49 years of age (Cohort 3) to those in subjects 60 through 64 years of age in Cohort 1.

In Study B7471008, lot consistency was demonstrated based on a 2-fold equivalence margin comparing the OPA geometric mean titers (GMTs) between each pair of 20vPnC lots for each serotype. The 2-sided 95% CIs for the model-based estimate of serotype-specific OPA GMRs 1 month after vaccination for each pair of lot comparisons (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) are contained in the pre-specified interval (0.5, 2.0) for each of the 20 serotypes.

The three Phase 3 trial safety assessments demonstrated that 20vPnC appears to have a similar safety profile to 13vPnC in pneumococcal vaccine naïve adults  $\geq 18$  years of age and in adults  $\geq 65$  years of age who have previously been vaccinated with 13vPnC only, PPSV23 only, or 13vPnC followed by PPSV23, as measured by the percentage of subjects reporting local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), and newly diagnosed chronic medical conditions (NDCMCs). I defer to the clinical reviewers on the acceptability of the safety profile of 20vPnC.

#### 1.4 Major Statistical Issues and Conclusions

There were no major statistical issues identified.

#### 1.5 Conclusion/Recommendation

The pre-specified success criteria were met for all primary immunogenicity comparisons except for the narrowly missed non-inferiority comparison of the serotype 8 immune responses between 20vPnC and 13vPnC in the pivotal study B7471007. There were no potential safety concerns identified in the studied population. Overall, from the statistical perspective, the submitted clinical study results support the approval of this application.

## 2. CLINICAL AND REGULATORY BACKGROUND

On September 29, 2017, FDA designated the 20vPnC development program for immunization of adults  $\geq 18$  years of age for the prevention of invasive disease and pneumonia caused by vaccine serotypes as a Fast Track Development Program.

On September 10, 2018, FDA determined that the 20vPnC development program for immunization of adults  $\geq 18$  years of age for the prevention of invasive disease and pneumonia caused by vaccine serotypes met the criteria for Breakthrough Therapy Designation.

On September 18, 2018 during the Type B/End of Phase 2 meeting, FDA accepted the proposed 2-fold noninferiority success criterion to support an IPD indication for the 20 vaccine serotypes and a pneumonia indication for the 13 matched serotypes. If the pre-specified statistical noninferiority criteria were not met for each of the 20 serotypes, the Agency would take into consideration the totality of immunogenicity data. FDA agreed to review a proposal for the use of the accelerated approval regulation using OPA as a surrogate to support a pneumonia indication for the 7 additional 20vPnC serotypes. FDA requested that enrollment in B7471007 be expanded for adults  $\geq 65$  years of age, with

both B7471006 and B7471007 to include minimum targets for enrollment for subjects 65-69, 70-79, and  $\geq 80$  years of age. FDA also agreed that results from a study evaluating the safety and immunogenicity of 20vPnC when administered concomitantly with seasonal inactivated influenza vaccine (b) (4)

On November 08, 2019, FDA agreed in principle that an indication for the prevention of pneumonia caused by the 7 additional serotypes could be supported by immune responses as measured by OPA assay under an accelerated approval pathway. Continued approval for this indication would be contingent upon verification and description of clinical benefit in a confirmatory post authorization commitment, real-world observational effectiveness study.

On December 3, 2020, FDA granted priority review designation for the BLA and the action due date (ADD) is June 8, 2021.

### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

#### 3.1 Submission Quality and Completeness

The quality of the submission was sufficient for a statistical evaluation.

#### 3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues in the pivotal studies were identified.

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

Deferred to reviewers from other disciplines.

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

#### 5.1 Review Strategy

The statistical review of this BLA comprises two parts: clinical (immunogenicity and safety) data and non-clinical data. This review focus on the clinical data.

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

The following submissions were reviewed:

- 125731/0.1 Module 2.5 Clinical Overview
- 125731/0.1 Module 2.7 Clinical Summary
- 125731/0.1 Module 5 Clinical Study Reports
- 125731/0.11 Module 1.11.3 Clinical Information Amendment

#### 5.3 Table of Studies/Clinical Trials

Table 1 provides an overview of the clinical trials providing immunogenicity/safety data for this application.

**Table 1. Overview of All Trials**

Protocol No. (Country)	Study Design and Primary Objectives	Subject Age/Prior Pneumococcal Vaccination Status	No. of Subjects (by Treatment Group)	Study Start/Status
B7471001 (USA)	Phase 1, first-in-human, randomized, controlled, observer-blinded study with a 2-arm parallel design  <b>Primary Objective:</b> To describe the safety profile of 20vPnC in adults	18-49 yrs of age/ Pneumococcal vaccine naïve	20vPnC: Randomized: 33  Tdap (control): Randomized: 33	03Nov2016/ Completed 01Aug2017
B7471005 (USA)	Phase 1b, randomized, controlled, double-blind study with a 3-arm parallel design, in adults of Japanese descent  <b>Primary Objective:</b> To describe the safety profile of 20vPnC and c7vPnC in the study population	18-49 yrs of age/ Pneumococcal vaccine naïve	20vPnC: Randomized: 35  c7vPnC: Randomized: 34  13vPnC (control): Randomized: 35	29Aug2018/ Completed 29Mar2019
B7471002 (USA)	Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design  <b>Primary Objective:</b> To describe the safety profile of 20vPnC in the study population	60-64 yrs of age/ Pneumococcal vaccine naïve	20vPnC/Saline: Randomized: 222  13vPnC/PPSV23 (control): Randomized: 222	10Oct2017/ Completed 10Dec2018
B7471006 (USA and Sweden)	Phase 3, multicenter, randomized, open-label study with a 3-cohort design based on prior pneumococcal vaccination status  <b>Primary Objectives:</b> To describe the safety profile of 20vPnC  To describe the immune responses to 20vPnC in adults previously vaccinated with PPSV23, previously vaccinated with 13vPnC, or previously vaccinated with both 13vPnC and PPSV23	≥65 yrs of age  Cohort A: vaccinated with PPSV23 ≥1 year and ≤5 yrs prior to vaccination in the study, and no prior 13vPnC vaccination  Cohort B: vaccinated with 13vPnC ≥6 months prior to vaccination in the study, and no prior PPSV23 vaccination  Cohort C: vaccinated with 13vPnC followed by PPSV23 (PPSV23 vaccination ≥1 year prior to vaccination in the study)	Cohort A 20vPnC: Randomized: 253 13vPnC: Randomized: 122  Cohort B 20vPnC: Randomized: 248 PPSV23: Randomized: 127  Cohort C 20vPnC: Randomized: 125	12Feb2019/ Completed 12Feb2020



**Table 1. Overview of All Trials (Continued)**

Protocol No. (Country)	Study Design and Primary Objectives	Subject Age/Prior Pneumococcal Vaccination Status	No. of Subjects (by Treatment Group)	Study Start/Status
B7471007 (USA and Sweden)	<p>Phase 3, multicenter, randomized, double-blind study with an age-based 3-cohort design</p> <p><b>Primary Objectives:</b> To describe the safety profile of 20vPnC in adults 18 yrs of age and Older</p> <p>To demonstrate that the immune responses to the 13 serotypes in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 20vPnC in adults 60 yrs of age and older are noninferior to the immune response induced by 13vPnC</p> <p>To demonstrate that the immune responses to the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by 20vPnC in adults 60 yrs of age and older are noninferior to the immune response induced by PPSV23</p>	≥18 yrs of age/ Pneumococcal vaccine naïve	<p>Cohort 1 20vPnC/Saline: Randomized: 1514 13vPnC/PPSV23: Randomized: 1495</p> <p>Cohort 2 20vPnC: Randomized: 334 13vPnC: Randomized: 111</p> <p>Cohort 3 20vPnC: Randomized: 336 13vPnC: Randomized: 112</p>	12Dec2018/ Completed 16Dec2019
B7471008 (USA)	<p>Phase 3, multicenter, randomized, double-blind, lot consistency study with a 4-arm parallel design</p> <p><b>Primary Objectives:</b> To describe the safety profile of 20vPnC</p> <p>To demonstrate that the immune responses to the 20 serotypes induced by 20vPnC were equivalent across 3 lots</p>	18-49 yrs of age/ Pneumococcal vaccine naïve	<p>20vPnC Lot 1: Randomized: 489</p> <p>20vPnC Lot 2: Randomized: 490</p> <p>20vPnC Lot 3: Randomized: 486</p> <p>13vPnC: Randomized: 245</p>	14Feb2019/ Completed 09Oct2019

Source: Adapted from the table in Module 5.2 Tabular listing submitted to BLA 125731/0.1.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1: 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

### *6.1.1 Objectives*

#### Primary Objectives:

- To describe the safety profile of 20vPnC.
- To describe the immune responses to 20vPnC in adults previously vaccinated with PPSV23, previously vaccinated with 13vPnC, or previously vaccinated with both 13vPnC and PPSV23.

### *6.1.2 Design Overview*

This was a Phase 3, multicenter, randomized, open-label study conducted at investigator sites in the United States and Sweden. Approximately 875 adults  $\geq 65$  years of age were targeted to be enrolled into 3 different cohorts based on their prior pneumococcal vaccination history. Participants in Cohort A were enrolled at both US and Swedish sites, while participants in Cohorts B and C were enrolled only at US sites.

Cohort A: Approximately 375 participants who had received PPSV23  $\geq 1$  to  $\leq 5$  years previously but had not been vaccinated with 13vPnC were to be randomized (2:1) to receive either 20vPnC or 13vPnC.

Cohort B: Approximately 375 participants who had received 13vPnC  $\geq 6$  months previously, but had not been vaccinated with PPSV23, were to be randomized (2:1) to receive either 20vPnC or PPSV23.

Cohort C: Approximately 125 participants who had previously received 13vPnC followed by PPSV23 (PPSV23 vaccination must have been given  $\geq 1$  year prior to vaccination in this study) were to receive 20vPnC.

### *6.1.3 Population*

Adults  $\geq 65$  years of age who have been previously vaccinated with various pneumococcal vaccines (PPSV23, 13vPnC, or both 13vPnC and PPSV23).

### *6.1.4 Study Treatments or Agents Mandated by the Protocol*

One 0.5-mL dose of 20vPnC, 13vPnC, or PPSV23 was administered intramuscularly in the deltoid muscle of the nondominant arm at Visit 1 based on cohort and randomization.

### *6.1.5 Directions for Use*

Please refer to clinical reviewer's memo.

### *6.1.6 Sites and Centers*

Thirty-three sites in the United States and 8 sites in Sweden.

### *6.1.7 Surveillance/Monitoring*

Please refer to clinical reviewer's memo.

### *6.1.8 Endpoints and Criteria for Study Success*

#### Primary Safety Endpoints:

- Reported prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination
- Reported prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination
- Reported AEs within 1 month after vaccination
- Reported SAEs and newly diagnosed chronic medical conditions (NDCMCs) within 6 months after vaccination

#### Primary Immunogenicity Endpoint:

- Pneumococcal serotype-specific OPA titers 1 month after vaccination

### *6.1.9 Statistical Considerations & Statistical Analysis Plan*

The study size in each cohort was not based on any formal hypothesis test for a safety or immunogenicity endpoint. All statistical analyses of safety and immunogenicity were to be descriptive.

### *6.1.10 Study Population and Disposition*

#### *6.1.10.1 Populations Enrolled/Analyzed*

As planned, the study enrolled 375, 375, and 125 subjects in Cohorts A through C, respectively. Among all participants randomized to the 20vPnC groups, 247 (97.6%) participants in Cohort A (prior PPSV23 only), 243 (98.0%) participants in Cohort B (prior 13vPnC only) and 121 (96.8%) participants in Cohort C (prior 13vPnC and PPSV23) were included in the evaluable immunogenicity population.

The median age of participants at vaccination ranged from 68.0 to 69.0 years across the vaccine groups. Cohort B enrolled the highest percentages of participants 80 years of age and older (9.8% for 20vPnC and 9.4% for PPSV23), while Cohort A had the lowest percentages (2.0% for 20vPnC and 1.6% for 13vPnC). In Cohort A, 35.5% of the participants were enrolled in Sweden. The majority of participants in any vaccine group ( $\geq 90.2\%$ ) were white and there was a slight predominance of females (52.5% to 55.3% across groups).

### *6.1.11 Efficacy and Immunogenicity Analyses*

#### *6.1.11.1 Analyses of Primary Endpoints*

Immune responses to all 20 vaccine serotypes were observed 1 month after 20vPnC based on OPA GMTs in all 3 cohorts (Table 2).

At baseline, OPA GMTs for the 13vPnC serotypes were generally highest in Cohort C (prior 13vPnC and PPSV23), ranging from 20.5 (serotype 3) to 352.4 (serotype 9V), followed by Cohort B (prior 13vPnC only), ranging from 15.4 (serotype 3) to 339.2

(serotype 9V). Baseline GMTs were lowest in Cohort A (prior PPSV23 only), ranging from 12.8 (serotype 3) to 212.1 (serotype 14).

At baseline, OPA GMTs for the 7 additional serotypes were generally highest in participants with prior 13vPnC and PPSV23, ranging from 138.8 (serotype 8) to 1352.8 (serotype 33F), followed by participants with prior PPSV23 only, ranging from 55.4 (serotype 8) to 1128.8 (serotype 33F). Baseline GMTs were lowest in participants with prior 13vPnC only, ranging from 27.9 (serotype 8) to 605.8 (serotype 33F).

At 1 month after 20vPnC, OPA GMTs for most of the 20 vaccine serotypes tended to be highest in participants with prior 13vPnC only, ranging from 54.3 (serotype 3) to 4156.5 (serotype 22F) and lowest in participants with prior PPSV23 only, ranging from 31.1 (serotype 3) to 2026.2 (serotype 33F). OPA GMTs in participants with prior 13vPnC and PPSV23 generally fell in between, ranging from 39.3 (serotype 3) to 2717.8 (serotype 22F).

#### *6.1.11.2 Analyses of Secondary Endpoints*

- Pneumococcal OPA geometric mean fold rises (GMFRs) from before to 1 month after vaccination

Increases in OPA titers for all 20 vaccine serotypes were observed based on OPA GMFRs from before to 1 month after 20vPnC in all 3 cohorts. For the 13vPnC serotypes, the GMFRs appeared to be generally highest in Cohort B (prior 13vPnC only), ranging from 2.3 (serotypes 5 and 14) to 9.3 (serotype 23F), followed by Cohort A (prior PPSV23 only), ranging from 1.8 (serotype 14) to 12.6 (serotype 6A) and lowest in Cohort C (prior 13vPnC and PPSV23), ranging from 1.6 (serotype 7F) to 6.5 (serotype 6A). As PPSV23 does not contain the polysaccharide for serotype 6A, participants previously vaccinated with PPSV23 only were naïve to vaccination for that serotype.

For the 7 additional serotypes, GMFRs were higher in participants with prior 13vPnC only, who were naïve to these vaccine serotypes prior to receiving 20vPnC, ranging from 5.4 (serotype 33F) to 66.9 (serotype 22F), than in participants with prior PPSV23 only, ranging from 1.8 (serotype 33F) to 11.1 (serotype 22F), and in participants with prior 13vPnC and PPSV23, ranging from 1.8 (serotype 33F) to 9.8 (serotype 22F).

- Proportion of participants achieving a  $\geq 4$ -fold rise in pneumococcal OPA titers from before to 1 month after vaccination

For most of the 13vPnC serotypes, the proportions of participants who achieved a  $\geq 4$ -fold rise in OPA titers from before to 1 month after 20vPnC were generally numerically highest in Cohort B (prior 13vPnC only), ranging from 24.9% (serotype 14) to 58.7% (serotype 23F), followed by Cohort A (prior PPSV23 only), ranging from 15.7% (serotype 14) to 61.5% (serotype 6A). The proportions of participants who achieved a  $\geq 4$ -fold rise in OPA titers from before to 1 month after 20vPnC were lowest in Cohort C (prior 13vPnC and PPSV23), ranging from 14.3% (serotype 7F) to 44.9% (serotype 6A).

**Table 2. Pneumococcal OPA GMTs – Evaluable Immunogenicity Population**

Sero type	Sampling Time Point	A	A	A	B	B	B	C	C	C
		n	GMT	(95% CI)	n	GMT	(95% CI)	n	GMT	(95% CI)
<b>1</b>	Before vaccination	246	23.7	(19.9, 28.2)	243	33.5	(27.6, 40.7)	121	42.2	(31.9, 55.8)
	1 Month after vaccination	246	50.8	(41.6, 62.0)	243	115.3	(96.3, 137.9)	120	82.1	(61.2, 110.1)
<b>3</b>	Before vaccination	247	12.8	(11.2, 14.6)	241	15.4	(13.4, 17.7)	121	20.5	(16.8, 25.0)
	1 Month after vaccination	243	31.1	(26.7, 36.1)	242	54.3	(46.9, 62.8)	119	39.3	(32.0, 48.2)
<b>4</b>	Before vaccination	242	28.5	(23.3, 34.9)	235	66.6	(52.5, 84.3)	120	73.1	(53.1, 100.7)
	1 Month after vaccination	236	149.9	(118.2, 190.1)	241	334.9	(273.8, 409.5)	116	193.7	(143.2, 262.0)
<b>5</b>	Before vaccination	244	27.3	(23.8, 31.3)	243	37.8	(32.2, 44.4)	121	46.6	(36.9, 58.9)
	1 Month after vaccination	244	62.8	(52.7, 74.9)	243	87.3	(73.2, 104.2)	120	83.5	(64.8, 107.6)
<b>6A</b>	Before vaccination	244	56.6	(45.8, 69.9)	236	125.1	(98.8, 158.3)	118	161.0	(115.7, 224.1)
	1 Month after vaccination	242	748.7	(576.7, 972.0)	241	1080.9	(880.2, 1327.4)	121	1085.3	(796.9, 1478.1)
<b>6B</b>	Before vaccination	242	107.0	(86.3, 132.6)	240	173.9	(137.9, 219.4)	119	258.9	(190.7, 351.6)
	1 Month after vaccination	243	727.3	(573.6, 922.1)	241	1159.4	(950.7, 1413.8)	121	1033.3	(754.6, 1414.8)
<b>7F</b>	Before vaccination	240	155.7	(132.1, 183.7)	241	209.9	(175.3, 251.2)	120	205.8	(163.9, 258.5)
	1 Month after vaccination	240	378.1	(316.4, 451.9)	243	555.4	(466.8, 660.9)	120	345.8	(277.0, 431.7)
<b>9V</b>	Before vaccination	231	203.0	(171.0, 241.0)	234	339.2	(281.8, 408.2)	118	352.4	(270.2, 459.4)
	1 Month after vaccination	241	550.3	(454.0, 666.9)	237	1085.0	(893.5, 1317.5)	117	723.4	(558.1, 937.6)
<b>14</b>	Before vaccination	242	212.1	(166.4, 270.3)	238	282.2	(223.7, 355.9)	121	335.5	(237.9, 473.1)
	1 Month after vaccination	240	391.2	(314.6, 486.3)	242	664.9	(554.1, 797.9)	119	580.5	(433.7, 777.0)
<b>18C</b>	Before vaccination	247	172.8	(137.3, 217.5)	242	219.3	(176.8, 272.0)	120	277.8	(209.1, 369.2)
	1 Month after vaccination	245	551.9	(445.1, 684.4)	240	845.9	(692.5, 1033.1)	120	621.2	(469.9, 821.3)
<b>19A</b>	Before vaccination	244	81.6	(66.4, 100.3)	240	123.6	(100.0, 152.8)	118	182.1	(140.9, 235.4)
	1 Month after vaccination	242	238.6	(197.5, 288.4)	242	365.1	(303.0, 440.0)	120	340.6	(264.1, 439.2)
<b>19F</b>	Before vaccination	246	60.9	(51.9, 71.3)	242	88.9	(74.0, 106.8)	121	120.2	(93.7, 154.2)
	1 Month after vaccination	244	159.0	(131.4, 192.3)	242	242.3	(199.4, 294.3)	118	217.7	(168.1, 281.8)
<b>23F</b>	Before vaccination	244	22.8	(18.3, 28.3)	242	47.9	(37.2, 61.8)	120	65.9	(46.1, 94.1)
	1 Month after vaccination	245	151.6	(115.3, 199.3)	243	450.2	(357.8, 566.4)	120	292.6	(203.6, 420.5)

**Table 2. Pneumococcal OPA GMTs – Evaluable Immunogenicity Population (Continued)**

Sero type	Sampling Time Point	A	A	A	B	B	B	C	C	C
		n	GMT	(95% CI)	n	GMT	(95% CI)	n	GMT	(95% CI)
<b>8</b>	Before vaccination	239	55.4	(45.4, 67.5)	236	27.9	(23.6, 33.0)	113	138.8	(98.6, 195.4)
	1 Month after vaccination	230	211.9	(172.0, 261.0)	226	602.9	(482.9, 752.8)	109	293.8	(220.0, 392.4)
<b>10A</b>	Before vaccination	221	211.6	(166.2, 269.5)	231	141.2	(112.9, 176.6)	119	399.6	(280.8, 568.5)
	1 Month after vaccination	219	1012.1	(806.7, 1269.8)	210	2005.4	(1586.0, 2535.7)	110	1580.3	(1175.9, 2123.8)
<b>11A</b>	Before vaccination	208	510.0	(396.2, 656.4)	210	269.0	(211.0, 343.0)	106	550.4	(385.7, 785.3)
	1 Month after vaccination	216	1473.2	(1192.4, 1820.2)	206	1908.2	(1541.5, 2362.2)	102	1566.6	(1140.7, 2151.4)
<b>12F</b>	Before vaccination	230	147.0	(112.1, 192.9)	227	53.2	(43.3, 65.4)	113	367.8	(236.3, 572.5)
	1 Month after vaccination	224	1054.5	(822.0, 1352.7)	214	1763.4	(1371.8, 2266.7)	110	1401.2	(1001.8, 1959.7)
<b>15B</b>	Before vaccination	231	140.2	(104.3, 188.6)	215	74.1	(55.9, 98.3)	110	190.0	(124.0, 291.0)
	1 Month after vaccination	225	647.1	(490.8, 853.1)	201	1479.5	(1093.0, 2002.8)	110	1066.9	(721.3, 1578.1)
<b>22F</b>	Before vaccination	236	167.5	(122.0, 229.9)	223	60.4	(44.6, 81.7)	116	286.4	(179.7, 456.4)
	1 Month after vaccination	218	1772.8	(1354.7, 2319.8)	206	4156.5	(3243.8, 5326.2)	108	2717.8	(1978.4, 3733.4)
<b>33F</b>	Before vaccination	231	1128.8	(935.8, 1361.7)	226	605.8	(507.3, 723.4)	115	1352.8	(1036.9, 1764.9)
	1 Month after vaccination	216	2026.2	(1684.3, 2437.4)	208	3174.9	(2579.1, 3908.3)	103	2182.9	(1638.6, 2907.8)

A: Cohort A; B: Cohort B; C: Cohort C

Source: Table 8 in the CSR for Study B7471006.

For the 7 additional serotypes, the proportions of participants with a  $\geq 4$ -fold rise in OPA titers from before to 1 month after 20vPnC were higher in participants with prior 13vPnC only, who were naïve to these vaccine serotypes prior to receiving 20vPnC, ranging from 53.6% (serotype 33F) to 83.2% (serotype 22F), than in participants with prior PPSV23 only, ranging from 18.7% (serotype 33F) to 57.0% (serotype 22F) and participants with prior 13vPnC and PPSV23, ranging from 19.2% (serotype 33F) to 54.8% (serotype 22F).

- Proportion of participants with pneumococcal OPA Titers  $\geq$  LLOQ

The majority of participants had OPA titers  $\geq$  LLOQ 1 month after 20vPnC. Proportions ranged from 64.8% (serotype 5) to 94.0% (serotype 22F) in Cohort A (prior PPSV23 only), 74.9% (serotype 5) to 99.0% (serotype 22F) in Cohort B (prior 13vPnC only), and 72.5% (serotype 5) to 98.3% (serotype 19A) in Cohort C (prior 13vPnC and PPSV23).

#### 6.1.11.3 Subpopulation Analyses

OPA GMTs before and 1 month after 20vPnC by sex were calculated. Please refer to Section 7 for a review of this subgroup analysis.

### 6.1.11.5 Exploratory and Post Hoc Analyses

N/A

### 6.1.12 Safety Analyses

The number of subjects included in the safety evaluation are 253 (20vPnC group) and 121 (13vPnC group) in Cohort A, 245 (20vPnC group) and 126 (PPSV23 group) in Cohort B, and 125 (20vPnC group) in Cohort C.

The proportions of participants who experienced prompted local reactions within 10 days after 20vPnC were generally similar across cohorts regardless of prior pneumococcal vaccination and were also generally similar to the corresponding control groups within Cohorts A (prior PPSV23 only) and B (prior 13vPnC only) (Table 3). In the 20vPnC groups, pain at injection site was slightly higher in participants with prior 13vPnC only (61.2%) than in those with prior PPSV23 only (50.2%) or prior 13vPnC and PPSV23 (Cohort C, 52.8%).

**Table 3. Local Reactions Within 10 Days After Vaccination**

	Cohort A	Cohort A	Cohort B	Cohort B	Cohort C
	20vPnC (N = 253)	13vPnC (N = 121)	20vPnC (N = 245)	PPSV23 (N = 126)	20vPnC (N = 125)
Local Reaction	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
Redness	20 (7.9) (4.9, 11.9)	3 (2.5) (0.5, 7.1)	21 (8.6) (5.4, 12.8)	16 (12.7) (7.4, 19.8)	6 (4.8) (1.8, 10.2)
Swelling	25 (9.9) (6.5, 14.2)	8 (6.6) (2.9, 12.6)	23 (9.4) (6.0, 13.8)	18 (14.3) (8.7, 21.6)	5 (4.0) (1.3, 9.1)
Pain at injection site	127 (50.2) (43.9, 56.5)	52 (43.0) (34.0, 52.3)	150 (61.2) (54.8, 67.4)	71 (56.3) (47.2, 65.2)	66 (52.8) (43.7, 61.8)
Any local reaction	134 (53.0) (46.6, 59.2)	53 (43.8) (34.8, 53.1)	157 (64.1) (57.7, 70.1)	73 (57.9) (48.8, 66.7)	68 (54.4) (45.3, 63.3)

Source: Adapted from Table 13 in the CSR for Study B7471006.

The proportions of participants who experienced prompted systemic events within 7 days after 20vPnC were generally similar across cohorts regardless of prior pneumococcal vaccination and were also generally similar to the corresponding control groups within Cohorts A (prior PPSV23 only) and B (prior 13vPnC only) (Table 4). A higher percentage of muscle pain was reported after PPSV23 (46.0%) than after 20vPnC (33.9%) in participants with prior 13vPnC only. Fever was reported after 20vPnC in 2 participants with prior PPSV23 only, and after PPSV23 in 2 participants with prior 13vPnC only.

**Table 4. Systemic Events Within 7 Days After Vaccination**

	Cohort A	Cohort A	Cohort B	Cohort B	Cohort C
	20vPnC (N = 253)	13vPnC (N = 121)	20vPnC (N = 245)	PPSV23 (N = 126)	20vPnC (N = 125)
Systemic Event	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
Fever ( $\geq 38.0^{\circ}\text{C}$ )	2 (0.8) (0.1, 2.8)	0 (0.0, 3.0)	0 (0.0, 1.5)	2 (1.6) (0.2, 5.6)	0 (0.0, 2.9)
Fatigue	73 (28.9) (23.4, 34.9)	27 (22.3) (15.2, 30.8)	76 (31.0) (25.3, 37.2)	42 (33.3) (25.2, 42.3)	41 (32.8) (24.7, 41.8)
Headache	45 (17.8) (13.3, 23.1)	22 (18.2) (11.8, 26.2)	33 (13.5) (9.5, 18.4)	27 (21.4) (14.6, 29.6)	24 (19.2) (12.7, 27.2)
Muscle pain	81 (32.0) (26.3, 38.1)	38 (31.4) (23.3, 40.5)	83 (33.9) (28.0, 40.2)	58 (46.0) (37.1, 55.1)	47 (37.6) (29.1, 46.7)
Joint pain	17 (6.7) (4.0, 10.5)	13 (10.7) (5.8, 17.7)	29 (11.8) (8.1, 16.6)	20 (15.9) (10.0, 23.4)	21 (16.8) (10.7, 24.5)
Any systemic event	131 (51.8) (45.4, 58.1)	53 (43.8) (34.8, 53.1)	123 (50.2) (43.8, 56.6)	75 (59.5) (50.4, 68.2)	66 (52.8) (43.7, 61.8)
Use of antipyretic or pain medication	40 (15.8) (11.5, 20.9)	18 (14.9) (9.1, 22.5)	42 (17.1) (12.6, 22.5)	25 (19.8) (13.3, 27.9)	22 (17.6) (11.4, 25.4)

Source: Adapted from Table 14 in the CSR for Study B7471006.

In the 20vPnC groups, the proportions of subjects reporting AEs were generally similar across the 3 cohorts (7.5% in Cohort A [prior PPSV23 only], 4.9% in Cohort B [prior 13vPnC only], and 10.4% in Cohort C [prior 13vPnC and PPSV23]) and were similar to the proportions after 13vPnC (9.0%) and after PPSV23 (11.0%). The proportions of participants who reported any AE that was considered by the investigator to be related to study vaccine from vaccination to 1 month after vaccination were  $\leq 2.4\%$  in all vaccine groups.

The proportions of participants who reported any SAEs within 6 months after vaccination were  $\leq 2.4\%$  in all vaccine groups. Less than 1% of participants reported any SAE within 1 month after vaccination in each vaccine group. No reported SAEs were considered by the investigator to be related to study vaccine. The proportions of participants who reported any NDCMC within 6 months after vaccination were  $\leq 4.0\%$  in all vaccine groups.

## 6.2 Trial #2: 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

### 6.2.1 Objectives

Primary Objectives:

- To describe the safety profile of 20vPnC in adults 18 years of age and older.
- To demonstrate that the immune responses to the 13 serotypes in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 20vPnC in adults 60



years of age and older are noninferior to the immune response induced by 13vPnC.

- To demonstrate that the immune responses to the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by 20vPnC in adults 60 years of age and older are noninferior to the immune response induced by PPSV23.

Secondary Objectives:

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 50 through 59 years of age are noninferior to the immune responses induced by 20vPnC in adults 60 through 64 years of age.
- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 18 through 49 years of age are noninferior to the immune responses induced by 20vPnC in adults 60 through 64 years of age.
- To describe the immune responses to 20vPnC in adults 60 years of age and older, 50 through 59 years of age, and 18 through 49 years of age, in terms of 1) Fold rise in serotype-specific OPA titers from before to 1 month after vaccination; 2)  $\geq 4$ -Fold rise in serotype-specific OPA titers from before to 1 month after vaccination; and 3) Serotype-specific OPA titers  $\geq$  LLOQ 1 month after vaccination.

### 6.2.2 Design Overview

This was a Phase 3, multicenter, randomized, double-blind study conducted at sites in the United States and Sweden. Approximately 3880 adults 18 years of age and older with no history of pneumococcal vaccination were to be enrolled and assigned to 1 of 3 cohorts based on their age at enrollment and randomized to a 20vPnC group or a control group.

Cohort 1: Approximately 3000 participants were enrolled. Two thousand participants were 60 through 64 years of age, and 1000 participants were 65 years of age and older. Participants were stratified by age and randomized (1:1) to receive either 20vPnC or 13vPnC (control vaccine) at Vaccination 1 (Visit 1). Participants who received 20vPnC at Vaccination 1 received saline at Vaccination 2 (Visit 2), and those who received 13vPnC at Vaccination 1 received PPSV23 at Vaccination 2 (Visit 2).

Cohort 2: Approximately 440 participants 50 through 59 years of age were enrolled and randomized (3:1) to receive a single dose of 20vPnC or 13vPnC at Visit 1.

Cohort 3: Approximately 440 participants 18 through 49 years of age were enrolled and randomized (3:1) to receive a single dose of 20vPnC or 13vPnC at Visit 1.

### 6.2.3 Population

Approximately 3880 adults 18 years of age and older with no history of pneumococcal vaccination.

#### *6.2.4 Study Treatments or Agents Mandated by the Protocol*

At Vaccination 1 in Cohort 1 and for the single vaccination administered to Cohorts 2 and 3, a 0.5-mL dose of 20vPnC or 13vPnC was administered intramuscularly in the deltoid muscle of the nondominant arm by a blinded site staff member (20vPnC and 13vPnC have the same appearance).

At Vaccination 2 (Cohort 1 only), a 0.5-mL dose of saline or PPSV23 was prepared and administered by third-party unblinded site staff member(s) and was administered intramuscularly in the deltoid muscle of the nondominant arm to blinded participants.

#### *6.2.5 Directions for Use*

Please refer to the clinical reviewer's memo.

#### *6.2.6 Sites and Centers*

Sixty-one sites in the United States and Sweden.

#### *6.2.7 Surveillance/Monitoring*

Please refer to the clinical reviewer's memo.

#### *6.2.8 Endpoints and Criteria for Study Success*

Primary Safety Endpoints:

- Reported prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination
- Reported prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination
- Reported AEs within 1 month after vaccination
- Reported SAEs and newly diagnosed chronic medical conditions (NDCMCs) within 6 months after vaccination

Primary Immunogenicity Endpoint:

- pneumococcal serotype-specific OPA titers 1 month after vaccination

#### *6.2.9 Statistical Considerations & Statistical Analysis Plan*

For the primary objective, hypothesis testing was performed to assess noninferiority by comparing the serotype-specific OPA titers of the 20vPnC/saline group to those from the 13vPnC/PPSV23 group in Cohort 1.

##### Statistical Hypothesis:

$H_0: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.5)$  versus  $H_1: \ln(\mu_A) - \ln(\mu_B) > \ln(0.5)$ , where

- $\ln(0.5)$  corresponds to a 2-fold margin for noninferiority.
- $\ln(\mu_A)$  is the natural log of the geometric mean OPA titer 1 month after 20vPnC administration for the 20vPnC/saline group.
- $\ln(\mu_B)$  is the natural log of the geometric mean OPA titer 1 month after 13vPnC administration for the 13vPnC/PPSV23 group when the endpoint is the geometric

mean OPA titer from 1 of the shared 13 serotypes in 13vPnC, or,  $\ln(\mu_B)$  is the natural log of the geometric mean OPA titer 1 month after PPSV23 administration for the 13vPnC/PPSV23 group when the endpoint is the geometric mean OPA titer from 1 of the 7 additional serotypes.

Sample Size Determination:

Sample size and power for Cohort 1 were based on simulations with assumptions supported by the OPA results from a Phase 2 study of 20vPnC (B7471002). Assuming that the true GMRs and variance-covariance matrix were the same as those obtained from B7471002, with 1350 evaluable subjects in each group the estimated probabilities to demonstrate noninferiority for at least 18 out of 20, at least 19 out of 20, and for all 20 serotypes in Cohort 1 were approximately 99%, 96%, and 72%, respectively.

With the planned sample sizes in Cohorts 2 and 3 and assuming that approximately 900 evaluable subjects enrolled in Cohort 1 were 60 through 64 years of age, the study had greater than 90% power to demonstrate noninferiority in serotype-specific OPA GMRs for all 20 serotypes in Cohorts 2 and 3, assuming the true OPA GMRs between each of the younger age cohorts and the subjects 60 through 64 years of age from Cohort 1 were 1 and the variance-covariance matrix for the 20 serotype-specific OPA titers was similar to that observed in Study B7471002.

Statistical Method and Success Criteria: For the comparison of OPA results in Cohort 1, the primary approach was based on a linear regression model. The following terms were included in the regression model: corresponding baseline OPA titer, age, sex (male or female), smoking status (current smoker, ex-smoker, never smoked), and vaccine group. The difference between these least squares (LS) means on the natural log scale and associated CI estimated from the linear regression model was transformed back to the original scale to obtain the GMR and CI.

Noninferiority for serotype-specific OPA titers was formally evaluated by a 2-sided 95% confidence interval (CI) for the ratio of serotype-specific OPA geometric mean titers (GMTs) (the 20vPnC/saline group to the 13vPnC/PPSV23 group) with results from 1 month after vaccination with 20vPnC (Visit 2) and 1 month after 13vPnC (Visit 2) for the 13 matched serotypes. For the 7 additional serotypes, the CI was calculated for the ratio of serotype-specific OPA GMTs from the 20vPnC/saline group at Visit 2 to that from the 13vPnC/PPSV23 group at Visit 3. Noninferiority for a serotype would be declared if the lower bound of the 2-sided 95% CI for the geometric mean ratio (GMR) for that serotype was greater than 0.5.

For secondary objective comparing Cohorts 2 and 3 to subjects 60 through 64 years of age in Cohort 1, hypothesis testing was performed to assess noninferiority between each of the younger cohorts (subjects 50 through 59 years of age in Cohort 2 and subjects 18 through 49 years of age in Cohort 3) and subjects 60 through 64 years of age from Cohort 1 for each of the 20 serotype-specific OPA titers. Testing was performed only for subjects receiving 20vPnC. The testing method was the same as the method for the primary objective.

## 6.2.10 Study Population and Disposition

### 6.2.10.1 Populations Enrolled/Analyzed

The proportions of participants in Cohort 1 included in the evaluable 13-matched, evaluable 7-additional, and all-available immunogenicity populations were similar in the 20vPnC/saline and 13vPnC/PPSV23 groups (Table 5). No analyses in Cohort 1 were conducted using the all-available immunogenicity population due to  $\leq 5\%$  difference in sample size between the all-available population and each of the evaluable populations: the evaluable 13-matched and evaluable 7-additional populations.

Similarly, analyses of immunogenicity results for Cohorts 2 and 3 in comparison with Cohort 1 (Table 6) were performed using the evaluable-20 immunogenicity population only.

There was a relatively higher representation of female participants (approximately 60%) in Cohort 1. There was a goal to include older participants in this study, and 12.9% of participants in Cohort 1 were  $\geq 70$  years of age, making up nearly 40% of those  $\geq 65$  years of age. Approximately 60% of participants were female in Cohort 2. The overall proportion of female participants in Cohort 3 was approximately 65%, slightly higher than the proportions in Cohorts 1 and 2. Overall, the demographic characteristics and smoking history in the 20vPnC and 13vPnC groups in all three age cohorts were similar.

**Table 5. Evaluable and All-Available Immunogenicity Populations – Cohort 1**

	<b>20vPnC/Saline</b>	<b>13vPnC/PPSV23</b>	<b>Total</b>
	n (%)	n (%)	n (%)
Randomized	1514 (100%)	1495 (100%)	3009 (100%)
Evaluable 13-matched immunogenicity population	1435 (94.8)	1420 (95.0)	2855 (94.9)
60-64 Years of age	945 (62.4)	948 (63.4)	1893 (62.9)
$\geq 65$ Years of age	490 (32.4)	472 (31.6)	962 (32.0)
Evaluable 7-additional immunogenicity population	1433 (94.6)	1383 (92.5)	2816 (93.6)
60-64 Years of age	945 (62.4)	917 (61.3)	1862 (61.9)
$\geq 65$ Years of age	488 (32.2)	466 (31.2)	954 (31.7)
All-available immunogenicity population	1476 (97.5)	1456 (97.4)	2932 (97.4)
60-64 Years of age	974 (64.3)	972 (65.0)	1946 (64.7)
$\geq 65$ Years of age	502 (33.2)	484 (32.4)	986 (32.8)

Source: Adapted from Table 8 in the CSR for Study B7471007.

**Table 6. Evaluable-20 Immunogenicity Populations – 20vPnC Vaccination in Cohort 1 Subjects 60 Through 64 Years of Age, Cohort 2, and Cohort 3**

	<b>20vPnC/Saline Group in Cohort 1 (60 Through 64 Years of Age)</b>	<b>20vPnC Group in Cohort 2</b>	<b>20vPnC Group in Cohort 3</b>
	n (%)	n (%)	n (%)
Randomized	996 (100.0)	334 (100.0)	336 (100.0)
Evaluable-20 immunogenicity population	946 (95.0)	321 (96.1)	317 (94.3)

Source: Adapted from Table 9 in the CSR for Study B7471007.

### 6.2.11 Immunogenicity Analyses

#### 6.2.11.1 Analyses of Primary Endpoints

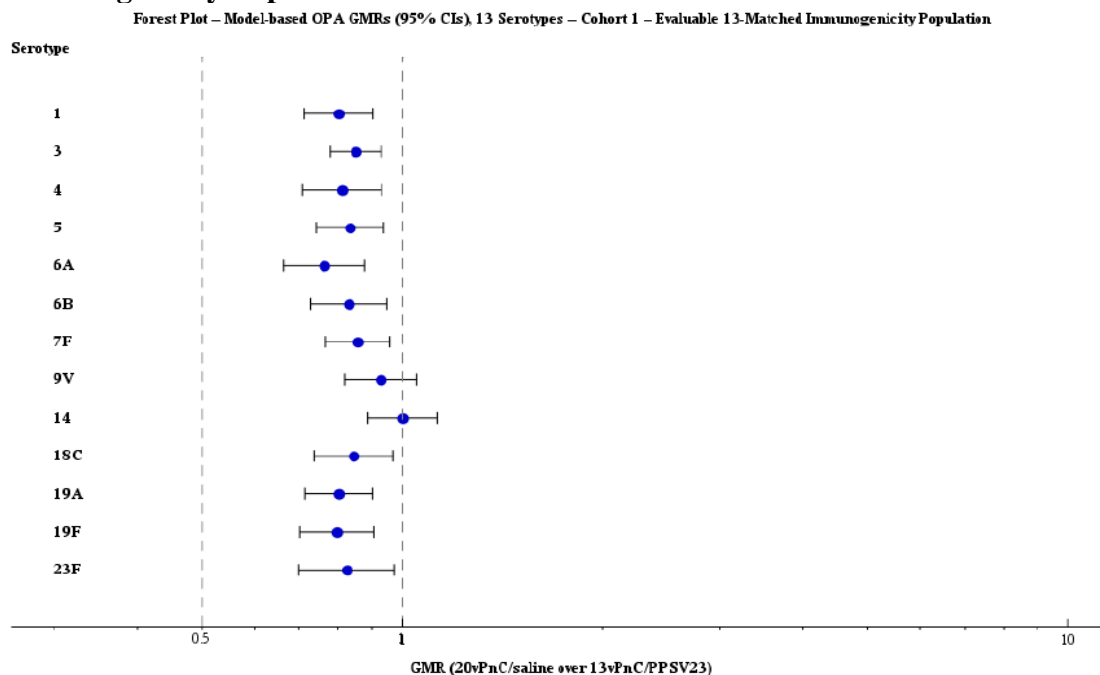
20vPnC met the primary immunogenicity objective for the 13-matched vaccine serotypes. One month after 20vPnC or 13vPnC, the immune responses to all 13-matched vaccine serotypes induced by 20vPnC were noninferior to those induced by 13vPnC, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (20vPnC/saline relative to 13vPnC/PPSV23 group) >0.5 (Table 7, Figure 1). The observed OPA GMRs for the 13 matched serotypes were between 0.76 and 1.00.

**Table 7. Pneumococcal OPA GMTs and GMRs for the 13vPnC Serotypes 1 Month After Vaccination – Linear Regression Model – Cohort 1 – Evaluable 13- Matched Immunogenicity Population**

	20vPnC/ Saline	20vPnC/ Saline	20vPnC/ Saline	13vPnC/ PPSV23	13vPnC/ PPSV23	13vPnC/ PPSV23	Vaccine Comparison	
Serotype	n	GMT	(95% CI)	n	GMT	(95% CI)	GMR	(95% CI)
1	1430	123.4	(112.3, 135.5)	1419	153.8	(140.2, 168.8)	0.80	(0.71, 0.90)
3	1415	40.7	(38.0, 43.6)	1411	47.8	(44.7, 51.2)	0.85	(0.78, 0.93)
4	1415	508.7	(456.5, 566.9)	1409	626.9	(563.5, 697.4)	0.81	(0.71, 0.93)
5	1418	91.6	(83.4, 100.5)	1395	109.7	(100.1, 120.3)	0.83	(0.74, 0.94)
6A	1403	889.0	(795.0, 994.1)	1390	1165.1	(1043.3, 1301.0)	0.76	(0.66, 0.88)
6B	1413	1115.2	(1003.1, 1239.8)	1401	1341.3	(1208.5, 1488.8)	0.83	(0.73, 0.95)
7F	1409	968.8	(887.0, 1058.3)	1391	1129.2	(1034.7, 1232.4)	0.86	(0.77, 0.96)
9V	1399	1455.5	(1317.5, 1608.0)	1391	1567.8	(1420.5, 1730.5)	0.93	(0.82, 1.05)
14	1418	746.7	(679.0, 821.2)	1408	746.7	(679.8, 820.1)	1.00	(0.89, 1.13)
18C	1420	1252.6	(1123.1, 1397.0)	1403	1482.3	(1330.5, 1651.5)	0.85	(0.74, 0.97)
19A	1420	517.9	(472.2, 568.0)	1398	645.3	(588.9, 707.1)	0.80	(0.71, 0.90)
19F	1421	265.8	(240.2, 294.1)	1403	333.3	(301.5, 368.3)	0.80	(0.70, 0.91)
23F	1424	276.5	(242.5, 315.2)	1409	335.1	(294.4, 381.4)	0.83	(0.70, 0.97)

Source: Adapted from Table 16 in the CSR for Study B7471007.

**Figure 1. Model-Based OPA GMRs of 20vPnC to 13vPnC With 95% CIs 1 Month After Vaccination for 13vPnC Serotypes – Cohort 1 – Evaluable 13-Matched Immunogenicity Population**



Source: Figure 1 in the CSR for Study B7471007.

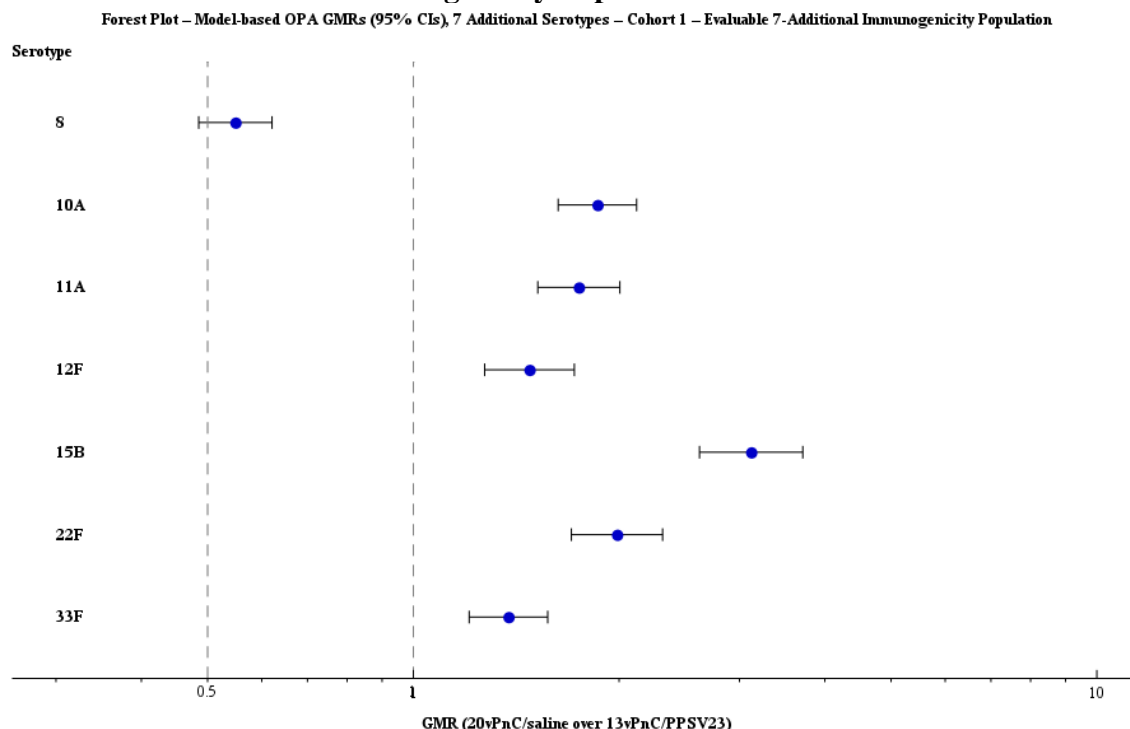
20vPnC met the primary immunogenicity objective for 6 of the 7 additional vaccine serotypes. One month after 20vPnC or PPSV23, the immune responses to 6 of the 7 additional vaccine serotypes induced by 20vPnC were noninferior to those induced by PPSV23, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (20vPnC/saline relative to 13vPnC/PPSV23 group)  $>0.5$  (Figure 2). The model-based GMR (2-sided 95% CI) for serotype 8 was 0.55 (0.49, 0.62), narrowly missing the statistical NI criterion (Table 8). Additional analyses of secondary endpoints were performed to further characterize the immune responses to serotype 8.

**Table 8. Pneumococcal OPA GMTs and GMRs for the 7 Additional Serotypes 1 Month After Vaccination – Linear Regression Model – Cohort 1 – Evaluable 7-Additional Immunogenicity Population**

	20vPnC/ Saline	20vPnC/ Saline	20vPnC/ Saline	13vPnC/ PPSV23	13vPnC/ PPSV23	13vPnC/ PPSV23	Vaccine Comparison	
Serotype	n	GMT	(95% CI)	n	GMT	(95% CI)	GMR	(95% CI)
8	1374	465.6	(422.5, 513.1)	1319	848.1	(769.1, 935.2)	0.55	(0.49, 0.62)
10A	1310	2007.6	(1808.0, 2229.1)	1263	1079.9	(972.1, 1199.7)	1.86	(1.63, 2.12)
11A	1198	4426.8	(3965.5, 4941.8)	1209	2534.9	(2276.8, 2822.3)	1.75	(1.52, 2.01)
12F	1294	2538.7	(2255.3, 2857.7)	1222	1716.6	(1521.8, 1936.3)	1.48	(1.27, 1.72)
15B	1283	2398.2	(2090.6, 2751.2)	1249	768.5	(669.7, 881.9)	3.12	(2.62, 3.71)
22F	1274	3666.2	(3244.4, 4143.0)	1227	1846.2	(1636.6, 2082.6)	1.99	(1.70, 2.32)
33F	1157	5125.9	(4611.3, 5698.0)	1201	3720.6	(3356.2, 4124.6)	1.38	(1.21, 1.57)

Source: Adapted from Table 17 in the CSR for Study B7471007.

**Figure 2. Model-Based OPA GMRs of 20vPnC to PPSV23 With 95% CIs 1 Month After Vaccination for 7 Additional Serotypes in 20vPnC – Cohort 1 – Evaluable 7-Additional Immunogenicity Population**



Source: Figure 2 in the CSR for Study B7471007.

#### 6.2.11.2 Analyses of Secondary Endpoints

##### 60 Years of Age and Older (Cohort 1)

- Pneumococcal OPA GMFRs

For the 13-matched vaccine serotypes, substantial increases in OPA GMTs from before vaccination to 1 month after 20vPnC or 13vPnC were observed in both groups. The GMFRs ranged from 4.8 (serotype 3) to 34.3 (serotype 6A) in the 20vPnC/saline group, and from 5.8 (serotype 3) to 42.6 (serotype 6A) in the 13vPnC/PPSV23 group.

Substantial increases in OPA GMTs from before Vaccination 1 to 1 month after 20vPnC or PPSV23 were also observed for the 7 additional vaccine serotypes in both groups. The GMFRs ranged from 7.5 (serotype 33F) to 78.5 (serotype 22F) in the 20vPnC/saline group and from 5.7 (serotype 33F) to 47.3 (serotype 12F) in the 13vPnC/PPSV23 group. A GMFR of 22.1 was observed for serotype 8 from before vaccination to 1 month after 20vPnC, which was within the range of the observed GMFRs for the 13-matched vaccine serotypes from before vaccination to 1 month after 13vPnC in the 13vPnC/PPSV23 group.

- Proportion of participants achieving a  $\geq 4$ -fold rise in pneumococcal OPA titers

For the 13-matched vaccine serotypes, the proportions of participants achieving a  $\geq 4$ -fold rise in OPA titers from before vaccination to 1 month after 20vPnC or 13vPnC were similar in both groups. Proportions ranged from 55.6% (serotype 5) to 80.5% (serotype

6A) in the 20vPnC/saline group and from 54.0% (serotype 14) to 84.0% (serotype 6A) in the 13vPnC/PPSV23 group.

For the 7 additional vaccine serotypes, the estimated proportions of participants achieving a  $\geq 4$ -fold rise in OPA titers from before Vaccination 1 to 1 month after 20vPnC were higher than those after PPSV23, except for serotype 8. Proportions ranged from 59.2% (serotype 11A) to 87.4% (serotype 12F) in the 20vPnC/saline group and from 51.9% (serotype 11A) to 86.8% (serotype 8) in the 13vPnC/PPSV23 group. After 20vPnC, 77.8% of participants achieved a  $\geq 4$ -fold rise in OPA titers for serotype 8, which was within the range of that observed for the 13-matched vaccine serotypes after 13vPnC in the 13vPnC/PPSV23 group.

- Proportion of participants with pneumococcal OPA titers  $\geq$  LLOQ

For the 13-matched vaccine serotypes, there were increases in proportions of participants with OPA titers  $\geq$  LLOQ 1 month after 20vPnC or 13vPnC compared to baseline (before vaccination). At 1 month after vaccination, proportions ranged from 71.9% (serotype 5) to 96.3% (serotype 19A) in the 20vPnC/saline group and from 76.0% (serotype 5) to 96.6% (serotype 19A) in the 13vPnC/PPSV23 group.

For the 7 additional vaccine serotypes, there were increases in proportions of participants with OPA titers  $\geq$  LLOQ 1 month after 20vPnC or PPSV23 compared to baseline (before Vaccination 1). At 1 month after vaccination, proportions ranged from 92.9% (serotype 8) to 98.6% (serotype 22F) in the 20vPnC/saline group, and from 83.3% (serotype 15B) to 96.6% (serotype 8) in the 13vPnC/PPSV23 group. After 20vPnC, the proportion of participants with OPA titers  $\geq$  LLOQ for serotype 8 was within the range of the 13 matched vaccine serotypes observed after 13vPnC in the 13vPnC/PPSV23 group.

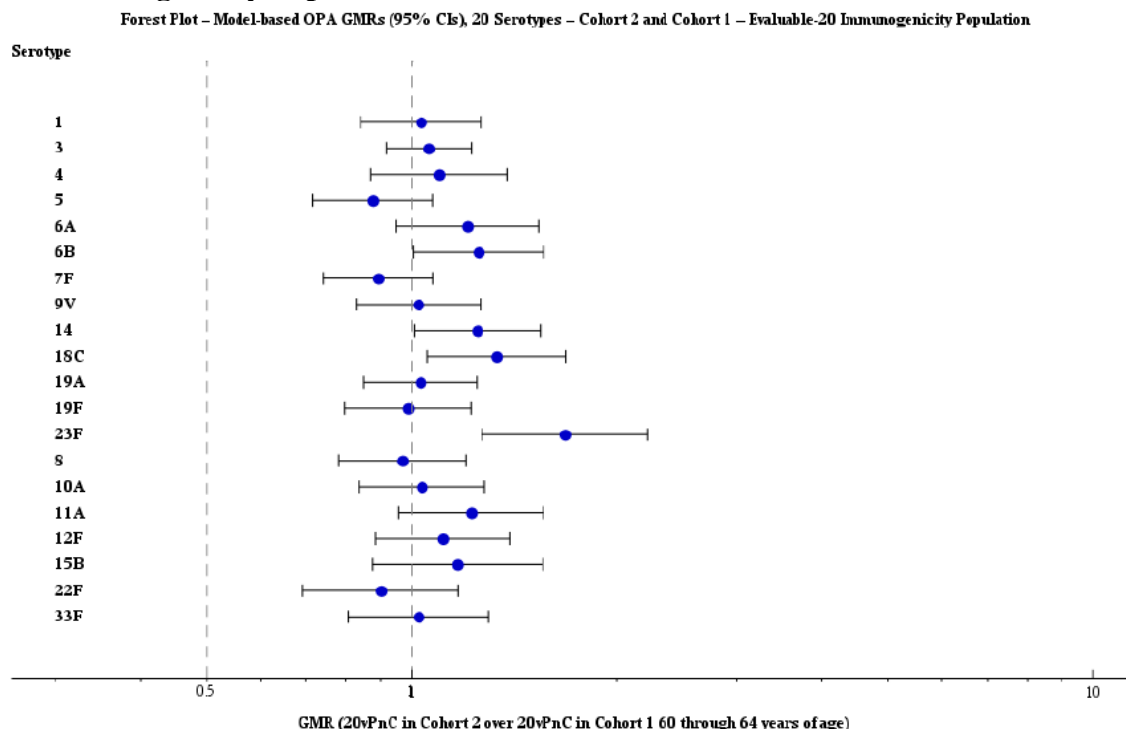
#### 50 Through 59 Years of Age (Cohort 2)

- Noninferiority of 20vPnC in Cohort 2 compared with Cohort 1 (participants 60 through 64 years of age) – Pneumococcal OPA GMTs and GMRs

20vPnC met the secondary immunogenicity objective for all 20 vaccine serotypes based on comparison of the immune responses in participants 50 through 59 years of age (Cohort 2) to those in participants 60 through 64 years of age in Cohort 1. One month after 20vPnC, the immune responses to all 20 vaccine serotypes in Cohort 2 were noninferior to those in Cohort 1 participants 60 through 64 years of age, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (20vPnC in Cohort 2 relative to 20vPnC in Cohort 1 participants 60 through 64 years of age)  $> 0.5$  (Figure 3).



**Figure 3. Model-Based OPA GMRs of Cohort 2 to Cohort 1 60 Through 64 Years of Age With 95% CIs 1 Month After Vaccination for 20vPnC Serotypes – Evaluable-20 Immunogenicity Population**



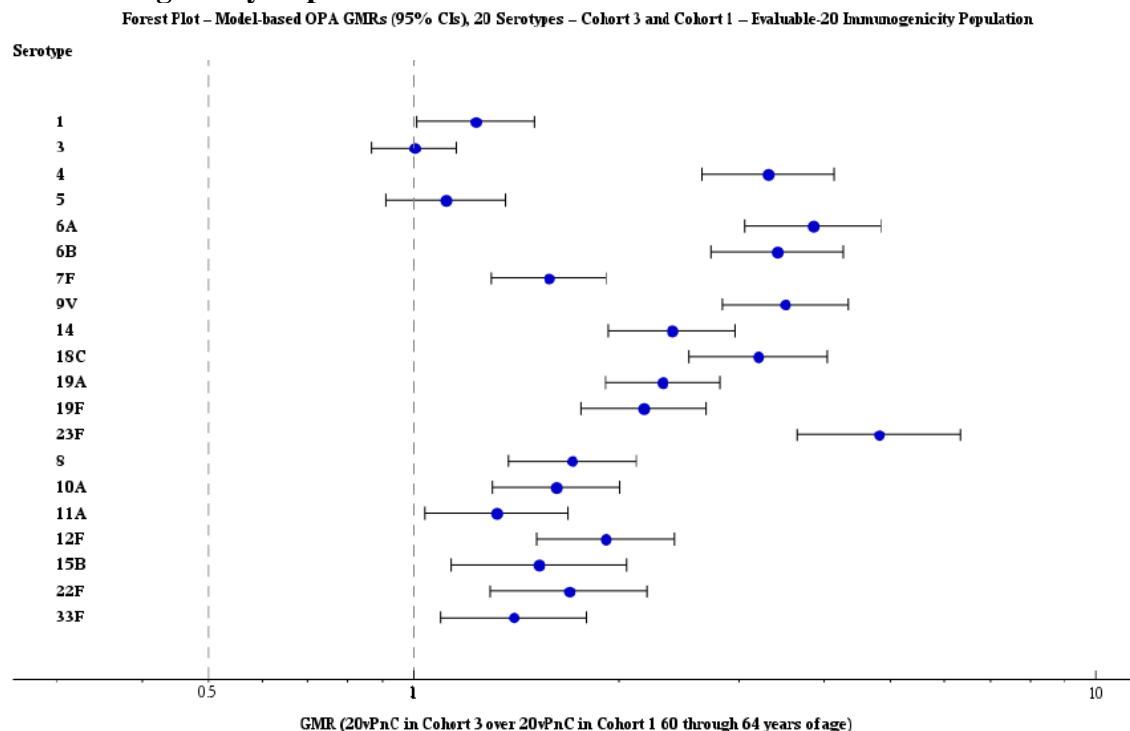
Source: Figure 3 in the CSR for Study B7471007.

### 18 through 49 Years of Age (Cohort 3)

- Noninferiority of 20vPnC in Cohort 3 compared with Cohort 1 (participants 60 through 64 years of age) – Pneumococcal OPA GMTs and GMRs

20vPnC met the secondary immunogenicity objective for all 20 vaccine serotypes based on comparison of the immune responses in participants 18 through 49 years of age (Cohort 3) to those in participants 60 through 64 years of age in Cohort 1. One month after 20vPnC, the immune responses to all 20 vaccine serotypes in Cohort 3 were noninferior to those in Cohort 1 participants 60 through 64 years of age, as demonstrated by the lower bounds of the 2-sided 95% CIs for the primary analysis of model-based OPA GMRs (20vPnC in Cohort 3 relative to 20vPnC in Cohort 1 participants 60 through 64 years of age)  $>0.5$  (Figure 4).

**Figure 4. Model-Based OPA GMRs of Cohort 3 to Cohort 1 60 Through 64 Years of Age With 95% CIs 1 Month After Vaccination for 20vPnC Serotypes – Evaluable-20 Immunogenicity Population**



Source: Figure 4 in the CSR for Study B7471007.

### 6.2.11.3 Subpopulation Analyses

- Pneumococcal OPA GMTs and GMFRs by risk status for 20vPnC recipients pooled from all 3 cohorts

Substantial increases in OPA GMTs from before vaccination to 1 month after 20vPnC were observed in both subgroups of participants with and without risk factors. The OPA GMFRs ranged from 4.4 (serotype 3) to 63.9 (serotype 22F) in participants with risk factors and from 5.1 (serotype 3) to 108.9 (serotype 12F) in participants without risk factors.

- Additional subgroup analyses for each cohort

In Cohort 1, robust immune responses to all 20 vaccine serotypes 1 month after 20vPnC were observed for each of the subgroups defined by sex, race, age group, or country, and the responses were generally similar for most vaccine serotypes relative to 13vPnC or PPSV23. Table 9 presents OPA GMTs by age group for the 13vPnC serotypes in Cohort 1. Table 10 presents OPA GMTs by age group for the 7 additional serotypes in Cohort 1. The immune responses generally decrease in older age groups.

**Table 9. Pneumococcal OPA GMTs 1 month after Vaccination 1 by Age Group for the 13vPnC Serotypes – Cohort 1**

Serotype	Age Group	20vPnC n	20vPnC GMT	20vPnC (95% CI)	13vPnC n	13vPnC GMT	13vPnC (95% CI)
1	60-64	941	163.2	(146.8, 181.4)	948	208.0	(187.3, 231.1)
	65-69	305	144.6	(118.7, 176.3)	294	175.7	(145.5, 212.2)
	70-79	151	114.4	(88.5, 147.9)	146	117.1	(88.1, 155.6)
	≥80	33	84.7	(46.7, 153.4)	31	93.4	(50.5, 172.6)
3	60-64	935	44.6	(41.3, 48.2)	945	50.5	(46.8, 54.5)
	65-69	302	42.2	(36.6, 48.7)	294	50.7	(43.9, 58.6)
	70-79	146	40.8	(32.7, 51.0)	141	48.1	(38.8, 59.6)
	≥80	32	43.0	(25.9, 71.3)	31	53.5	(32.9, 86.9)
4	60-64	931	717.6	(638.7, 806.2)	940	844.9	(752.6, 948.6)
	65-69	302	685.9	(551.8, 852.8)	294	721.2	(578.3, 899.3)
	70-79	149	360.3	(258.5, 502.1)	144	522.7	(374.6, 729.4)
	≥80	33	242.7	(123.7, 476.0)	31	429.4	(201.3, 916.1)
5	60-64	935	109.9	(99.1, 121.9)	936	133.5	(120.3, 148.1)
	65-69	301	93.6	(77.7, 112.8)	289	107.7	(89.0, 130.3)
	70-79	149	84.2	(64.2, 110.5)	140	98.4	(75.2, 128.7)
	≥80	33	60.2	(33.9, 106.7)	30	122.1	(63.2, 235.8)
6A	60-64	921	1148.6	(1015.4, 1299.2)	922	1470.7	(1301.3, 1662.2)
	65-69	301	1014.8	(809.5, 1272.3)	293	1414.0	(1148.2, 1741.4)
	70-79	148	589.1	(429.2, 808.7)	144	849.5	(605.1, 1192.7)
	≥80	33	469.0	(221.7, 992.2)	31	481.2	(200.5, 1154.8)
6B	60-64	933	1387.5	(1236.5, 1557.0)	935	1724.8	(1536.6, 1936.0)
	65-69	299	1449.8	(1175.3, 1788.5)	291	1684.4	(1360.3, 2085.7)
	70-79	148	641.9	(464.8, 886.3)	144	769.1	(549.7, 1076.0)
	≥80	33	495.2	(229.1, 1070.5)	31	590.9	(271.7, 1285.1)
7F	60-64	924	1255.8	(1143.2, 1379.4)	928	1435.9	(1303.4, 1582.0)
	65-69	302	966.3	(817.1, 1142.7)	289	1222.8	(1035.4, 1444.1)
	70-79	150	485.8	(373.8, 631.4)	144	676.2	(527.5, 866.8)
	≥80	33	652.1	(372.1, 1142.8)	30	407.2	(205.8, 805.5)
9V	60-64	922	1938.6	(1743.8, 2155.1)	928	2000.8	(1795.4, 2229.7)
	65-69	296	1517.0	(1250.7, 1840.0)	294	1653.8	(1364.3, 2004.6)
	70-79	148	977.2	(725.4, 1316.2)	139	1067.7	(813.8, 1400.9)
	≥80	33	645.2	(328.4, 1267.8)	30	641.7	(287.4, 1432.6)
14	60-64	933	807.8	(724.5, 900.7)	941	854.6	(770.3, 948.0)
	65-69	301	752.9	(617.9, 917.5)	294	739.1	(616.0, 886.7)
	70-79	151	623.5	(469.9, 827.3)	142	673.9	(505.1, 899.0)
	≥80	33	415.6	(229.0, 754.4)	31	423.8	(214.0, 839.0)
18C	60-64	937	1523.3	(1350.3, 1718.5)	938	1925.4	(1710.7, 2167.0)
	65-69	300	1453.3	(1187.0, 1779.4)	291	1469.7	(1174.6, 1838.9)
	70-79	150	782.4	(562.8, 1087.7)	143	956.8	(699.6, 1308.7)
	≥80	33	776.7	(378.1, 1595.7)	31	618.3	(294.8, 1296.8)

**Table 9. Pneumococcal OPA GMTs 1 month after Vaccination 1 by Age Group for the 13vPnC Serotypes – Cohort 1 (Continued)**

Serotype	Age Group	20vPnC n	20vPnC GMT	20vPnC (95% CI)	13vPnC n	13vPnC GMT	13vPnC (95% CI)
19A	60-64	932	667.0	(603.4, 737.4)	934	833.6	(753.9, 921.6)
	65-69	304	492.6	(408.1, 594.5)	292	700.9	(581.5, 844.8)
	70-79	151	395.4	(302.0, 517.7)	141	426.8	(317.1, 574.5)
	≥80	33	524.4	(303.0, 907.7)	31	277.9	(143.2, 539.4)
19F	60-64	937	321.1	(288.0, 358.0)	936	397.4	(353.9, 446.3)
	65-69	303	277.3	(226.5, 339.4)	292	382.2	(310.6, 470.2)
	70-79	149	232.5	(178.0, 303.7)	144	219.3	(160.0, 300.5)
	≥80	32	187.4	(94.2, 372.5)	31	260.8	(147.1, 462.3)
23F	60-64	937	346.5	(298.3, 402.5)	939	383.9	(329.9, 446.7)
	65-69	303	267.1	(202.7, 351.8)	294	419.7	(322.5, 546.2)
	70-79	152	218.5	(151.3, 315.6)	145	210.6	(142.1, 312.0)
	≥80	32	218.5	(86.4, 552.4)	31	189.3	(83.4, 429.8)

Source: Adapted from Table 14.72 in the CSR for Study B7471007.

**Table 10. Pneumococcal OPA GMTs 1 month after Vaccination by Age Group for the 7 Additional Serotypes – Cohort 1**

Serotype	Age Group	20vPnC n	20vPnC GMT	20vPnC (95% CI)	13vPnC n	13vPnC GMT	13vPnC (95% CI)
8	60-64	901	583.1	(522.9, 650.2)	875	1110.3	(1001.8, 1230.6)
	65-69	293	609.7	(502.2, 740.2)	273	926.8	(753.8, 1139.5)
	70-79	148	307.6	(232.2, 407.4)	141	628.1	(490.9, 803.6)
	≥80	32	281.7	(141.6, 560.4)	30	317.3	(158.0, 637.0)
10A	60-64	857	2679.0	(2399.8, 2990.6)	827	1398.8	(1231.1, 1589.4)
	65-69	277	2109.0	(1726.2, 2576.6)	270	1254.3	(996.0, 1579.6)
	70-79	143	1138.1	(860.5, 1505.1)	136	672.0	(495.9, 910.7)
	≥80	33	907.8	(474.7, 1735.9)	30	347.0	(162.1, 742.9)
11A	60-64	796	5712.0	(5126.0, 6364.9)	794	3312.4	(2966.5, 3698.6)
	65-69	252	5313.7	(4347.8, 6494.1)	257	2829.2	(2279.3, 3511.8)
	70-79	123	3234.3	(2349.2, 4452.8)	127	1847.8	(1383.4, 2468.0)
	≥80	27	4161.4	(1753.6, 9875.2)	31	1161.1	(662.7, 2034.2)
12F	60-64	855	3739.5	(3328.6, 4201.1)	808	2757.4	(2403.5, 3163.5)
	65-69	271	3015.0	(2435.5, 3732.3)	254	1851.2	(1396.0, 2455.0)
	70-79	137	1612.2	(1186.9, 2190.0)	133	1427.3	(1011.7, 2013.6)
	≥80	31	1358.5	(604.1, 3055.0)	27	271.2	(101.8, 722.4)

**Table 10. Pneumococcal OPA GMTs 1 month after Vaccination by Age Group for the 7 Additional Serotypes – Cohort 1 (Continued)**

Serotype	Age Group	20vPnC	20vPnC	20vPnC	13vPnC	13vPnC	13vPnC
		n	GMT	(95% CI)	n	GMT	(95% CI)
15B	60-64	830	3177.9	(2759.8, 3659.4)	828	1035.7	(880.8, 1217.9)
	65-69	284	2410.2	(1927.4, 3013.9)	262	801.4	(591.5, 1085.8)
	70-79	140	1468.5	(1026.8, 2100.2)	132	543.2	(356.1, 828.7)
	≥80	29	2118.4	(1036.0, 4331.6)	27	422.3	(170.2, 1047.9)
22F	60-64	835	5248.5	(4627.0, 5953.5)	816	2540.1	(2205.8, 2925.1)
	65-69	277	4031.0	(3221.1, 5044.5)	251	2214.2	(1678.5, 2921.0)
	70-79	134	2876.2	(2107.6, 3925.1)	132	1630.3	(1173.5, 2265.0)
	≥80	28	2808.4	(1499.3, 5260.4)	28	457.4	(187.5, 1115.5)
33F	60-64	765	6657.1	(5936.2, 7465.7)	790	5118.1	(4569.4, 5732.7)
	65-69	253	6068.0	(5000.4, 7363.6)	259	3873.5	(3130.3, 4793.2)
	70-79	120	4543.2	(3419.1, 6036.9)	124	2636.6	(2032.5, 3420.2)
	≥80	19	1630.0	(893.2, 2974.6)	28	1138.7	(586.3, 2211.5)

Source: Adapted from Table 14.76 in the CSR for Study B7471007.

In Cohorts 2 and 3, robust immune responses to all 20 vaccine serotypes 1 month after 20vPnC were observed for each of the subgroups defined by sex or race, and the responses were generally similar for most vaccine serotypes relative to 13vPnC. Please refer to Section 7 for further review of the subgroup analysis by sex.

#### 6.2.11.5 Exploratory and Post Hoc Analyses

N/A

#### 6.2.12 Safety Analyses

The proportions of participants in Cohort 1 who experienced prompted local reactions within 10 days after 20vPnC or 13vPnC were similar in the 20vPnC/saline and 13vPnC/PPSV23 groups (Table 11). The most frequent local reaction reported was pain at injection site.

The proportions of participants in Cohort 2 who experienced prompted local reactions within 10 days after 20vPnC or 13vPnC were similar in the 20vPnC and 13vPnC groups (Table 12). The most frequent local reaction reported was pain at injection site.

The proportions of participants in Cohort 3 who experienced prompted local reactions within 10 days after 20vPnC or 13vPnC were similar in the 20vPnC and 13vPnC groups (Table 13). The most frequent local reaction reported was pain at injection site.

**Table 11. Local Reactions Within 10 Days After Vaccination 1 – Cohort 1**

	20vPnC/Saline (N = 1505)		13vPnC/PPSV23 (N = 1483)		Difference	
Local Reaction	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)
Redness	110 (7.3)	(6.0, 8.7)	92 (6.2)	(5.0, 7.6)	1.1	(-0.7, 2.9)
Swelling	113 (7.5)	(6.2, 9.0)	118 (8.0)	(6.6, 9.5)	-0.4	(-2.4, 1.5)
Pain at injection site	834 (55.4)	(52.9, 57.9)	803 (54.1)	(51.6, 56.7)	1.3	(-2.3, 4.8)
Any local reaction	864 (57.4)	(54.9, 59.9)	830 (56.0)	(53.4, 58.5)	1.4	(-2.1, 5.0)

Source: Adapted from Table 35 in the CSR for Study B7471007.

**Table 12. Local Reactions Within 10 Days After Vaccination 1 – Cohort 2**

	20vPnC/Saline (N = 331)		13vPnC/PPSV23 (N = 111)		Difference	
Local Reaction	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)
Redness	27 (8.2)	(5.4, 11.6)	6 (5.4)	(2.0, 11.4)	2.8	(-3.6, 7.4)
Swelling	29 (8.8)	(5.9, 12.3)	12 (10.8)	(5.7, 18.1)	-2.0	(-9.7, 3.7)
Pain at injection site	240 (72.5)	(67.4, 77.2)	77 (69.4)	(59.9, 77.8)	3.1	(-6.2, 13.4)
Any local reaction	241 (72.8)	(67.7, 77.5)	78 (70.3)	(60.9, 78.6)	2.5	(-6.7, 12.7)

Source: Adapted from Table 36 in the CSR for Study B7471007.

**Table 13. Local Reactions Within 10 Days After Vaccination 1 – Cohort 3**

	20vPnC/Saline (N = 335)		13vPnC/PPSV23 (N = 112)		Difference	
Local Reaction	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)
Redness	30 (9.0)	(6.1, 12.5)	11 (9.8)	(5.0, 16.9)	-0.9	(-8.3, 4.7)
Swelling	39 (11.6)	(8.4, 15.6)	14 (12.5)	(7.0, 20.1)	-0.9	(-8.9, 5.5)
Pain at injection site	272 (81.2)	(76.6, 85.2)	92 (82.1)	(73.8, 88.7)	-0.9	(-8.5, 8.0)
Any local reaction	272 (81.2)	(76.6, 85.2)	92 (82.1)	(73.8, 88.7)	-0.9	(-8.5, 8.0)

Source: Adapted from Table 37 in the CSR for Study B7471007.

The proportions of participants in Cohort 1 who experienced prompted systemic events within 7 days after 20vPnC or 13vPnC were similar in the 20vPnC/saline and 13vPnC/PPSV23 groups (Table 14). The most frequent systemic event reported was muscle pain.

The proportions of participants in Cohort 2 who experienced prompted systemic events within 7 days after 20vPnC or 13vPnC were similar in the 20vPnC and 13vPnC groups (Table 15). The most frequent systemic event reported was muscle pain.

**Table 14. Systemic Events Within 7 Days After Vaccination 1 – Cohort 1**

	20vPnC/Saline (N = 1505)		13vPnC/PPSV23 (N = 1483)		Difference	
Systemic Event	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)
Fever ( $\geq 38.0^{\circ}\text{C}$ )	14 (0.9)	(0.5, 1.6)	12 (0.8)	(0.4, 1.4)	0.1	(-0.6, 0.8)
Fatigue	454 (30.2)	(27.9, 32.6)	455 (30.7)	(28.3, 33.1)	-0.5	(-3.8, 2.8)
Headache	324 (21.5)	(19.5, 23.7)	345 (23.3)	(21.1, 25.5)	-1.7	(-4.7, 1.3)
Muscle pain	588 (39.1)	(36.6, 41.6)	553 (37.3)	(34.8, 39.8)	1.8	(-1.7, 5.3)
Joint pain	190 (12.6)	(11.0, 14.4)	203 (13.7)	(12.0, 15.5)	-1.1	(-3.5, 1.4)
Any systemic event	831 (55.2)	(52.7, 57.7)	822 (55.4)	(52.9, 58.0)	-0.2	(-3.8, 3.4)
Use of antipyretic or pain medication	278 (18.5)	(16.5, 20.5)	303 (20.4)	(18.4, 22.6)	-2.0	(-4.8, 0.9)

Source: Adapted from Table 38 in the CSR for Study B7471007.

**Table 15. Systemic Events Within 7 Days After Vaccination 1 – Cohort 2**

	20vPnC/Saline (N = 331)		13vPnC/PPSV23 (N = 111)		Difference	
Systemic Event	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)
Fever ( $\geq 38.0^{\circ}\text{C}$ )	5 (1.5)	(0.5, 3.5)	1 (0.9)	(0.0, 4.9)	0.6	(-3.5, 2.8)
Fatigue	130 (39.3)	(34.0, 44.8)	40 (36.0)	(27.1, 45.7)	3.2	(-7.4, 13.2)
Headache	107 (32.3)	(27.3, 37.7)	40 (36.0)	(27.1, 45.7)	-3.7	(-14.2, 6.2)
Muscle pain	165 (49.8)	(44.3, 55.4)	55 (49.5)	(39.9, 59.2)	0.3	(-10.4, 10.9)
Joint pain	51 (15.4)	(11.7, 19.8)	23 (20.7)	(13.6, 29.5)	-5.3	(-14.5, 2.5)
Any systemic event	230 (69.5)	(64.2, 74.4)	75 (67.6)	(58.0, 76.1)	1.9	(-7.7, 12.3)
Use of antipyretic or pain medication	81 (24.5)	(19.9, 29.5)	31 (27.9)	(19.8, 37.2)	-3.5	(-13.5, 5.6)

Source: Adapted from Table 39 in the CSR for Study B7471007.

The proportions of participants in Cohort 3 who experienced prompted systemic events within 7 days after 20vPnC or 13vPnC were similar in the 20vPnC and 13vPnC groups (Table 16). The most frequent systemic event reported was muscle pain.

**Table 16. Systemic Events Within 7 Days After Vaccination 1 – Cohort 3**

	20vPnC/Saline (N = 335)		13vPnC/PPSV23 (N = 112)		Difference	
Systemic Event	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)
Fever ( $\geq 38.0^{\circ}\text{C}$ )	4 (1.2)	(0.3, 3.0)	2 (1.8)	(0.2, 6.3)	-0.6	(-5.2, 1.7)
Fatigue	143 (42.7)	(37.3, 48.2)	49 (43.8)	(34.4, 53.4)	-1.1	(-11.7, 9.3)
Headache	130 (38.8)	(33.6, 44.3)	38 (33.9)	(25.3, 43.5)	4.9	(-5.6, 14.7)
Muscle pain	223 (66.6)	(61.2, 71.6)	83 (74.1)	(65.0, 81.9)	-7.5	(-16.6, 2.5)
Joint pain	45 (13.4)	(10.0, 17.6)	20 (17.9)	(11.3, 26.2)	-4.4	(-13.2, 2.9)
Any systemic event	266 (79.4)	(74.7, 83.6)	93 (83.0)	(74.8, 89.5)	-3.6	(-11.2, 5.3)
Use of antipyretic or pain medication	86 (25.7)	(21.1, 30.7)	26 (23.2)	(15.8, 32.1)	2.5	(-7.2, 11.0)

Source: Adapted from Table 40 in the CSR for Study B7471007.

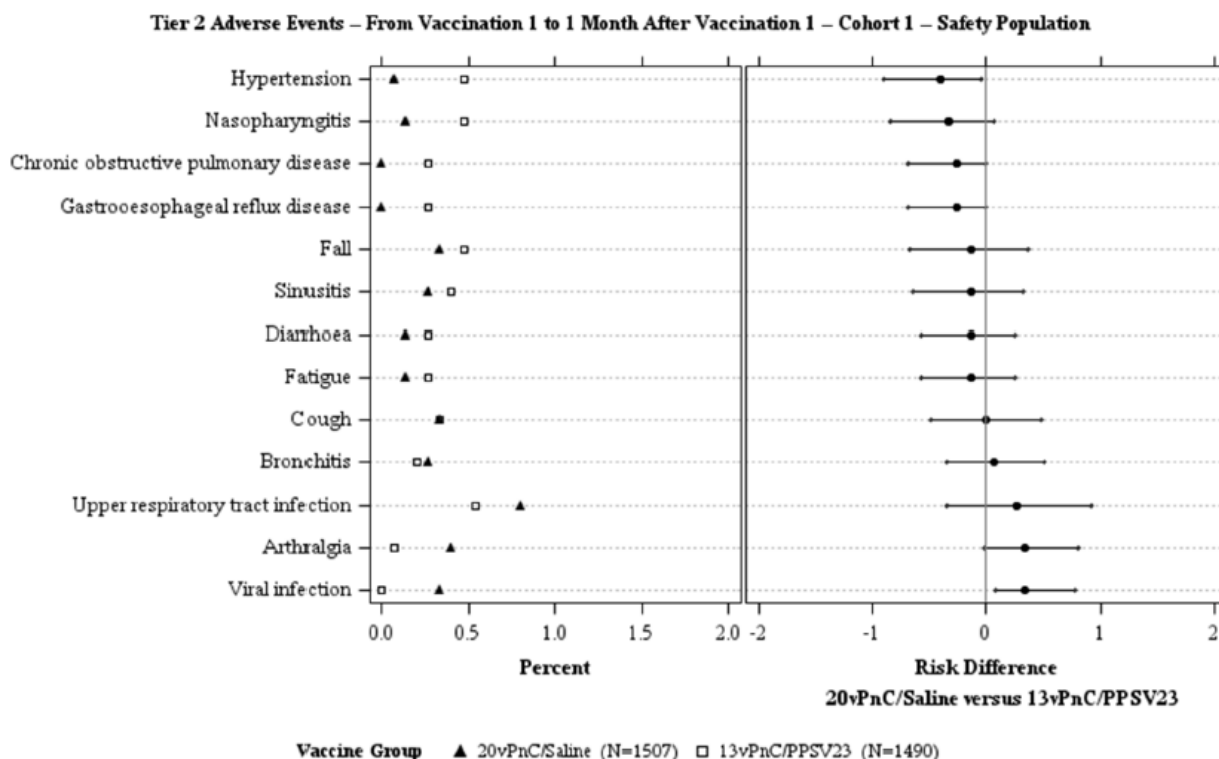
In Cohort 1, the safety population from Vaccination 1 to 1 Month After Vaccination 1 included 1507 and 1490 subjects for 20vPnC/Saline and 13vPnC/PPSV23 groups, respectively. The proportions of participants reporting any AEs from vaccination with 20vPnC or 13vPnC to 1 month after vaccination were similar (9.8% after 20vPnC and 11.1% after 13vPnC) in both groups. The proportions of participants reporting each of the Tier 2 AEs within 1 month after 20vPnC or 13vPnC were  $<1\%$  and similar in the 20vPnC/saline and 13vPnC/PPSV23 groups (Figure 5). A Medical Dictionary for Regulatory Activities (MedDRA) preferred term is defined as a Tier 2 event if there are at least 4 subjects with the AE term in at least 1 vaccine group in the cohort. The most frequently reported Tier 2 AE was upper respiratory tract infection in both groups (0.8% and 0.5% in the 20vPnC/Saline and 13vPnC/PPSV23 groups, respectively).

The proportions of participants in Cohort 1 reporting any SAEs were similar in the 20vPnC/saline (2.4%) and 13vPnC/PPSV23 (1.9%) groups within 6 months after the first vaccination. Less than 1% of participants reported any SAE within 1 month after 20vPnC or 13vPnC and from the administration of saline or PPSV23 through 1 month of follow-up in the study. No reported SAEs were considered by the investigator to be related to study vaccine.

Fewer than 1% of participants in Cohort 1 reported any NDCMC in either the 20vPnC/saline or 13vPnC/PPSV23 group after the first vaccination through 1 month of follow-up and from the administration of saline or PPSV23 through 1 month of follow-up. The proportions of participants in Cohort 1 who reported NDCMCs was 2.3% in each of the 20vPnC/saline and 13vPnC/PPSV23 groups within 6 months after vaccination.



**Figure 5. Tier 2 Adverse Events Reported From Vaccination 1 to 1 Month After Vaccination 1 – Cohort 1 – Safety Population**



Source: Figure 5 in the CSR for Study B7471007.

In Cohort 2, the safety population from Vaccination 1 to 1 Month After Vaccination 1 included 334 and 111 subjects for 20vPnC/Saline and 13vPnC/PPSV23 groups, respectively. The proportions of participants reporting any AEs from vaccination to 1 month after vaccination were  $\leq 10.2\%$  and similar in the 20vPnC and 13vPnC groups. The most frequently reported Tier 2 AE was upper respiratory tract infection in both groups (1.2% and 2.7% in the 20vPnC/Saline and 13vPnC/PPSV23 groups, respectively).

In Cohort 2, 1 participant in the 20vPnC group reported 2 SAEs, and 1 participant in the 13vPnC group reported 1 SAE from vaccination to 1 month after vaccination; no new SAEs were reported from 1 month after vaccination through 6 months after vaccination. No SAEs were considered by the investigator to be related to study vaccine.

Fewer than 1% of participants in Cohort 2 reported any NDCMC in either the 20vPnC or 13vPnC group after vaccination through 1 month of follow-up. The proportions of participants in Cohort 2 who reported NDCMCs were  $\leq 1.5\%$  in the 20vPnC and 13vPnC groups within 6 months after vaccination.

In Cohort 3, the safety population from Vaccination 1 to 1 Month After Vaccination 1 included 335 and 112 subjects for 20vPnC/Saline and 13vPnC/PPSV23 groups, respectively. The proportions of participants in Cohort 3 reporting any AEs from vaccination to 1 month after vaccination were similar in the 20vPnC and 13vPnC groups (15.2% after 20vPnC and 11.6% after 13vPnC). Tier 2 AEs reported from vaccination to

1 month after vaccination in Cohort 3 were  $\leq 2.1\%$  in both the 20vPnC and 13vPnC groups.

In Cohort 3, 1 participant in the 20vPnC group reported an SAE 1 month after vaccination, and 1 participant from each vaccine group reported an SAE between 1 month after vaccination and 6 months after vaccination. No SAEs were considered by the investigator to be related to study vaccine.

Two (2) (0.6%) participants in the 20vPnC group in Cohort 3 reported any NDCMC after vaccination through 1 month of follow-up. The proportions of participants in Cohort 3 who reported NDCMCs were  $\leq 1.8\%$  in the 20vPnC and 13vPnC groups within 6 months after vaccination.

### 6.3 Trial #3: 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

#### 6.3.1 Objectives

Primary Objectives:

- To describe the safety profile of 20vPnC.
- To demonstrate that the immune responses to the 20 serotypes induced by 20vPnC were equivalent across 3 lots.

Secondary Objectives:

- To describe the immune responses to 20vPnC in terms of 1) Fold rise in serotype-specific OPA titers from before to 1 month after vaccination; 2)  $\geq 4$ -Fold rise in serotype-specific OPA titers from before to 1 month after vaccination; and 3) Serotype-specific OPA titers  $\geq$  LLOQ 1 month after vaccination.

#### 6.3.2 Design Overview

This Phase 3, multicenter, randomized, double-blind study with a 4-arm parallel design was conducted at investigator sites in the United States. Approximately 1610 adults 18 through 49 years of age with no history of pneumococcal vaccination were planned to be enrolled and randomized to receive one of 3 lots of 20vPnC or 13vPnC. Participants were randomized into 1 of 4 groups in a 2:2:2:1 ratio (20vPnC Lot 1: 20vPnC Lot 2: 20vPnC Lot 3: 13vPnC) by site-based randomization.

#### 6.3.3 Population

Approximately 1610 adults 18 through 49 years of age with no history of pneumococcal vaccination.

#### 6.3.4 Study Treatments or Agents Mandated by the Protocol

All participants received a single dose (0.5-mL) of one of the 3 lots of 20vPnC or 13vPnC administered intramuscularly in the deltoid muscle of the nondominant arm by a staff member.

### *6.3.5 Directions for Use*

Please refer to the clinical reviewer's memo.

### *6.3.6 Sites and Centers*

Twenty-one sites in the United States.

### *6.3.7 Surveillance/Monitoring*

Please refer to the clinical reviewer's memo.

### *6.3.8 Endpoints and Criteria for Study Success*

Primary Safety Endpoints:

- Reported prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination
- Reported prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination
- Reported AEs within 1 month after vaccination
- Reported SAEs and newly diagnosed chronic medical conditions (NDCMCs) within 6 months after vaccination

Primary Immunogenicity Endpoint:

- Pneumococcal serotype-specific OPA titers 1 month after vaccination

### *6.3.9 Statistical Considerations & Statistical Analysis Plan*

The primary immunogenicity objective of the study was to demonstrate that the immune responses to the 20 serotypes induced by 20vPnC were equivalent across 3 lots. The lot-to-lot consistency was to be evaluated by each primary immunogenicity endpoint, serotype specific OPA titer 1 month after vaccination, using a 2-fold equivalence margin for each between-lot comparison of OPA titers.

#### Statistical Hypothesis:

$H_0: |\ln(\mu_1) - \ln(\mu_2)| \geq \ln(2) \text{ or } |\ln(\mu_1) - \ln(\mu_3)| \geq \ln(2) \text{ or } |\ln(\mu_2) - \ln(\mu_3)| \geq \ln(2)$ , where  $\ln(\mu_1)$   $\ln(\mu_2)$   $\ln(\mu_3)$  are the natural log-transformed OPA GMTs 1 month after vaccination from subjects receiving 20vPnC Lot 1, Lot 2, and Lot 3, respectively.

#### Sample Size Determination:

For each serotype, the natural log of OPA titers from the 3 lots were assumed to follow normal distributions with means of 0, 0, and  $\delta$ , with  $\delta$  being the true maximum difference in the serotype-specific OPA titers between any 2 lots. A  $\delta$  of 0.2 corresponded to an assumption that the true GMR of any lot to another lot was between 0.82 and 1.22.

The assumed standard deviations (SDs) for the 13 matching serotypes were based on results from the 13vPnC study 6115A1-004 in the same age group. The SDs for the 7 additional serotypes, which were not available in 6115A1-004, were assumed to be the median standard deviation from the 13 matching serotypes in that study. Given the proposed sample size and assumptions, the study had an overall power of 89.8% for declaring the overall equivalence of the 3 lots.

**Statistical Method and Success Criteria:** As the primary approach to calculate the GMR and CI for each serotype, a linear regression model that includes terms for age, corresponding baseline OPA titer, sex (male or female), smoking status (current smoker, ex-smoker, or never smoked), and 20vPnC lot (Lot 1, Lot 2, or Lot 3) was used to calculate the serotype-specific OPA GMR for each pair of lot comparisons (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3). The unadjusted serotype-specific OPA GMR and CI were also to be calculated for each of the serotypes by calculating differences in means and CIs on the natural log scale based on the t-distribution, then exponentiating the results. The 3 lots would be considered equivalent if each of the pairwise 2-sided 95% confidence intervals (CIs) for the geometric mean ratios (GMRs) of OPA titers was contained in the interval (0.5, 2.0). This required a total of 60 comparisons (3 pairwise between-lot comparisons for each of 20 serotypes).

### 6.3.10 Study Population and Disposition

#### 6.3.10.1 Populations Enrolled/Analyzed

The proportion of participants excluded from the evaluable immunogenicity population for each vaccine group was  $\leq 6.2\%$  (Table 17). Since the difference between the numbers of participants in the evaluable immunogenicity population and the all-available immunogenicity population was  $<10\%$ , no analyses on the all-available immunogenicity population were performed.

**Table 17. Evaluable and All-Available Immunogenicity Populations**

	20vPnC Lot 1	20vPnC Lot 2	20vPnC Lot 3	Pooled 20vPnC	13vPnC
	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized	489 (100.0)	490 (100.0)	486 (100.0)	1465 (100.0)	245 (100.0)
Evaluable immunogenicity population	463 (94.7)	473 (96.5)	456 (93.8)	1392 (95.0)	232 (94.7)
All-available immunogenicity population	474 (96.9)	481 (98.2)	470 (96.7)	1425 (97.3)	238 (97.1)

Source: Adapted from Table 6 in the CSR for Study B7471008.

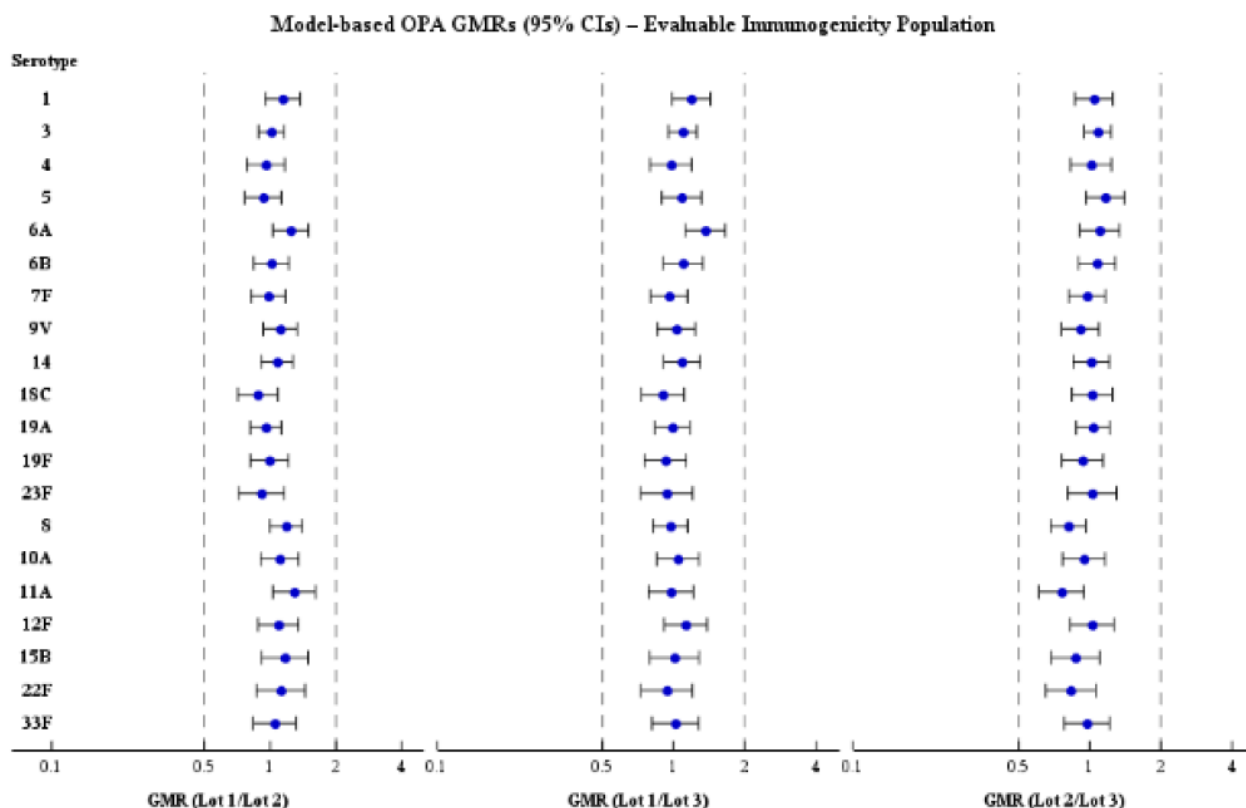
There was a relatively higher representation of female participants in each vaccine group (approximately 59% to 68%). Overall, the demographic characteristics and smoking history in three 20vPnC lots and 13vPnC group were similar.

### 6.3.11 Immunogenicity Analyses

#### 6.3.11.1 Analyses of Primary Endpoints

Lot consistency was demonstrated based on a 2-fold equivalence margin comparing the OPA GMTs between each pair of 20vPnC lots for each serotype. The 2-sided 95% CIs for the model-based estimate of serotype-specific OPA GMRs 1 month after vaccination for each pair of lot comparisons (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) are contained in the pre-specified interval (0.5, 2.0) for each of the 20 serotypes (Figure 6).

**Figure 6. Model-Based OPA GMRs With 95% CIs – Evaluable Immunogenicity Population**



Source: Figure 1 in the CSR for Study B7471008.

### 6.3.11.2 Analyses of Secondary Endpoints

- **Pneumococcal OPA GMFRs**

For each of the 20 vaccine serotypes, the OPA GMFR from before vaccination to 1 month after vaccination was generally similar across all 3 lots of 20vPnC, and ranged from 5.0 (serotype 3) to 175.5 (serotype 12F) in the 20vPnC Lot 1 group, from 5.0 (serotype 3 and 11A) to 174.6 (serotype 12F) in the 20vPnC Lot 2 group, and from 4.6 (serotype 3) to 175.7 (serotype 12F) in the 20vPnC Lot 3 group. The OPA GMFR in the pooled 20vPnC group ranged from 4.8 (serotype 3) to 175.3 (serotype 12F).

- **Proportion of participants achieving a  $\geq 4$ -fold rise in pneumococcal OPA titers**

For each of the 20 vaccine serotypes, the proportion of participants achieving a  $\geq 4$ -fold rise in OPA titers from before vaccination to 1 month after vaccination was generally similar across all 3 lots of 20vPnC, and ranged from 52.4% (serotype 11A) to 94.5% (serotype 6A) in the 20vPnC Lot 1 group, from 48.0% (serotype 11A) to 93.1% (serotype 6A and 12F) in the 20vPnC Lot 2 group, and from 42.2% (serotype 11A) to 93% (serotype 6A) in the 20vPnC Lot 3 group. The proportion of participants achieving a  $\geq 4$ -fold rise in OPA titers in the pooled 20vPnC group ranged from 47.4% (serotype 11A) to 93.5% (serotype 6A).

- Proportion of participants with pneumococcal OPA titers  $\geq$  LLOQ

For each of the 20 vaccine serotypes, the proportion of participants with OPA titers  $\geq$  LLOQ 1 month after vaccination was generally similar across all 3 lots of 20vPnC, and ranged from 80.3% (serotype 5) to 99.7% (serotype 10A and 22F) in the 20vPnC Lot 1 group, from 84.3% (serotype 5) to 100% (serotype 19A) in the 20vPnC Lot 2 group, and from 81.3% (serotype 5) to 99.5% (serotype 11A and 22F) in the 20vPnC Lot 3 group. The proportion of participants with OPA titers  $\geq$  LLOQ for the pooled 20vPnC group ranged from 82.0% (serotype 5) to 99.6% (serotype 19A).

#### 6.3.11.4 Subpopulation Analyses

Robust immune responses to all 20 vaccine serotypes 1 month after vaccination in the pooled 20vPnC group were observed for each of the sex and race subgroups based on OPA GMTs before and 1 month after vaccination by sex and race.

#### 6.3.11.5 Exploratory and Post Hoc Analyses

N/A

#### 6.3.12 Safety Analyses

The proportions of participants who reported local reactions within 10 days after vaccination with 1 of the 3 lots of 20vPnC or 13vPnC were similar across each of the 20vPnC lot groups, and the group of all 20vPnC recipients (pooled) was similar to the 13vPnC control (Table 18). The most frequent local reaction across all vaccine groups was pain at injection site.

**Table 18. Local Reactions Within 10 Days After Vaccination**

	20vPnC Lot 1 (N = 486)	20vPnC Lot 2 (N = 489)	20vPnC Lot 3 (N = 481)	Pooled 20vPnC (N = 1456)	13vPnC (N = 243)	Pooled 20vPnC vs 13vPnC
Local Reaction	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	Difference (95% CI)
Any Redness	30 (6.2) (4.2, 8.7)	39 (8.0) (5.7, 10.7)	33 (6.9) (4.8, 9.5)	102 (7.0) (5.7, 8.4)	15 (6.2) (3.5, 10.0)	15 (6.2) (3.5, 10.0)
Any Swelling	52 (10.7) (8.1, 13.8)	39 (8.0) (5.7, 10.7)	33 (6.9) (4.8, 9.5)	124 (8.5) (7.1, 10.1)	21 (8.6) (5.4, 12.9)	-0.1 (-4.5, 3.2)
Pain at injection site	402 (82.7) (79.1, 86.0)	386 (78.9) (75.1, 82.5)	358 (74.4) (70.3, 78.3)	1146 (78.7) (76.5, 80.8)	184 (75.7) (69.8, 81.0)	3.0 (-2.4, 9.1)
Any local reaction	403 (82.9) (79.3, 86.2)	386 (78.9) (75.1, 82.5)	364 (75.7) (71.6, 79.4)	1153 (79.2) (77.0, 81.2)	184 (75.7) (69.8, 81.0)	3.5 (-2.0, 9.6)

Source: Adapted from Table 12 in the CSR for Study B7471008.

The proportions of participants who reported systemic events within 7 days after vaccination with 1 of the 3 lots of 20vPnC or 13vPnC were similar across each of the 20vPnC lot groups, and the group of all 20vPnC recipients (pooled) was similar to the 13vPnC control (Table 19). The most frequently reported systemic event across all

vaccine groups was muscle pain. The proportions of participants that reported antipyretic or pain medication use was similar across all vaccine groups.

The proportions of participants reporting any AEs from vaccination to 1 month after vaccination were  $\leq 7.4\%$  and were similar across all 3 lots of 20vPnC, and 20vPnC (pooled) was similar to the 13vPnC control. Among the 1463 subjects in the pooled 20vPnC group and 245 subjects in the 13vPnC control group, the proportions of participants reporting any AEs from vaccination to 1 month after vaccination were 6.8% and 5.3%, respectively. The proportions of participants who reported AEs from vaccination to 1 month after vaccination that were considered by the investigator to be related to study vaccine were 0.3% and 0.8% for the pooled 20vPnC and 13vPnC groups, respectively.

**Table 19. Systemic Events Within 7 Days After Vaccination**

	20vPnC Lot 1 (N = 486)	20vPnC Lot 2 (N = 489)	20vPnC Lot 3 (N = 481)	Pooled 20vPnC (N = 1456)	13vPnC (N = 243)	Pooled 20vPnC vs 13vPnC
Systemic Event	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	Difference (95% CI)
Fever ( $\geq 38.0^{\circ}\text{C}$ )	8 (1.6) (0.7, 3.2)	4 (0.8) (0.2, 2.1)	6 (1.2) (0.5, 2.7)	18 (1.2) (0.7, 1.9)	2 (0.8) (0.1, 2.9)	0.4 (-1.7, 1.4)
Fatigue	229 (47.1) (42.6, 51.7)	222 (45.4) (40.9, 49.9)	242 (50.3) (45.7, 54.9)	693 (47.6) (45.0, 50.2)	106 (43.6) (37.3, 50.1)	4.0 (-2.8, 10.6)
Headache	179 (36.8) (32.5, 41.3)	169 (34.6) (30.3, 39.0)	179 (37.2) (32.9, 41.7)	527 (36.2) (33.7, 38.7)	92 (37.9) (31.7, 44.3)	-1.7 (-8.4, 4.7)
Muscle pain	301 (61.9) (57.5, 66.3)	299 (61.1) (56.7, 65.5)	304 (63.2) (58.7, 67.5)	904 (62.1) (59.5, 64.6)	147 (60.5) (54.0, 66.7)	1.6 (-4.9, 8.3)
Joint pain	90 (18.5) (15.2, 22.3)	78 (16.0) (12.8, 19.5)	77 (16.0) (12.8, 19.6)	245 (16.8) (14.9, 18.8)	34 (14.0) (9.9, 19.0)	2.8 (-2.4, 7.2)
Any systemic event	370 (76.1) (72.1, 79.9)	366 (74.8) (70.8, 78.6)	375 (78.0) (74.0, 81.6)	1111 (76.3) (74.0, 78.5)	176 (72.4) (66.4, 77.9)	3.9 (-1.8, 10.2)
Use of antipyretic or pain medication	109 (22.4) (18.8, 26.4)	96 (19.6) (16.2, 23.4)	115 (23.9) (20.2, 28.0)	320 (22.0) (19.9, 24.2)	44 (18.1) (13.5, 23.5)	3.9 (-1.8, 8.8)

Source: Adapted from Table 13 in the CSR for Study B7471008.

The proportion of participants who reported at least 1 SAE within 6 months after vaccination in the pooled 20vPnC group was 0.7%; no SAEs were reported in the 13vPnC group. The proportions of participants who reported at least 1 SAE from vaccination to 1 month after vaccination and from 1 month after vaccination to 6 months after vaccination in the pooled 20vPnC group were 0.3%. No reported SAEs were considered by the investigator to be related to study vaccine.

Two percent or fewer of the participants in any vaccine group reported at least 1 NDCMC within 6 months after vaccination. No NDCMCs reported were considered by the investigator to be related to study vaccine.

#### 6.4 Supportive Studies

N/A

### 7. INTEGRATED OVERVIEW OF EFFICACY

The 6 trials listed in Table 1 supporting this submission are randomized controlled trials that evaluated the safety and immunogenicity of a single dose of 20vPnC. Each of the Phase 3 trials had distinct objectives, designs, and populations, and no formal meta-analysis of immunogenicity data pooled across trials was conducted. General observations across the Phase 3 trials are as follows:

- 20vPnC elicited immune responses that support the proposed indication.
  1. Responses to the 13 matched and to 6 of the 7 additional serotypes were noninferior to responses elicited by 13vPnC and PPSV23, respectively, in pneumococcal vaccine naïve adults  $\geq 60$  years of age.
  2. Only serotype 8 missed the statistical noninferiority criterion for the primary endpoint; however, based on the totality of data, results indicate that the pneumococcal capsular polysaccharide conjugate of serotype 8 will perform similarly to the other pneumococcal conjugate components in 20vPnC in preventing IPD and pneumonia.
  3. 20vPnC also elicited immune responses to all 20 vaccine serotypes in pneumococcal vaccine naïve adults 50 through 59 and 18 through 49 years of age that were noninferior to responses in pneumococcal vaccine naïve adults 60 through 64 years of age.
- Lot consistency was demonstrated; all 3 lots of 20vPnC elicited similar and robust immune responses at 1 month after vaccination to each of the 20 serotypes in pneumococcal vaccine naïve adults 18 through 49 years of age.
- 20vPnC elicited immune responses to all 20 vaccine serotypes in adults  $\geq 65$  years of age previously vaccinated with 13vPnC, PPSV23, or 13vPnC followed by PPSV23.
- Younger subjects had higher immune responses in the subgroup analysis by age (a similar pattern seen with 13vPnC). 20vPnC elicited responses in the subgroup of subjects with health conditions and other factors (current smoker) that placed them at increased risk of pneumococcal disease. Slightly lower OPA GMTs were observed in the subgroup of subjects with health conditions and other factors.

In the 2 trials that enrolled pneumococcal vaccine naïve subjects, B7471007 and B7471008, 5597 subjects received study vaccine, 3639 of whom received 20vPnC. Of the 3639 20vPnC recipients, 3466 were included in the evaluable immunogenicity population; 1436 were  $\geq 60$  years of age, 321 were 50 through 59 years, and 1709 were 18 through 49 years. Most subjects were female (59.1% to 66.9% across vaccine groups of



different age ranges); 73.6% to 86.6% of subjects were White, and 9.5% to 18.0% were Black or African American.

In the 2 trials that enrolled adults  $\geq 65$  years of age with different prior pneumococcal vaccine status, B7471007 and B7471006, 1885 subjects received study vaccine, 1138 of whom received 20vPnC. Of the 1138 20vPnC recipients, 1101 were included in the evaluable immunogenicity population; 490 were naïve to pneumococcal vaccine, and 611 had been previously vaccinated with PPSV23 (247 subjects), 13vPnC (243 subjects), or both 13vPnC and PPSV23 (121 subjects). Most subjects were 65 through 69 years of age (55.6% to 62.4% across vaccine groups with different prior pneumococcal vaccine status), followed by subjects 70 through 79 (31.0% to 41.3%), and subjects  $\geq 80$  (2.0% to 9.5%); 50.4% to 58.2% of subjects were female; 89.0% to 93.4% were White, and 3.3% to 9.6% were Black or African American. There were more Hispanic/Latino subjects in the 2 naïve groups (B7471007: 16.7% in the 20vPnC/saline group and 15.6% in the 13vPnC/PPSV23 group) than in subjects with prior vaccine (B7471006: range 1.6% to 2.5%).

Within each of the Phase 3 trials, immunogenicity results (not presented in this review) were analyzed by sex (B7471007, B7471008, B7471006), race (B7471007, B7471008), country ( $\geq 65$  years of age in B7471007), and age subgroup  $\geq 60$  years (B7471007). Subgroup analysis by sex in Study B7471006 and Cohort 1 in Study B7471007, in which older subjects were enrolled, appears to demonstrate that females generally had higher immune responses (OPA GMTs) than males for many serotypes among all 20 serotypes while females and males had similar OPA GMTs for the rest of the serotypes. In the two Phase 3 trials in which immunogenicity data were analyzed by race, the immune responses to all 20 vaccine serotypes 1 month after 20vPnC were generally similar for most vaccine serotypes relative to 13vPnC. In B7471007 Cohort 1, the number of Swedish subjects with OPA titers included in the immunogenicity summary was limited (between 67 to 83 subjects) and OPA GMTs after 20vPnC relative to after 13vPnC were higher in Swedish subjects compared with U.S. subjects for most of the 13 matched serotypes. In B7471007, the percentages of subjects in each age subgroup  $\geq 60$  years (Cohort 1, safety population) were: 60 through 64 years, 66.2%; 65 through 69 years, 20.8%; 70 through 79 years, 10.6%; and  $\geq 80$  years, 2.3%. The responses to 20vPnC relative to 13vPnC or PPSV23 from each subgroup were generally similar for most 20vPnC serotypes and the GMTs and GMFRs were generally lower in the oldest age subgroups.

*Reviewer's Comment:*

*The applicant concluded that in each of the three Phase 3 trials, no clinically important differences in immune response were observed between men and women. However, by comparing the applicant's subgroup analysis by sex in Study B7471006 (Table 14.4 in the CSR) and Cohort 1 in Study B7471007 (Tables 14.70 and 14.74 in the CSR), in which older subjects were enrolled, it appears that women generally had higher immune responses (OPA GMTs) than men for many of the 20 serotypes. However, this observed difference of immune responses between sexes was not noted in B7471008 and Cohort 3 in B7471007, in which younger adult subjects were enrolled.*

When I discussed this immunogenicity subgroup analysis by sex with the clinical reviewer, Dr. Mongeau, she shared her experience with the review of 13vPnC and mentioned that women 50 years and older had numerically higher OPA GMTs for most of the 13 serotypes in one pivotal study with 13vPnC. In another pivotal study conducted in adults 70 years and older, women had numerically higher OPA GMTs for about 6 of the 13 serotypes. However, in the CAPiTA trial with 13vPnC, in which efficacy of 13vPnC against IPD and pneumonia was demonstrated, the VE estimates among women and men did not appear to differ based on the primary endpoint (Table 20). Therefore, the increased immune responses in women may not reach clinical significance or indicate better protection against IPD and pneumonia. Dr. Mongeau also noted that women generally have higher rates of solicited local and systemic adverse reactions compared to men in 20vPnC studies, which was observed with 13vPnC as well. She commented that the finding of increased immune responses and reactogenicity in women is consistent with literature on sex-related differences with respect to other vaccines, including pneumococcal vaccines.

Although the applicant concluded that no clinically important differences in immune responses were observed between men and women across the Phase 3 trials, this statement will not be included in the prescribing information.

**Table 20. CAPiTA trial VE for subgroups, Primary Efficacy Endpoint of First Case of Confirmed VT Pneumococcal CAP**

Efficacy Endpoint Subgroup	Total # of Cases	PCV13 N=42,240 n	Placebo N=42,256 n	VE (%)	CI <sup>a</sup>
<b>First case of confirmed VT pneumococcal CAP</b>	139	49	90	45.56	(21.82, 62.49)
Age < 75	87	28	59	52.54	(24.38, 70.86)
Age ≥ 75	52	21	31	32.26	(-21.72, 63.00)
Age ≥ 75 and < 85	43	15	28	46.43	(-3.78, 73.41)
Age ≥ 85	9	6	3	-100.0	(-1135.92, 57.29)
Male	95	34	61	44.26	(13.85, 64.48)
Female	44	15	29	48.28	(0.32, 74.23)
Race: White	134	48	86	44.19	(19.64, 61.63)
Race: Nonwhite	5	1	4	75.00	(-152.63, 99.49)
Smoking	32	12	20	40.00	(-28.87, 73.26)
Nonsmoking	107	37	70	47.14	(20.18, 65.51)

Abbreviation: CAP = community-acquired pneumonia; CI = confidence interval; VE = vaccine efficacy; VT = vaccine-type; SSUAD: serotype-specific urinary antigen detection.

Note: The SSUAD assay does not distinguish between the vaccine-type serotype and closely related serotype(s) within their respective serogroup for 6A and 6C; 7F and 7A; 9V and 9A; 18C and 18A, 18B, and 18F.

<sup>a</sup> CI was derived using the Clopper-Pearson method. The lower limit of this CI must exceed 0.0 to conclude efficacy for this final analysis. A 95.2% CI (alpha = 0.048) was applied to row "First case of confirmed VT pneumococcal CAP" to control for one interim review. A 95% CI was applied to all subgroup rows, and type I error control for multiple comparisons across individual subgroups was not applied.

Source: Table 17 in clinical reviewer's memo for CAPiTA trial.

## 8. INTEGRATED OVERVIEW OF SAFETY

The three Phase 1 and Phase 2 trials evaluated 20vPnC administered to adults 18 through 49 years of age (B7471001 and B7471005) and 60 through 64 years of age (B7471002). These trials demonstrated that 20vPnC was well tolerated in this population, with a safety profile similar to that of 13vPnC, and supported the initiation of Phase 3 studies of 20vPnC in adults. Each Phase 3 trial had distinct study objectives and design, including different subject populations with regard to age and prior pneumococcal vaccination status. The only overlapping subject populations across studies are pneumococcal vaccine naïve subjects 18-49 years of age from B7471007 Cohort 3 and B7471008. Therefore, only safety data for subjects 18-49 years of age were pooled.

The methods for safety data collection and analysis were the same in all three Phase 3 trials. Safety was evaluated based on the following parameters.

- Specific reactions and events and use of antipyretic or pain medications were reported by subjects in response to specific prompts using an electronic diary (e-diary). These e-diary events included:
  - local reactions (redness, swelling, and pain at the injection site) occurring within 10 days after vaccination;
  - systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 7 days after vaccination; and
  - use of antipyretic or pain medications within 7 days after vaccination.
- Adverse events (AEs) occurring within 1 month after vaccination;
- Serious adverse events (SAEs) occurring within 6 months after vaccination;
- Newly diagnosed chronic medical conditions (NDCMCs) occurring within 6 months after vaccination.

Across the Phase 3 trials, 6470 subjects were vaccinated; 4263 subjects received 20vPnC and 2207 received control vaccine. Pneumococcal vaccine naïve subjects (5597) were enrolled and vaccinated in B7471007 ( $\geq 18$  years of age) and B7471008 (18-49 years of age): 3639 received 20vPnC and 1958 received control vaccine (13vPnC or 13vPnC/PPSV23). Across vaccine groups, 53.5% were  $\geq 60$  years, 8.0% were 50 through 59 years, and 38.5% were 18 through 49 years of age. Table 21 presents subjects reporting each local reaction within 10 days after vaccination in the pooled dataset for subjects 18-49 years of age. The local reactions were similar after 20vPnC or 13vPnC. The most frequently reported local reaction was pain at the injection site (79.2% after 20vPnC, 77.7% after 13vPnC).

**Table 21. Local Reactions Within 10 Days After Vaccination in 18 through 49 years of age – Pooled population**

	20vPnC (N = 1791)	13vPnC (N = 355)
Local Reaction	n (%)	n (%)
Any Redness	132 (7.4)	26 (7.3)
Any Swelling	163 (9.1)	35 (9.9)
Pain at injection site	1418 (79.2)	276 (77.7)
Any local reaction	1425 (79.6)	276 (77.7)

Source: Adapted from Table 4 in the summary of clinical safety submitted to Section 2.7.4.

Table 22 presents subjects reporting each systemic event within 7 days after vaccination in the pooled dataset for subjects 18-49 years of age. The systemic events were similar after 20vPnC or 13vPnC. The most frequently reported local reaction was muscle pain (62.9% after 20vPnC; 64.8% after 13vPnC).

**Table 22. Systemic Events Within 7 Days After Vaccination in 18 through 49 years of age – Pooled population**

	20vPnC (N = 1791)	13vPnC (N = 355)
Systemic Event	n (%)	n (%)
Fever ( $\geq 38.0^{\circ}\text{C}$ )	22 (1.2)	4 (1.1)
Fatigue	836 (46.7)	155 (43.7)
Headache	657 (36.7)	130 (36.6)
Muscle pain	1127 (62.9)	230 (64.8)
Joint pain	290 (16.2)	54 (15.2)
Any systemic event	1377 (76.9)	269 (75.8)
Use of antipyretic or pain medication	406 (22.7)	70 (19.7)

Source: Adapted from Table 6 in the summary of clinical safety submitted to Section 2.7.4.

Among subjects naïve to pneumococcal vaccine (B7471007 and B7471008), the proportions of subjects reporting any AE within 1 month after vaccination were similar across age groups and were similar for subjects who received 20vPnC (8.4% to 10.2%) and 13vPnC (7.3% to 11.1%). Few AEs (MedDRA Preferred Terms) were reported for more than 1% of subjects in either vaccine group within each age group (Table 23).

**Table 23. Adverse Events Reported in  $\geq 1\%$  Subjects in At Least One Group From Vaccination to 1 Month After Vaccination – Pneumococcal Vaccine Naïve Subjects by Study and Age Group –Safety Population**

	B7471007 $\geq 60$ Years		B7471007 50-59 Years		B7471007 and B7471008 18-49 Years	
	20vPnC (N = 1507)	13vPnC (N = 1490)	20vPnC (N = 334)	13vPnC (N = 111)	20vPnC (N = 1798)	13vPnC (N = 357)
Systemic Event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Event	148 (9.8)	166 (11.1)	34 (10.2)	9 (8.1)	151 (8.4)	26 (7.3)
Infections and Infestations	46 (3.1)	47 (3.2)	17 (5.1)	6 (5.4)	74 (4.1)	14 (3.9)
Upper respiratory tract infection	12 (0.8)	8 (0.5)	4 (1.2)	3 (2.7)	16 (0.9)	1 (0.3)
Injury, poisoning and procedural Complications	12 (0.8)	23 (1.5)	6 (1.8)	0	13 (0.7)	1 (0.3)
Fall	5 (0.3)	7 (0.5)	4 (1.2)	0	3 (0.2)	0

Source: Table 8 in the summary of clinical safety submitted to Section 2.7.4.

Among subjects  $\geq 65$  years of age by prior pneumococcal vaccination status (B7471006 and B7471007), the proportions of subjects reporting any AE within 1 month after vaccination were similar for subjects who received 20vPnC (4.9% to 10.4%) or control vaccines (9.0% to 11.6%). Few AEs (MedDRA Preferred Terms) were reported for more than 1% of subjects in any vaccine group (Table 24).

**Table 24. Adverse Events Reported in  $\geq 1\%$  of Subjects in at Least One Group From Vaccination to 1 Month After Vaccination – Subjects  $\geq 65$  Years of Age by Study and Prior Pneumococcal Vaccination Status – Safety Population**

	B7471007 Naïve		B7471006 Prior PPSV23		B7471006 Prior 13vPnC		B7471006 Prior 13vPnC and PPSV23
	20vPnC (N = 514)	13vPnC (N = 498)	20vPnC (N = 253)	13vPnC (N = 122)	20vPnC (N = 246)	13vPnC (N = 127)	20vPnC (N = 125)
Systemic event	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any event	47 (9.1)	58 (11.6)	19 (7.5)	11 (9.0)	12 (4.9)	14 (11.0)	13 (10.4)
Infections and Infestations	14 (2.7)	15 (3.0)	8 (3.2)	6 (4.9)	3 (1.2)	2 (1.6)	3 (2.4)
Nasopharyngitis	1 (0.2)	4 (0.8)	3 (1.2)	1 (0.8)	0	0	0
Urinary tract infection	1 (0.2)	1 (0.2)	0	2 (1.6)	1 (0.4)	0	1 (0.8)
Nervous system disorders	3 (0.6)	4 (0.8)	4 (1.6)	0	3 (1.2)	2 (1.6)	0
Dizziness	0	0	2 (0.8)	0	1 (0.4)	2 (1.6)	0

Source: Table 9 in the summary of clinical safety submitted to Section 2.7.4.

Among subjects naïve to pneumococcal vaccine, the proportions of subjects reporting one or more SAEs within 6 months after vaccination were similar after 20vPnC ( $\leq 2.4\%$ ) or

13vPnC ( $\leq 1.9\%$ ). SAEs were reported at a slightly higher frequency among subjects  $\geq 60$  years of age (2.4% after 20vPnC, 1.9% after 13vPnC) than in younger age groups ( $\leq 0.9\%$  after either vaccine). None of the SAEs reported were considered by the investigator to be related to study vaccine. The most frequently reported SAEs were in the Infections and infestations.

Among subjects  $\geq 65$  years of age by prior pneumococcal vaccination status, the proportions of subjects reporting one or more SAEs within 6 months after vaccination were similar after 20vPnC ( $\leq 3.7\%$ ) or control vaccine ( $\leq 2.8\%$ ). None of the SAEs reported were considered related to study vaccine by the investigator.

The proportions of subjects reporting NDCMCs within 6 months after vaccination was low, both among subjects naïve to pneumococcal vaccine ( $\leq 2.3\%$  after both 20vPnC and 13vPnC) and among subjects  $\geq 65$  years of age by prior pneumococcal vaccination status ( $\leq 4.0\%$  after 20vPnC;  $\leq 2.4\%$  after control vaccines). The most frequently reported NDCMCs were in the SOC of Musculoskeletal and connective tissue disorders, Metabolism and nutrition disorders (predominantly Type 2 diabetes mellitus), and Vascular disorders (predominantly hypertension). Overall, the NDCMCs reported were generally diseases and conditions often observed in adults in these age groups.

## 9. ADDITIONAL STATISTICAL ISSUES

N/A

## 10. CONCLUSIONS

The pre-specified success criteria were met for all primary immunogenicity comparisons except for the narrowly missed non-inferiority comparison of the serotype 8 immune responses between 20vPnC and 13vPnC in the pivotal study B7471007. There were no potential safety concerns identified in the studied population. Overall, from the statistical perspective, the submitted clinical study results support the approval of this application.