BLA Clinical Review Memorandum

Application Type	Biologics License Application
STN	125731/0
CBER Received Date	October 8, 2020
PDUFA Goal Date	June 8, 2021
Division / Office	Division of Vaccines and Related Product Applications (DVRPA)/Office of Vaccines Research and Review (OVRR)
Priority Review	Yes
Reviewer Name(s)	Tina Khoie Mongeau, MD, MPH Medical Officer, Clinical Review Branch 1 (CRB1)
Review Completion/ Stamped Date	June 8, 2021
Supervisory Concurrence	R. Douglas Pratt, MD, MPH Associate Director for Medical Affairs, DVRPA/OVRR
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Applicant	Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc.
Established Name	Pneumococcal 20-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)
(Proposed) Trade Name	Prevnar 20
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	• 2.2 µg of each of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F saccharides and 4.4 µg of *S. pneumoniae* serotype 6B saccharides • ~51 µg diphtheria cross reactive material (CRM_{197}) carrier protein* • 125 µg aluminum as aluminum phosphate adjuvant * CRM protein is approximate and dependent on the saccharide-to-protein ratio of the saccharides used in the formulation
Dosage Form and Route of Administration	Suspension for intramuscular injection
Dosing Regimen	Single dose
Indications and Intended Population(s)	Active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults ≥18 years of age
Orphan Designated	No

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GLOSSARY

ABCs	Active Bacterial Core surveillance
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
BLA	Biologics License Application
CAP	community-acquired pneumonia
CAPiTA	Community Acquired Pneumonia Immunization Trial in Adults
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CFR	Code of Federal Regulations
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRM197	cross-reacting material 197 (carrier protein)
CSF	cerebrospinal fluid
CSR	clinical study report
cTnI	cardiac troponin I
cTnT	cardiac troponin T
DMC	Data Monitoring Committee
DVRPA	Division of Vaccines and Related Products Applications
ECG	electrocardiogram
EOP2	end of Phase 2
FDA	Food and Drug Administration
FIH	first-in-human
GERD	gastrointestinal esophageal reflux disease
GMFR	geometric mean fold rise
GMT	geometric mean titer
IND	Investigational New Drug (application to the FDA)
IPD	invasive pneumococcal disease
IR	Information Request
ISS	Integrated Summary of Safety
LL	lower limit
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trial
NDCMC	newly diagnosed chronic medical condition
OPA	opsonophagocytic activity
OVRR	Office of Vaccines Research and Review
PCRU	Pfizer Clinical Research Unit
PCV7	Prevnar 7-valent pneumococcal conjugate vaccine
PCV13	Prevnar 13-valent pneumococcal conjugate vaccine
PCV20	Prevnar 20-valent pneumococcal conjugate vaccine
PeRC	Pediatric Review Committee
PPSV23	Pneumovax 23-valent pneumococcal polysaccharide vaccine
PREA	Pediatric Research Equity Act
PS	polysaccharide
PT	Preferred Term
SAE	serious adverse event
sBLA	Supplemental Biologics License Application

SD	standard deviation
SOC	System Organ Class
STN	Submission Tracking Number
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed
U.S.	United States
VT	vaccine type

1. Executive Summary

Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc., submitted this Biologics License Application (BLA) for their Pneumococcal 20-valent Conjugate Vaccine (proposed proprietary name, Prevnar 20), which is a successor to their Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein; Prevnar 13). Prevnar 20 is composed of capsular polysaccharides derived from the 13 *Streptococcus pneumoniae* serotypes contained in Prevnar 13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and from 7 additional pneumococcal serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F), each individually conjugated to non-toxic diphtheria cross reactive material (CRM_{197}) protein. The proposed indications for Prevnar 20 (PCV20) are for the active immunization of adults 18 years of age and older for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F. The proposed regimen consists of a single intramuscular injection.

Under this BLA, Wyeth is seeking traditional approval for the invasive pneumococcal disease (IPD) indication for all 20 serotypes in PCV20, as well as for the pneumonia indication for the Prevnar 13 (PCV13) serotypes in the vaccine. Wyeth has also submitted an accelerated approval request for the pneumonia indication for the 7 new non-PCV13 serotypes in the vaccine.

Background

Streptococcus pneumoniae is a leading cause of disease and death among older adults in the United States (U.S.). *S. pneumoniae* colonize the nasopharynx and can cause non-invasive disease (e.g., non-bacteremic pneumonia) as well as invasive disease (e.g., bacteremia and meningitis) in adults. Non-bacteremic pneumococcal pneumonia is a more common pneumococcal disease manifestation than IPD in adults.

Currently, there are two pneumococcal vaccines licensed and available in the U.S. for the prevention of pneumococcal disease in adults, Pneumovax® 23 (Pneumococcal Vaccine, Polyvalent: Merck Sharp & Dohme Corp.) and PCV13.

Pneumovax 23, a pneumococcal polysaccharide vaccine (PPSV23), is approved for the prevention of pneumococcal disease caused by the 23 vaccine serotypes in persons ≥50 years of age and persons ≥2 years of age who are at increased risk of pneumococcal disease. Each 0.5 mL dose contains 25 µg of purified (unconjugated) capsular polysaccharide from each of 23 pneumococcal serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22, 23F, and 33F) (Pneumovax 23, prescribing information). Available data suggest that the PPSV23 vaccine protects adults and the elderly against IPD, however no consistent vaccine effect has been observed for prevention of pneumonia (Gruber et al. 2008; Conaty et al. 2004). PPSV23 has been the only pneumococcal vaccine licensed in the U.S. for adults for the prevention of pneumococcal disease caused by the 7 new serotypes in PCV20. These 7 serotypes are responsible for a substantial proportion of the current burden of invasive and noninvasive pneumococcal disease in adults globally.

PCV13 was the first pneumococcal conjugate vaccine licensed for use in adults in the United States. It is a glycoconjugate vaccine consisting of purified capsular polysaccharide antigens of 13 *S. pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) individually linked to non-toxic diphtheria CRM_{197} protein. On December 30, 2011, the Center for Biologics Evaluation and Research (CBER) approved PCV13 for active immunization for the

prevention of invasive disease and pneumonia caused by the thirteen S*. pneumoniae* serotypes contained in the vaccine in persons ≥50 years of age based on an immunologic surrogate endpoint (opsonophagocytic activity (OPA) titer) as defined in the Accelerated Approval regulations (21 CFR 601.41). As a condition of accelerated approval, Wyeth completed a postmarketing study that confirmed and described the efficacy of PCV13 for the approved indications. On July 11, 2016, CBER approved a Supplemental BLA (sBLA) to expand the use of PCV13 for the approved indications to adults 18 through 49 years of age based on immunologic bridging studies.

PCV20 Clinical Development Program

IPD Indication

The PCV20 Phase 3 clinical development program uses an approach in which vaccine effectiveness against IPD caused by the 20 vaccine serotypes and against pneumonia caused by the 13 pneumococcal serotypes in PCV13 is inferred in adults ≥60 years of age from immunologic comparability (using an agreed-upon pre-specified non-inferiority criterion) to pneumococcal vaccines licensed in the U.S. CBER agreed that PCV20 effectiveness in younger age groups (18 through 49 and 50 through 59) could be supported by immunobridging to the established effectiveness in adults 60 through 64 years. A randomized, active-controlled efficacy trial of PCV20 was not considered feasible due to the sample size that would be required. A placebo-controlled trial was also considered not ethically justifiable in the U.S. where, at the time of PCV20 development, PCV13 was recommended routinely for adults ≥65 years of age, as well as for adults <65 years of age with certain underlying medical conditions that increase the risk of serious pneumococcal disease.

Pneumonia Indication

Although there is no established immune correlate of protection in adults (i.e., a threshold for an immune marker predictive of protection against pneumococcal disease applicable to all serotypes), the basis of the agreed upon licensure approach relies on the acceptance of OPA antibody titer as an established immunologic parameter that can be used to support traditional approval of new, higher valency pneumococcal conjugate vaccines for the prevention of IPD caused by any vaccine serotype, and the prevention of pneumonia caused by the 13 serotypes in PCV13. CBER considered this approach acceptable for PCV20 because: 1) OPA reflects relevant *in vivo* mechanisms of protection against pneumococcal disease; 2) efficacy against pneumonia caused by PCV13 serotypes had been confirmed in a clinical endpoint study (6115A1-3006; NCT 00744263); and 3) PCV20 and PCV13 vaccines have nearly identical manufacturing processes for the 13 common serotypes. A similar approach was used to support the initial licensure of PCV13 in infants and young children (see Section 2.3) for the prevention of IPD caused by the 13 vaccine serotypes and the prevention of otitis media caused by the original 7 serotypes in Prevnar (PCV7) (the first U.S.-licensed pneumococcal conjugate vaccine that was approved for use in infants and toddlers based on efficacy confirmed in clinical endpoint studies).

CBER did not consider immunogenicity data alone as sufficient to support a non-invasive disease indication (i.e., pneumonia or otitis media) for non-PCV13 serotypes in PCV20, because antibody levels have not been found to be indicative of prevention of non-invasive pneumococcal disease.

Similar to the PCV13 licensure approach for the adult pneumonia indication, approval of PCV20 for the prevention of pneumonia in adults caused by the 7 new serotypes is based on an

immunologic surrogate endpoint (OPA titer), as defined in the Accelerated Approval regulations (21 CFR 601.41), that is reasonably likely to predict prevention of pneumococcal pneumonia caused by the 7 new vaccine serotypes in PCV20. This regulation applies to biologics intended to treat or prevent serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (21 CFR 601.40). CBER considers protection of adults ≥18 years of age from non-bacteremic pneumococcal pneumonia to be a meaningful therapeutic benefit over existing treatments (i.e., PCV13 and PPSV23). Because pneumococcal pneumonia is a serious condition and PCV20 will provide meaningful therapeutic benefit to patients over existing treatments, the proposed indication meets the qualifying criteria for accelerated approval. As a condition of accelerated approval, Wyeth will conduct a post-approval real-world observational effectiveness study as a confirmatory study to verify and describe the clinical benefit for the prevention of pneumonia caused by the 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) in adults ≥ 65 years of age. CBER agreed that it would be reasonable to target adults ≥ 65 years of age for enrollment in the confirmatory study because of their higher rates of pneumococcal pneumonia. CBER considered that if PCV20 effectiveness against pneumonia due to the 7 new serotypes was confirmed in adults ≥ 65 years of age, it would be reasonable to infer vaccine effectiveness in adults 60 through 64 years of age. CBER also agreed that PCV20 vaccine effectiveness against pneumonia due to the 7 new serotypes in adults 18 through 49 years and adults 50 through 59 years of age could be bridged to the effectiveness in adults 60 through 64 years of age.

This application includes data obtained from 7048 immunocompetent adults ≥18 years of age in the U.S. and Sweden enrolled in 6 clinical trials; 4552 received PCV20, and 2496 received an active control vaccine (Table 1).

Phase 3 Non-inferiority Immunogenicity Study

Study B7471007 was the Phase 3 non-inferiority immunogenicity trial evaluating a single dose of PCV20 in pneumococcal-vaccine-naïve adults ≥18 years of age (Section 6.1). Effectiveness was inferred via non-inferiority comparisons to one of two U.S.-licensed pneumococcal vaccines (PCV13 or PPSV23) based on functional OPA titers to each of the 20 vaccine serotypes as measured by a microcolony OPA assay. PCV13 was selected as the active control for the non-inferiority comparisons for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (contained in both PCV13 and PCV20). PPSV23 was selected as an active control for the non-inferiority comparisons for serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F (contained in both PPSV23 and PCV20). PCV13 was also the active control for safety. For the primary immunogenicity objectives, non-inferiority comparisons between PCV20 and the respective active control were performed in subjects ≥60 years of age (Cohort 1). The secondary objectives aimed to bridge immune responses to PCV20 in younger cohorts (18 through 49 years and 50 through 59 years) to PCV20 responses in subjects 60 through 64 years of age in the older cohort (Cohort 1 subset).

For the primary endpoint analyses in adults ≥60 years of age, 19 of the 20 vaccine serotypes met the pre-specified 2-fold non-inferiority criterion (Tables 9 and 10). For serotype 8, the lower limit (LL) of the 95% CI for the GMT ratio ($GMT_{PCV20}/GMT_{active\ control}$) was 0.49, which was only slightly less than the pre-specified LL of 0.5. In supportive secondary analyses, 77.8% of subjects ≥60 years of age achieved a ≥4-fold increase in anti-serotype 8 OPA titers (Table 14).

The effectiveness of PCV20 in each of the younger cohorts (18 through 49 years of age and 50 through 59 years of age) was demonstrated by immunobridging to the established effectiveness in 60 through64-year-old subjects (Cohort 1 subset). The lower limit of the 95% CI for the GMT

ratio ($GMT_{18\text{-}49/50\text{-}59}/GMT_{60\text{-}64\ years}$) was >0.5 for each of the 20 vaccine serotypes (Tables 11 and 12).

Phase 3 Study in Adults Previously Immunized with PCV13 and/or PPSV23

Study B7471006 was a descriptive safety and immunogenicity study of PCV20 in adults ≥65 years of age previously vaccinated with PPSV23, previously vaccinated with PCV13, or previously vaccinated with PCV13 followed by PPSV23 (Section 6.3). OPA GMTs in participants who received PPSV23 1 to 5 years prior to Prevnar 20 were diminished compared to OPA GMTs in participants who received PCV 13 at least 6 months previously and compared to OPA GMTs in participants who received PCV13 followed by PPSV23, with the last PPSV23 dose given at least 1 year prior to PCV20. The safety and tolerability profile of PCV20 was generally similar in participants with different prior pneumococcal vaccine history and was generally similar to PCV13 and PPSV23 control groups.

Phase 3 Lot Consistency Study

Wyeth satisfactorily demonstrated manufacturing consistency based on comparisons of OPA GMTs between three different manufacturing scale lots of PCV20 in study B7471008 (Section 6.2.11.1 Table 26).

Safety Across All Submitted Studies

A total of 7,048 immunocompetent adults ≥18 years of age were evaluated for safety in six PCV20 pre-licensure trials. This includes 3,928 subjects and 2,247 subjects who received PCV20 or active control, respectively, in one of 5 randomized, double-blinded, active controlled clinical trials conducted in pneumococcal vaccine naïve adults ≥18 years of age in the U.S. and Sweden (172 subjects ≥65 years of age were randomized/enrolled in Sweden). In a sixth descriptive, open-label study in adults ≥65 years of age in the U.S. and Sweden, safety was evaluated in adults previously immunized with a pneumococcal vaccine prior to enrollment (624 PCV20 recipients and 245 active control recipients in B7471006).

Overall, the safety profile of PCV20 in adults was generally consistent with the known safety profile of U.S.-licensed PCV13 (the active control for safety). The most frequently reported adverse reactions were injection site pain, muscle pain, fatigue, headache and joint pain (Tables 15-20). Adverse reaction rates were highest among subjects in the youngest age cohort (18 through 49) and decreased with increasing age. The vast majority of reactions (≥97%) were mild or moderate in severity. No vaccine related serious adverse events were reported by study participants.

Pediatric Assessment and Pediatric Research Equity Act

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this application for a new active ingredient is required to contain an assessment of the safety and effectiveness of the product for the claimed indications in all pediatric age groups, unless the requirement is waived, deferred, or inapplicable.

Wyeth requested a full waiver of the pediatric study requirement in persons from birth through 16 years of age for the pneumonia indication, because the necessary studies are impossible or highly impracticable (505B(a)(4)(A)(i) of the Act). Wyeth requested a partial waiver of the pediatric study requirement in infants from birth to <6 weeks of age for the invasive pneumococcal disease indication, because PCV20 does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group, and Prevnar 20 is not likely to be used by a substantial number of pediatric patients in this age group (section

505B(a)(4)(B)(iii) of the Act). Wyeth is requesting a deferral of pediatric studies in persons 6 weeks through 16 years of age to support the invasive pneumococcal disease indication on the basis that Prevnar 20 is ready for approval for use in adults and the pediatric studies have not been completed (505B(a)(3)(A)(i) of the Act). Deferred studies to support U.S. licensure in pediatric age groups consist of three trials in children and adolescents 6 weeks through 17 years of age (studies B7471011, B7471013 and B7471014). Please see Section 11.6 for timelines for conducting each of these three required pediatric postmarketing studies under PREA. The Pediatric Study Plan was presented to FDA's Pediatric Review Committee (PeRC) on May 4, 2021. The committee agreed with the Pediatric Study Plan, including the full waiver, partial waiver, and deferral requests and the proposed timelines for each protocol submission, study completion and report submission.

Postmarketing Plans

Wyeth agrees to carefully monitor for any unanticipated risks in surveillance systems and postmarketing adverse reaction reports (i.e., routine pharmacovigilance).

As a condition of accelerated approval for prevention of pneumococcal pneumonia, Wyeth is required to conduct a post-approval confirmatory study to verify and describe the clinical benefit of PCV20 in adults ≥65 years of age. Wyeth submitted a protocol for study B7471015 (STN 125731/0.8) to fulfill this postmarketing requirement. Study B7471015 is a Phase 4, multicenter, real-world study using a test-negative design to evaluate the effectiveness of PCV20 against radiologically-confirmed community-acquired pneumonia (CAP) caused by the 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) in adults ≥65 years of age. The initial protocol synopsis was received on April 5, 2019, and initial CBER comments dated November 8, 2020 and July 20, 2020 were incorporated into a draft protocol which was submitted to this BLA. Further discussions between CBER and Wyeth will be needed post-approval to finalize the protocol.

Postmarketing studies that Wyeth is required to conduct under PREA following licensure include studies B7471011, B7471013 and B7471014. These studies have been initiated and are ongoing. Study B7471011 will evaluate the safety and effectiveness of a 4-dose series of PCV20 administered in the U.S. at 2, 4, 6 and 12 months of age in infants 6 weeks through 12 months of age. Study B747103 will evaluate the safety of 2, 4, 6, and 12-month schedule of PCV20 in infants in the U.S., Europe, and Canada. Study B7471014 will evaluate the safety and effectiveness of PCV20 in children and adolescents 15 months through 17 years of age. The protocols for each of these studies were submitted in 2020. Please see Section 11.6 for the agreed upon timelines for study report submission.

A safety and immunogenicity trial of PCV20 co-administered with seasonal inactivated influenza vaccine in adults ≥65 years of age is currently ongoing. (b) (4)

Clinical Reviewer Conclusion/Recommendation

The clinical data submitted in this application support approval of PCV20 for active immunization for the prevention of invasive disease and pneumonia caused by serotypes 1,3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in adults ≥18 years of age.

The approval of PCV20 for the prevention of pneumonia in adults ≥18 years of age caused by the 7 new vaccine serotypes (8, 10A, 11A 12F, 15B, 22F, and 33F) is based on the accelerated approval regulations. As a condition of accelerated approval, Wyeth is required to conduct a postmarketing study (B7471015) to verify and describe the clinical benefit of PCV20 in

preventing pneumococcal pneumonia caused by the 7 new vaccine serotypes in adults ≥65 years of age and has provided a satisfactory plan to do so.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each Phase 3 study, the demographic characteristics were reviewed individually (Sections 6.1.10.1.1, 6.2.10.1.1, and 6.3.10.1.1).

Within the Phase 3 studies, subgroup analyses by age (B7471007 only), sex (B7471007, B7471008, B7471006), race (B7471007 and B7471008) and country (B7471007 only) were conducted when the numbers of subjects in the subgroup were large enough to provide a meaningful interpretation of the data.

Immunogenicity Subgroup Analyses

- *Age*: Serotype-specific OPA GMTs generally decreased in older age groups in study B7471007.
- *Sex*: In Cohorts 1 (≥ 60 years) and 2 (50-59 years) of study B7471007, serotype-specific OPA GMTs for the 20 vaccine serotypes were generally higher among females compared to males. In Cohort 3 (18-49 years) of study B7471007, in study B7471008, and study B7471006, OPA GMTs appeared similar with no clear trend when comparing those achieved by females and males.
- *Race*: (study B7471007 and B7471008): In Cohort 1 of study B7471007 and in study B7471008, serotype-specific OPA GMTs for the 20 vaccine serotypes generally appeared similar with no clear trend across racial subgroups. In Cohorts 2 and 3, serotype-specific OPA GMTs for the 20 vaccine serotypes were generally lower among Black subjects compared to White subjects.
- *Country*: In study B7471007 subjects ≥65 years of age, serotype-specific OPA GMTs for the 20 vaccine serotypes generally appeared similar between country subgroups.

Safety Subgroup Analyses

- *Age:* Rates of injection site reactions generally decreased with age in study B7471007. With the exception of fever, rates of systemic adverse reactions (including use of antipyretic or pain medication) generally decreased with increasing age; the rate of fever was generally highest in the eldest age subgroup (≥80 years).
- *Sex:* Rates of solicited local and systemic adverse events were generally more frequent among females than males, although this varied by study and by age cohort within study B7471007.
- *Race:* Solicited local and systemic adverse events were generally less frequent among Black subjects compared to White subjects, although this varied by study and by age cohort within study B7471007.

1.2 Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Streptococcus pneumoniae is a leading cause of disease and death among older adults in the U.S. *S. pneumoniae* colonize the nasopharynx and can cause non-invasive disease (e.g., non-

bacteremic pneumonia) as well as invasive disease (e.g., bacteremia and meningitis) in adults. IPD is defined by isolation of *S. pneumoniae* from a normally sterile site (i.e., blood, cerebrospinal, pleural or peritoneal fluid). The most common manifestations of IPD in adults aged 50 years and older include invasive (bacteremic) pneumonia, bacteremia without a focus, and meningitis (Neuzil and Jackson 2008; Gruber et al. 2008). Among patients hospitalized with community-acquired pneumonia, approximately 5%-10% will have pneumococcal bacteremia (Neuzil and Jackson 2008). Non-bacteremic pneumococcal pneumonia remains a more common disease manifestation, accounting for approximately 13%-34% of pneumonia hospitalizations among adults (Gruber et al. 2008).

Adults at highest risk for serious pneumococcal disease include those with immunosuppressive conditions, functional or anatomic asplenia, renal disease, and age ≥65 years of age. Other conditions that increase the risk in adults include chronic heart disease, lung disease (including asthma), liver disease, smoking cigarettes, alcoholism, a CSF leak, and having a cochlear implant (Gierke 2021b).

Currently, 100 different serotypes have been identified, which vary both by the chemical structure of their seroreactive capsular polysaccharides and in their ability to cause disease, with the majority of invasive disease caused by a relatively limited number of serotypes (Ganaie et al. 2020). The presence of antibiotic resistance in a proportion of pneumococcal isolates can further complicate treatment and in some cases lead to treatment failure and/or worse clinical outcomes.

PCV20 is intended to prevent IPD and pneumococcal pneumonia caused by the 20 pneumococcal serotypes contained in the vaccine. The 7 non-PCV13 serotypes included in PCV20 (8, 10A, 11A, 12F, 15B, 22F and 33F) were selected based on their relative prevalence as a cause of IPD, their general geographic distribution and other factors such as presence of antibiotic resistance (11A, 15B), association with outbreaks (8, 12F), and greater disease severity such as meningitis or with relatively high mortality (10A, 11A, 22F). Wyeth noted that serotypes 22F, 11A, 33F, 8 and 15B were the 5 most prevalent causes of IPD in the U.S. according to Active Bacterial Core surveillance (ABCs) data from the Center for Disease Control and Prevention (CDC).[1] Based on ABCs data, the 7 new serotypes were isolated from approximately 30% of IPD cases in adults ≥19 years of age from 2017-2018 (Gierke 2021a). Altogether, the 20 serotypes in PCV20 were isolated from approximately 55%-64% of all IPD cases among adults during this same time period (Gierke 2021a). Serotype 15B, which is closely related to 15C[2], has been shown to contribute 1.5% of IPD in adults ≥65 years of age. The proportion of all-cause CAP caused by serotypes contained in PCV20 has been estimated to be 7.1% in 2014-2016 and 6.3% in 2019-2020 based on preliminary data from Wyeth presented by the CDC (Gierke 2021a).

2.2 Currently Available, Pharmacologically Unrelated Treatment for Proposed Indications

Available therapy for IPD and pneumococcal pneumonia in adults includes antibiotic therapy, however treatment has been complicated by increased frequency of antibiotic-resistant strains.

[1] STN 125731/0.1, module 2 Clinical Overview, p16.

[2] Serotype 15B and 15C capsules differ structurally by the presence of an *O*-acetyl group in 15B, while 15C isolates express small and variable amounts of *O*-acetylation. This difference can only be detected biochemically, as the capsular polysaccharide biosynthetic pathways for both serotypes are the same.

2.3 Safety and Efficacy of Pharmacologically Related Products

Two pneumococcal vaccines are currently licensed and available in the U.S. for the prevention of pneumococcal disease in adults.

Pneumovax 23, the 23-valent pneumococcal polysaccharide vaccine (PPSV23), was licensed in the U.S. in 1983 (Pneumovax 23, prescribing information). It replaced an earlier 14-valent formulation that had been licensed in 1977. PPSV23 is approved for use in persons ≥50 years of age and persons ≥2 years of age who are at increased risk of pneumococcal disease. Each 0.5 mL dose contains 25 µg of purified capsular polysaccharide from each of 23 pneumococcal serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22, 23F, and 33F) (Pneumovax 23, prescribing information). These polysaccharide antigens are thought to be T-independent antigens that stimulate mature B-lymphocytes, but not T-lymphocytes.

Licensure of PPSV23 was based on demonstrated efficacy of earlier 6-valent, 12-valent, and 13-valent polysaccharide vaccines and immunogenicity and safety data from a 22-valent and 23-valent vaccine formulation. One randomized controlled trial in adults ≥55 years of age with chronic medical conditions who received a 14-valent pneumococcal polysaccharide vaccine did not support vaccine efficacy for nonbacteremic pneumonia (Simberkoff et al. 1986). Available data suggest that the PPSV23 vaccine protects adults and the elderly against IPD, however no consistent vaccine effect has been observed for prevention of pneumonia (Gruber et al. 2008; Conaty et al. 2004). Please refer to the Pneumovax 23 package insert for details regarding its efficacy and safety profile (Pneumovax 23, prescribing information).

Prevnar 13 (PCV13) was the first pneumococcal conjugate vaccine licensed for use in adults in the U.S. It is a glycoconjugate vaccine consisting of purified capsular polysaccharide antigens of 13 *S. pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) individually linked to non-toxic diphtheria CRM_{197} protein. On December 30, 2011,CBER approved PCV13 for active immunization for the prevention of invasive disease and pneumonia caused by the 13 S*. pneumoniae* serotypes contained in the vaccine in persons ≥50 years of age based on a serological endpoint (OPA titer) as defined in the Accelerated Approval regulations (21 CFR 601.41). As a condition of accelerated approval, Wyeth completed a postmarketing study that confirmed and described the efficacy of Prevnar 13 for the approved indications. On July 11, 2016, CBER approved a sBLA to expand the use of Prevnar 13 for the approved indications to adults 18-49 years of age based on immunologic bridging studies.

Clinical efficacy of PCV13 in adults was assessed in a randomized, double-blind, placebo-controlled study (study 6115A1-3006; NCT00744263) conducted over approximately 4 years in the Netherlands (Prevnar 13, prescribing information). A total of 84,496 subjects 65 years and older received a single dose of PCV13 or placebo. PCV13 demonstrated statistically significant vaccine efficacy in preventing first episodes of vaccine-type pneumococcal community-acquired pneumonia (VT-CAP) (45.6%; 95.2% CI 21.8, 62.5), non-bacteremic/non-invasive VT-CAP (45%; 95% CI 14.2, 65.3), and vaccine-type IPD (75%; 95% CI 41.1, 90.9). VT-CAP was defined as the presence of ≥2 specified clinical criteria (chest x-ray consistent with CAP as determined by a central committee of radiologists; and positive VT-specific urinary antigen detection assay or isolation of VT *S. pneumoniae* from blood or other sterile site). Non-bacteremic/noninvasive CAP was defined as an episode of VT-CAP for which the culture results for blood or any other sterile site were negative for *S. pneumoniae*. IPD was defined as the presence of VT *S. pneumoniae* from a sterile site. Please refer to the PCV13 package insert for additional details regarding the PCV13 efficacy and safety profile.

ACIP Recommendations for Pneumococcal Vaccinations

The Advisory Committee on Immunization Practices (ACIP) recommends PCV13 in series with PPSV23, given 8 weeks apart, for adults aged ≥19 years of age with certain medical conditions that increase the risk of pneumococcal disease (i.e., those with an immunocompromising condition, cerebrospinal fluid (CSF) leak, or cochlear implant) and who have not previously received PPSV23. This 8-week interval was selected to minimize the time during which an at-risk individual would be left unprotected from IPD caused by serotypes unique to PPSV23 and to provide enhanced opportunity for compliance with a multi-dose regimen (Bennett et al. 2021).

For immunocompetent adults ≥65 years of age, the ACIP recommends a routine single dose of PPSV23. Shared decision-making is recommended regarding administration of PCV13 to persons aged ≥65 years of age who do not have an immunocompromising condition, CSF leak, or cochlear implant, and who have not previously received PCV13 (Matanock et al. 2019). If a decision is made to administer PCV13, it should be administered before PPSV23; clinical studies have demonstrated a higher OPA antibody response to serotypes common to both vaccines when the conjugate vaccine is given first (Kobayashi et al. 2015).

For immunocompetent adults ≥65 years of age, the ACIP-recommended interval between sequential administration of PCV13 and PPSV23 in adults is as follows (Kobayashi et al. 2015):

- For immunocompetent adults ≥65 years of age who are pneumococcal vaccine naïve, PPSV23 should be administered ≥1 year after an initial dose of PCV13
- For immunocompetent adults who previously received PPSV23 at age ≥65 years, PCV13 should be administered ≥1 year after the prior dose of PPSV23
- For immunocompetent adults ≥65 years of age who previously received PPSV23 prior to 65 years of age and for whom an additional dose of PPSV23 is indicated when aged ≥65 years of age, a second dose of PPSV23 should be administered ≥1 year after PCV13 and ≥5 years after the last dose of PPSV23.

In a review of previous clinical studies evaluating the safety and immunogenicity of the sequential administration of PCV7 or PCV13 followed by PPSV23 among immunocompetent adults, the ACIP concluded that 1) shorter intervals (e.g., 8 weeks) may be associated with increased local reactogenicity when compared with longer intervals, and 2) longer intervals (e.g., ≥1 year) may lead to higher antibody responses against serotypes in both vaccines compared with a single dose of PCV13 or PPSV23 (Kobayashi et al. 2015). Studies have demonstrated that OPA titers elicited by PCV13 when given one year after an initial dose of PPSV23 were lower for shared serotypes (hyporesponsive immune response[3]) compared to corresponding OPA titers in pneumococcal vaccine-naïve adults (Bennet et al. 2012; STN 125324/262 clinical review executive summary; PCV13 package insert).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

At this time, PCV20 is not approved/authorized for use in any country. PCV13 was first approved in the U.S. in 2010. Please refer to the PCV13 prescribing information regarding previous human experience with PCV13 (Prevnar 13, prescribing information). Please also refer to the postmarketing/pharmacovigilance review of Dr. Phillip Blanc in the Office of Biostatistics and Epidemiology.

[3] The hyporesponsive phenomenon is an inability to mount an immune response following a second vaccination that is greater than or equal to the corresponding response after a primary vaccination.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

During an end-of-Phase 2 meeting, Wyeth and CBER came to an agreement on the Phase 3 clinical development program and approach to support licensure of PCV20 for the IPD indication in adults 18 years of age and older. A randomized, active-controlled efficacy trial of PCV20 evaluating prevention of pneumococcal disease was not considered feasible by Wyeth due to the sample size that would be required. A placebo-controlled trial was also not ethically justifiable in the U.S. where PCV13 was recommended routinely for adults ≥65 years of age as well as for adults <65 years of age with certain underlying conditions that increase their risk of pneumonia or invasive disease caused by the 13 *S. pneumoniae* serotypes contained in the vaccine.

Although there is no established immune correlate of protection in adults (i.e., a threshold level of an immune marker of protection for pneumococcal disease), a licensure approach was agreed upon as described below for each proposed indication. The basis of the agreement relies on following: 1) OPA reflects relevant *in vivo* mechanisms of protection against pneumococcal disease; 2) efficacy against pneumonia caused by PCV13 serotypes has been confirmed in an adult clinical endpoint study (6115A1-3006; NCT 00744263); and 3) PCV20 and PCV13 vaccines have nearly identical manufacturing processes for the 13 common serotypes.

IPD Indication

CBER has agreed that clinical development of new polysaccharide-based pneumococcal vaccines (conjugated and non-conjugated) can use an approach in which vaccine effectiveness against IPD is inferred from immunologic comparability to licensed pneumococcal vaccines using OPA as an established immunologic parameter that can be used to support traditional approval for the prevention of IPD caused by the 20 vaccine serotypes.

Pneumonia Indication

For the 13 original serotypes, PCV20 effectiveness against pneumonia was supported by comparable OPA antibody responses to PCV13 and nearly identical manufacturing processes for PCV20 and PCV13 vaccines. A similar approach was used to support the approval of PCV13 in infants for the prevention of otitis media due to the 7 original serotypes in Prevnar (PCV 7) (STN 125324/0).

CBER has not agreed to accept immunogenicity data alone to support a pneumonia or otitis media indication, because 1) there is no scientific consensus regarding serologic criteria for assessing effectiveness of new pneumococcal conjugate vaccines against noninvasive disease, and 2) antibody levels have not been found to be indicative of prevention of non-invasive pneumococcal disease.

In a letter dated November 8, 2019, CBER agreed to Wyeth's proposal for the initial approval of PCV20 for the pneumonia indication in adults for the 7 new vaccine serotypes to be based on an immunological surrogate endpoint (OPA titer), as defined in the accelerated approval regulation (601.41) considered reasonably likely to predict prevention of pneumococcal pneumonia caused by the 7 new vaccine serotypes. Since pneumococcal pneumonia is a serious condition and PCV20 will provide meaningful therapeutic benefit to patients over existing treatments (see Section 2.3), the proposed indication met the qualifying criteria for accelerated approval. As a condition of accelerated approval, Wyeth will conduct a post-approval real-world observational effectiveness study as a confirmatory study to verify and describe clinical benefit for the prevention of pneumonia caused by the 7 new serotypes in PCV20 (study B7471015). The initial protocol synopsis was received on April 5, 2019, and initial

CBER comments dated November 8, 2020 and July 20, 2020 were incorporated into a final draft protocol which was submitted to this BLA.

PCV20 Regulatory Timeline

- Feb 7, 2013: Pre-IND meeting to discuss clinical and CMC plans for early clinical trials.
- Aug 2013: CBER informed of delay in IND submission due to unexpected repeat-dose tox study findings (cardiac-related toxicity in (b) (4) rabbits).
- Dec 16, 2014: Type C meeting to discuss findings from initial repeat-dose toxicity study and subsequent investigations with a (b) (4) 20-valent conjugate vaccine
- Jan 14, 2015: Original Master File submission received with 24 rabbit studies (18 historical and 6 new) for consolidated review by CBER.
- May 7, 2015: Type C meeting to discuss proposed first-in-human (FIH) Phase 1 study in 50-64-year-old adults. CBER concluded available data were inadequate to support initiation of the proposed FIH study. A re-analysis of the toxicity findings was requested.
- Oct 13, 2015: Internal meeting to discuss toxicology reanalysis and root cause analysis.
- Oct 19, 2015: Type C meeting to discuss toxicology reanalysis and root cause analysis. CBER informed of initiation of saline only study. [4] CBER proposed an additional toxicology study with improved study design that could be conducted in parallel with a FIH clinical trial with cardiac monitoring. Phase 1 study clinical comments issued.
- May 24, 2016: Internal CBER meeting to discuss saline-only study results.
- Jun 2, 2016: Type C meeting to discuss results from a saline-only study and Wyeth's proposal to conduct a FIH study with cardiac monitoring.
- Jun 21, 2016: MF Amendment 13 – FIH, Phase 1 Protocol synopsis.
- Aug 2, 2016: Consult obtained from Division of Cardiovascular and Renal Products.
- Aug 15, 2016: Internal meeting to discuss Phase 1 protocol and cardiology consult
- Aug 30, 2016: CBER issued comments regarding FIH, Phase 1 protocol synopsis.
- Jun 19, 2017: agreement to proceed to Phase 2 trials
- Sep 18, 2018: End-of-Phase 2 meeting

2.6 Other Relevant Background Information

Evolution of ACIP Recommendations for Pneumococcal Vaccination of Adults

On June 20, 2012, following approval of PCV13 for use in adults (via accelerated approval licensure pathway) the ACIP recommended routine use of PCV13 for adults ≥19 years of age with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants. PCV13 was to be administered in addition to PPSV23, the vaccine that was already recommended at the time for these groups of adults. For those previously vaccinated with ≥1 dose of PPSV23, a dose of PCV13 was to be administered ≥1 year after the last PPSV23 dose (Matanock et al. 2019). For those who had not previously received PCV13 or PPSV23, a dose of PCV13 was to be administered first followed by a dose of PPSV23 at least 8 weeks later (Bennett et al. 2012). The PCV13/PPSV23 sequence is preferred, based on studies demonstrating a better response to serotypes common to both vaccines when the conjugate vaccine is given first (Bennet et al. 2012; Kobayashi et al. 2015).

[4] At the Oct 19, 2015 Type C meeting, Wyeth informed CBER about a planned saline-only study. This study was conducted without CBER input or support. CBER stated that a saline-only study would not address the Agency's concerns and would therefore be of limited use and not alleviate the need for an additional toxicology study(ies) or cardiac monitoring during the first-in-human clinical study. CBER also indicated that results from the saline-only study could not be used to support regulatory decision making.

On August 13, 2014, following the completion of the CAPiTA trial (which confirmed clinical benefit of PCV13 in adults ≥50 years of age), the ACIP recommended routine use of PCV13 in series with PPSV23 given 6-12 months apart (minimum acceptable interval of 8 weeks) for all adults ≥65 years of age (Tomczyk et al. 2014). The ACIP also recommended that all adults ≥65 years of age previously immunized with PPSV23 should receive a dose of PCV13 ≥1 year after the last PPSV23 dose. The recommended intervals were based on available evidence from immunogenicity studies which evaluated intervals of 2, 6, or 12 months or 3-4 years between PCV7 or PCV13 and PPSV23 (Kobayashi et al. 2015). The ACIP recognized that, while in the short term, routine PCV13 use among adults ≥65 years of age was warranted, continued indirect effects from PCV13 use in children (i.e., reduced disease burden among adults through reduced carriage and transmission of serotypes from vaccinated children) might limit the utility of this recommendation. Therefore, ACIP proposed to reevaluate this recommendation for routine PCV13 use in adults ≥65 years of age and older 4 years after implementation and revise as needed (Tomczyk et al. 2014).

On June 25, 2015, to harmonize pneumococcal vaccination recommendations, the ACIP changed the recommended interval between PCV13 followed by PPSV23 from 6-12 months to ≥1 year for immunocompetent adults ≥65 years of age (Kobayashi et al. 2015). This change resulted in harmonization with the 1-year interval for the PPSV23-PCV13 sequence in the same age group. This change was also based on data suggesting that 1) shorter intervals (e.g., 8 weeks) may be associated with increased local reactogenicity when compared with longer intervals, and 2) longer intervals (e.g., ≥1 year) may lead to an improved immune response against serotypes in both vaccines compared with a single dose of PCV13 or PPSV23. The ACIP continued to recommend an 8-week interval between an initial dose of PCV13 and a subsequent dose of PPSV23 in persons ≥2 years of age with medical conditions that increase the risk of pneumococcal disease.

In June 2019, after reviewing evidence accrued during the preceding 3 years and cost-effectiveness analysis, ACIP voted to rescind the recommendation for routine PCV13 use among adults ≥65 years of age and to recommend use of PCV13 based on shared decision making for adults ≥ 65 years of age who do not have an immunocompromised condition, cerebrospinal fluid leak or cochlear implant and who have not previously received PCV13 (Matanock et al. 2019). This decision was based on a review of accrued evidence which showed that the incidence of PCV13-type disease had been reduced to historically low levels among adults ≥ 65 years of age through PCV13 indirect effects, such that the implementation of a PCV13 recommendation for all adults ≥ 65 years of age in 2014 had a minimal impact on PCV13-type disease at the population level in this age group and the cost-effectiveness analysis no longer supported this routine recommendation in this age group. The ACIP's recommendation for PPSV23 and the recommended interval between PCV13 and PPSV23 remained unchanged.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of this BLA was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The six studies provide in this BLA were conducted in accordance with Good Clinical Practices and according to the requirement of 21 CFR Part 56 (Institutional Review Boards) and 21 CFR

Part 50 (Informed Consent). A total of 984 investigators participated in studies submitted to this BLA. Bioresearch Monitoring (BIMO) inspections were issued for the following three clinical study sites that participated in the conduct of study protocol B7471007: site 1004 in Wilmington, NC (192 enrolled); site 1015 in Salt Lake City, UT (175 enrolled); and 1028 in St. Louis, MO (134 enrolled). These sites were selected based upon previous BIMO inspection history, sponsor-reported adverse events, protocol deviations and total number of subjects enrolled. They comprise about 12.9% (501/3889) of the total subjects enrolled under protocol B7471007. The inspections did not reveal substantive problems impacting the data submitted in the application. Please refer to the CBER BIMO review memo for more details.

3.3 Financial Disclosures

Covered clinical studies: B7471002, B7471005, B7471006, B7471007, B7471008
Was a list of clinical investigators provided? ☒ Yes ☐ No
Total number of investigators identified: 984
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5[a]
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 4 Is an attachment provided with details of the disclosable financial interests/arrangements? ☒ Yes ☐ No Is a description of the steps taken to minimize potential bias provided? ☒ Yes ☐ No

[a] A consolidated Form FDA 3455 (Disclosure statement) listed three investigators (Dr. Nicola P. Klein, Dr. Susan Edwards, and Dr. Peter J. Winkle) with disclosable financial interests as only 1 Form 3455 is to be submitted for each investigator with financial information to disclose. However, because investigators must fill out a financial disclosure form for each study that they take part in and because one of these investigators (Dr. Susan Edwards) participated in three studies, Dr. Susan Brown and was counted 3 times by Wyeth in the count of total investigators (i.e., she was counted as 3 of the 984 investigators). Thus, the total number of investigators with disclosable financial interests is five (Dr. Klein, Dr. Winkle, and Dr. Edwards counted three times).

Three investigators had disclosable financial interests to disclose:

- Dr. Nicola P. Klein (study B7471008, center 1028);
- Dr. Susan Edwards (study B7471006 center 1028, B7471007 center 1048, and study B7471008 center 1016); and
- Dr. Peter J. Winkle (study B7471002 center 1006).

Dr. Klein reported other significant payments totaling (b) (4) ; these payments were for clinical and research collaborations. Wyeth notes that all investigator-initiated research grants associated with clinical investigators are paid directly to the Institution rather than to the

individual clinical investigator. Drs. Edwards and Winkle reported significant equity interest totaling (b) (4) as of February 13, 2019, and (b) (4) as of September 15, 2017.

The five investigators with disclosable financial interests (n=5/984) represented 0.5% of the 984 total investigators who participated in covered clinical studies.

Efforts reported to eliminate bias for the covered studies consisted of the following:

- Randomized, double-blind and multicenter study design as well as pre-specified statistical methods and employment of a statistical analysis plan
- Frequent monitoring of investigator trial sites and auditing of study sites
- Validity of data collected was confirmed by standard monitoring procedures
- Data processing involved cleaning checks (querying data through electronic edit checks) to ensure that errors were identified and corrected
- Data were reviewed by clinicians and queries were generated in case of inconsistencies during the course of the trial
- The study report underwent review by the project team and Quality Control; and
- Study sites performing safety evaluations were determined acceptable based on appropriate certification or historical performance and/or qualifications and credentials.

Reviewer Comment: *The clinical team has concluded that the financial disclosure information would be unlikely to impact the quality of the study data.*

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

4.1 Chemistry, Manufacturing, and Controls

The CBER product reviewers concluded that this submission is complete, and they recommend approval of PCV20. The CMC reviewers noted that there have been no significant changes to the approved manufacturing processes for CRM_{197} with either casamino acid-yeast extract based medium (CRM_{197}-CY) or defined medium (CRM_{197}-DM). Under the new license for PCV20, (b) (4) Both processes are currently approved for manufacture of PCV13. There have been no significant changes to the approved processes for the production of the 13 serotypes common to PCV13, although some of the analytical methods and parameters have evolved. Manufacture of the seven new polysaccharide serotypes differs in several ways from the PCV13 serotypes. Please refer to the CMC review for more details. PCV20 is presented in the same syringes and stoppers as PCV13.

4.2 Assay Validation

4.3 Nonclinical Pharmacology/Toxicology

The toxicology reviewer concluded that this submission is acceptable with regards to nonclinical toxicology, and no toxicologic issues identified would preclude approval of this BLA. There was no clinically-relevant evidence of maternal toxicity (to include female fertility) or teratology when PCV20 was administered to pregnant rabbit does. The clinical relevance and translatability of the non-clinical cardiac toxicity findings observed in a repeat-dose toxicity study performed in rabbits to human subjects should be considered inconclusive (see information below). The toxicology review does not include a recommendation to include these rabbit findings within the

PCV20 prescribing information (i.e., Section 13.2). The tox reviewer recommends postmarketing surveillance for cardiac symptoms and further exploration of the cardiac changes in rabbits could be considered. Please refer to the detailed toxicology review by Dr. Andrew O'Carroll for more information.

Reviewer Comments:

- *Wyeth proposes routine postmarketing safety surveillance (consisting of monitoring for any unanticipated risks in surveillance systems and postmarketing adverse reaction reports), which will include an assessment for cardiac-related safety signals. The clinical team and pharmacoepidemiology team agree with the proposed postmarketing plan.*
- *According to 21 CFR 201.57 (c)(14)(ii), Section 13.2 of the prescribing information must include significant animal data necessary for the safe and effective use of the drug in humans. Given the lack of any cardiac-related clinical findings in the human trials (including the Phase 1 study B7471001 which included cardiac monitoring), this information is not viewed as necessary for the safe and effective use of PCV20.*

Background on Non-Clinical Cardiac Toxicity Findings

During the pre-IND stage of PCV20 development, unexpected cardiac findings (diffuse, patchy areas of inflammation and/or irreversible necrosis) were identified on histopathology in a small number of otherwise healthy-appearing rabbits in the initial repeat-dose toxicity study that were not observed following PCV13. A consolidated review was subsequently conducted of 18 historical rabbit studies and six new studies with the pneumococcal conjugate vaccines (submitted to MF (b) (4) to investigate this finding. Overall, cardiac findings were observed following administration of (b) (4) , and 20-valent investigational vaccine formulations and following administration of aluminum phosphate adjuvant (plus vaccine excipients) without any pneumococcal antigen. No similar findings were seen with saline alone. Several Type C meetings were held between December 2014 and June 2016 to discuss this finding, a toxicology reanalysis and root cause analysis[5] in addition to the proposed Phase 1 first-in-human study (listed in Section 2.5).

Because the non-clinical data available were not definitive on the causal relationship between the toxicology findings and the investigational products, CBER informed Wyeth that cardiac monitoring and risk mitigation would be necessary in their Phase 1 first-in-human clinical trial. On June 21, 2016, Wyeth submitted to MF (b) (4) a protocol synopsis with cardiac monitoring. CBER obtained an intercenter consult within CBER's Division of Cardiovascular and Renal Products with specific questions regarding the adequacy of the proposed cardiac monitoring in study B7471001. After reviewing the protocol synopsis and obtaining consultant feedback, CBER issued comments regarding the proposed protocol synopsis to Wyeth on August 30, 2016. No safety concerns were identified in this Phase 1 study, including no cardiac-related safety findings. Please see Section 6.6 for the results from this study.

[5] The root cause analysis was meant to determine whether any CMC changes to components of the pneumococcal conjugate vaccine matrix might have accounted for the tox findings.

Reviewer Comment: *Study B7471001, which incorporated cardiac monitoring, did not identify evidence of any abnormalities in cTnI (a sensitive marker of cardiac tissue damage) or other cardiac-related safety concerns in human subjects. Further studies were not required to include cardiac monitoring due to lack of safety concerns in the Phase 1 study. See Section 6.6 for more details regarding study B7471001.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

PCV20 elicits an opsonophagocytic antibody response. Nonclinical and clinical data support OPA, as measured by a microcolony OPA assay. The OPA assay[6] provides an in vitro measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant in vivo mechanisms of protection against pneumococcal disease. Microcolony OPA titers are expressed as the reciprocal of the highest serum dilution resulting in 50% reduction in the number of bacterial colony-forming units, when compared with the control without test serum. No specific threshold of OPA titer has been identified that correlates with protection against IPD or pneumonia in adults.

4.5 Statistical

The statistical reviewer concludes that, from the statistical perspective, the submitted clinical study results support the approval of this BLA. The statistical reviewer also concludes that the validation reports for the 7 new serotypes in PCV20 appear to be acceptable. Please refer to the two detailed statistical reviews (one covering non-clinical assay data and one covering clinical data) by Dr. Ruoxuan Xiang for more information.

4.6 Pharmacovigilance

The pharmacovigilance reviewer concluded that the proposed pharmacovigilance plan (i.e., routine postmarketing safety surveillance consisting of monitoring for any unanticipated risks in surveillance systems and postmarketing adverse reaction reports) is adequate to monitor postmarketing safety. Please refer to the detailed review by Dr. Phillip Blanc.

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

5.1 Review Strategy

This review covers data submitted from 6 clinical trials evaluating PCV20 in adults and focuses on the three Phase 3 trials submitted to BLA 125731: 1) Study B7471007, which evaluated safety and effectiveness of PCV20 in pneumococcal vaccine-naïve adults ≥18 years of age; 2) study B7471008, which evaluated safety and manufacturing consistency of PCV20 in 18-49-year-old adults; and 3) study B7471006, which was a descriptive, open-label study of PCV20 in adults ≥65 years of age who had previously received PCV13, PPSV23 or both PCV13 and PPSV23. An integrated summary of safety, consisting of safety data from each of the Phase 3 studies submitted to this BLA, was also evaluated.

[6] OPA assays quantitatively assess functional anti-*S. pneumoniae* antibodies by measuring complement-mediated bacterial killing in reactions containing serially diluted test sera, complement (baby rabbit serum), and phagocytes (differentiated HL-60 cells).

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

The following modules of the BLA 125731/0.1 were reviewed:

- m1.3 Administrative Information
- m1.6 Correspondence Regarding Meetings
- m1.9 Pediatric Administrative Information
- m1.14 Labeling
- m1.16 Risk Management Plan
- m1.17 Postmarketing Studies
- m2 Common Technical Document Summaries
- m5 Clinical Study Reports

Amendments (Am) reviewed in the BLA are provided below by amendment number:

- Am 7: Updated Draft Prescribing Information, Submitted 1/8/2021
- Am 8: Draft protocol for Phase 4 Test-Negative Design Study (B7471015), Submitted 1/15/21
- Am 11: Response to 1/14/21 Clinical Information Request (IR), Submitted 1/28/2021
- Am 17: Response to 2/1/21 IR regarding clinical datasets, Submitted 2/23/21
- Am 22: Response to 3/3/21 IR with clarifications on 1/14 response, Submitted 3/10/21
- Am 23: Response to 3/1/21 IR with clarifications on 2/1 Response, Submitted 3/11/21
- Am 26: Response to 3/18/21 IR with updates to deferred pediatric study dates
- Am 30: Response to Phase 4 Study B7471015 comments, Submitted 4/20/21
- Am 32: Labeling Responses, Submitted
- Am 33: Responses to P4 Study B7471015 comments and labeling comments, Submitted 5/5/21
- Am 35: PMC and PMR commitments, Submitted 5/20/21
- Am 37: Labeling responses, Submitted 5/25/21
- Am 40: Labeling responses, Submitted 6/3/21
- Am 41: Labeling responses, Submitted 6/4/21

5.3 Table of Studies/Clinical Trials

Table 1. Clinical Studies Submitted in Support of Efficacy and Safety Determinations for Prevnar 20 (PCV20), Total N=7048 (PCV20: N=4552; Control: N=2496)

Study (Country) NCT #	Study Description	Study Population	Study Groups/ Vaccine Schedule	Number Vaccinated	Total
B7471007 (U.S. and Sweden) NCT03760146	Phase 3, randomized, double-blind safety and immunogenicity study with an age-based 3-cohort design • Among 60-64-year-old adults (Cohort 1 subset): noninferiority comparisons to PCV13 and PPSV23 • Among 18-59-year-old adults: immunobridging to 60-64-year old Cohort 1 subset	Pneumococcal vaccine-naïve adults ≥18 years of age Cohort 1: ≥60 years[a] Cohort 2: 50-59 years Cohort 3: 18-49 years	Cohort 1 • PCV20 then saline one month later • PCV13 then PPSV23 one month later Cohorts 2 and 3 PCV20 or PCV13	Cohort 1 PCV20/saline: 1507 PCV13/PPSV23: 1490 Cohort 2 PCV20: 334 PCV13: 111 Cohort 3 PCV20: 335 PCV13: 112	PCV20: 2176 Control: 1713
B7471008 (U.S.) NCT03828617	Phase 3, randomized, double-blind lot consistency study with a 4-arm parallel design	Pneumococcal vaccine-naïve adults 18-49 years of age	PCV20 Lot 1 PCV20 Lot 2 PCV20 Lot 3 PCV13	Lot 1: 488 Lot 2: 489 Lot 3: 486 PCV13: 245	PCV20: 1463 PCV13: 245
B7471006 (U.S. and Sweden) NCT03835975	Phase 3, randomized, open-label descriptive safety and immunogenicity study in adults ≥65 years of age with a 3-cohort design based on prior pneumococcal vaccination status	Pneumococcal experienced adults ≥65 years of age • Cohort A: PPSV23 ≥1 year and ≤5 years prior to study; no prior PCV13 • Cohort B: PCV13 ≥6 months prior to study; no prior PPSV23 • Cohort C: prior PCV13 and PPSV23 (PPSV23 ≥1 year prior to study)	Cohort A PCV20 or PCV13 Cohort B PCV20 or PPSV23 Cohort C PCV20	Cohort A PCV20: 253 PCV13: 122 Cohort B PCV20: 246 PPSV23: 127 Cohort C PCV20: 125	PCV20: 624 Control: 249
B7471002 (U.S.) NCT03313037	Phase 2, randomized, controlled, double-blind safety and immunogenicity study	60-64 years of age, pneumococcal vaccine naïve	• PCV20 then saline 1 month later • PCV13 then PPSV23 1 month later	221 222	PCV20: 221 Control: 222

Study (Country) NCT #	Study Description	Study Population	Study Groups/ Vaccine Schedule	Number Vaccinated	Total
B7471001 (U.S.) NCT02955160	Phase 1, first-in-human, controlled, randomized, observer-blind safety and immunogenicity study	18-49 years of age, pneumococcal vaccine naïve	PCV20 Tdap (active control)	33 33	PCV20: 33 Control: 33
B7471005 (U.S.) NCT03642847	Phase 1b, randomized, controlled, double-blind safety and immunogenicity study	18-49-year-old adults of Japanese descent, pneumococcal vaccine naïve	PCV20 c7vPnC PCV13	35 34 34	PCV20: 35 PCV13: 34

NCT #: ClinicalTrials.gov study identification code. PCV13: Prevnar 13; PPSV23: Pneumovax 23; Tdap: tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed manufactured by Sanofi Pasteur. c7vPnC: investigational complementary 7-valent pneumococcal conjugate vaccine manufactured by Pfizer.
Note: In Phase 3 trials, the OPA assay was validated for all vaccine serotypes. MedDRA version 22.1 coding dictionary was applied in all Phase 3 studies.
[a] Enrollment in Cohort 1 was stratified by age. A total of 993 and 992 subjects 60-64 years of age were vaccinated with PCV20/saline and PCV13/PPSV23, respectively and a total of 514 and 498 subjects ≥65 years of age were vaccinated with PCV20/saline or PCV13/PPSV23, respectively within Cohort 1.
Source: STN 125731/0.1, Module 5.2, Tabular Listing of al Clinical Studies

5.5 Literature Reviewed

Bennett, NM, CG Whitney, M Moore, T Pilishvili, and KL Dooling, 2012, Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP).

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study B7471007

Study B7471007 was designed to evaluate the safety and immunogenicity of a single dose of PCV20 when administered to pneumococcal vaccine-naïve adults ≥18 years of age enrolled into 1 of 3 age-based cohorts. Cohort 1 subjects (≥60 years of age) were randomized 1:1 to receive either PCV20 followed by saline placebo approximately one month later (PCV20/saline) or PCV13 followed by PPSV23 approximately one month later (PCV13/PPSV23). Cohort 2 subjects (50 through 59 years) and Cohort 3 subjects (18 through 49 years) were randomized 3:1 to receive PCV20 or PCV13. The study aimed to provide noninferiority comparisons of the OPA GMTs induced by PCV20 relative to PCV13 for the 13 matched serotypes and the OPA GMTs induced by PCV20 relative to PPSV23 for the 7 new serotypes among subjects ≥ 60 years of age (Cohort 1). The study was also designed to bridge serotype-specific OPA GMTs induced by PCV20 among younger adult cohorts 2 and 3 (18 through 49 years of age and 50 through 59 years of age, respectively) to the corresponding OPA GMTs induced by PCV20 among adults 60 through 64 years of age (Cohort 1 subset). This study was conducted between December 12, 2018 and April 9, 2020; a total of 3,889 subjects were vaccinated. The clinical study report was dated June 11, 2020.

> **Reviewer Comment:** *The study design, objectives, endpoints and success criteria for study B7471007 were discussed and agreed to during an EOP2 meeting on September 18, 2018.*
>
> *Non-inferiority comparisons to licensed pneumococcal vaccines were performed in pneumococcal-vaccine naïve adults ≥60 years of age. An age-bridging strategy was considered more suitable than administering PPSV23 to healthy adults <60 years of age, due to concerns about hyporesponsiveness (i.e., reduced OPA titers to serotypes common to both vaccines when PCV13 is administered after an initial dose of PPSV23) (Poolman et al, 2011), (O'Brien et al, 2007), (STN 125324/262 Clinical Review). This age-bridging strategy, bridging OPA titers from adults 18 through 49 years and 50 through 59 years of age to the corresponding titers from adults 60 through 64 years of age, was based on the approach used to evaluate PCV13 effectiveness in adults 50 years and older (STN 125324/262). The 60 through 64-year age group was also selected, because it was considered a more stringent comparator relative to the ≥ 60-year age group due to immunosenescence, which results in declining immune function with increasing age.*

Two non-inferiority trials were conducted to support the initial licensure of PCV13 in adults 50 years of age and older (accelerated approval pathway). One trial was conducted in pneumococcal vaccine naïve adults 18 through 64 years of age (data in adults 18 through 49 were not ready for submission at the time of initial licensure of PCV13 in adults) and the second trial was conducted in adults ≥70 years of age previously immunized with at least 1 dose of PPSV23 at least 5 years prior to enrollment. In the trial conducted in 18 through 64-year-old pneumococcal vaccine naïve adults, non-inferiority comparisons of PCV13 to PPSV23 were limited to adults 60 through 64 years of age. This was because adults 50 through 59 years of age were not given PPSV23 as a comparator, because of the risk of hyporesponsiveness (decreased immune responses with repeat vaccinations later in life). PCV13 effectiveness in the 18 through 49 and 50 through 59-year age groups were supported by immunobridging analyses comparing responses to those achieved by 60 through 64-year-old adults.

6.1.1 Objectives

Primary Safety Objective

- To describe the safety profile of PCV20 in adults 18 years of age and older.
- Primary safety endpoints:
  - Reported prompted local reactions (injection site redness, swelling and pain) within 10 days after vaccination
  - Reported prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination
  - Reported AEs within1 month after vaccination.
  - Reported serious adverse events (SAEs) and newly diagnosed chronic medical condition (NDCMCs) within 6 months after vaccination

Primary Immunogenicity Objectives

1. To demonstrate that the immune responses to the 13 serotypes in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by PCV20 in adults 60 years of age and older (Cohort 1) are noninferior to the immune response induced by PCV13.
   - Primary endpoint: serotype-specific opsonophagocytic activity (OPA) titers 1 month after the respective vaccination (PCV20 or PCV13)
   - Noninferiority criterion: Noninferiority was declared for a serotype if the lower bound of the 2-sided 95% CI for the geometric mean titer (GMT) ratio (GMT_{PCV20}/GMT_{PCV13}) was >0.5 (2-fold criterion).

2. To demonstrate that the immune responses to the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by PCV20 in adults 60 years of age and older (Cohort 1) are noninferior to the immune response induced by PPSV23.
   - Primary endpoint: serotype-specific OPA titers 1 month after the respective vaccination (PCV20 or PPSV23). Note: for the 7 new serotypes, OPA titers were measured 1 month after PCV20 and 1 month after PPSV23 (i.e., 2 months after the initial dose of PCV13).
   - Noninferiority criterion: Noninferiority was declared for a serotype if the lower bound of the 95% CI for the GMT ratio (GMT_{PCV20}/GMT_{PPSV23}) was >0.5 (2-fold criterion).

Reviewer Comment: *CBER agreed to the primary study objectives, endpoints and success criteria, as described above, after reviewing the final protocol received on November 5, 2018. The 2-fold non-inferiority criterion (LL of 95% CI > 0.5) was agreed to as the most appropriate criterion because the OPA assay variability made a smaller margin impracticable. Of note, a 2-fold non-inferiority criterion was also pre-specified in the PCV13 prelicensure non-inferiority studies supporting the approval for the use of PCV13 in adults.*

Secondary Immunogenicity Objectives

1. To compare the immune responses to the 20 serotypes in PCV20 induced in adults 50-59 years of age (Cohort 2) to the corresponding immune responses induced by PCV20 in adults 60-64 years of age (Cohort 1 subset).
    - Primary endpoint: serotype-specific OPA titers 1 month after vaccination with PCV20
    - Immune-bridging success criterion: Success was declared for a serotype if the lower bound of the 2-sided 95% CI for the GMT ratio ($GMT_{50\text{-}59}$ years/$GMT_{60\text{-}64}$ years) was >0.5 (2-fold criterion).

2. To compare the immune responses to the 20 serotypes in PCV20 induced in adults 18-49 years of age (Cohort 3) to the corresponding immune responses induced by PCV20 in adults 60-64 years of age (Cohort 1 subset).
    - Primary endpoint: serotype-specific OPA titers 1 month after vaccination with PCV20
    - Immune-bridging success criterion: Success was declared for a serotype if the lower bound of the 2-sided 95% CI for the GMT ratio ($GMT_{18\text{-}49}$ years/$GMT_{60\text{-}64}$ years) was >0.5 (2-fold criterion).

3. To describe the immune responses to PCV20 in adults ≥60 years of age (Cohort 1), 50-59 years of age (Cohort 2), and 18-49 years of age (Cohort 3).
    - Secondary endpoints:
        - ≥4-fold rise in serotype-specific OPA titers from pre- to 1 month post-vaccination
        - Fold rise in serotype-specific OPA titers from pre- to 1 month post-vaccination
        - Serotype-specific OPA titers ≥ lower limit of quantitation (LLOQ[7]) 1 month after vaccination

7 The LLOQ is defined as the lowest sample concentration that can be measured by the assay with acceptable accuracy, linearity and precision.

Reviewer Comment: *Among the secondary endpoints listed under secondary objective #3, this review focuses on the % of subjects achieving a ≥4-fold rise in serotype-specific OPA titers from pre- to 1 month post-vaccination. A 4-fold rise in OPA antibody titers has historically been considered to be an acceptable vaccine response in the evaluation of pneumococcal serotypes (e.g., the evaluation of a ≥4-fold rise in antibody against serotype 6A in Prevnar 13; sBLA 125324/1196). However, the a) geometric mean of the fold rise (GMFR) in serotype-specific OPA titers from pre- to 1 month post-vaccination and b) serotype-specific OPA titers ≥ LLOQ at 1 month post-vaccination are not considered by CBER to be the best measures of vaccine response to support vaccine effectiveness. In addition, the proportion of subjects achieving serotype-specific assay LLOQs reflects the adequacy of the serotype-specific assay.*

Exploratory Objectives

1. To further describe the immune responses to PCV20 in adults ≥60 years of age, 50-59 years of age, and 18-49 years of age

    - Exploratory endpoints:
      - ≥4-Fold rise in pneumococcal serotype 15C OPA titer from before to 1 month after vaccination
      - Pneumococcal serotype 15C OPA titer ≥ LLOQ 1 month post-vaccination
      - Pneumococcal serotype 15C OPA titer 1 month after vaccination
      - Fold rise in pneumococcal serotype 15C OPA titer from before to 1 month after vaccination

    Reviewer Comment*: Serotype 15C is not a polysaccharide (PS) conjugate contained in PCV20, but the 15C capsular PS is structurally related to the vaccine serotype 15B. The PS of serotype 15B shares the identical PS structure to 15C except that the 15B PS is O-acetylated. Thus, immunization with PCV20, which contains the PS conjugate of 15B has the potential to induce functional antibodies against both the PS backbone structure shared by both 15B and 15C and the epitope(s) unique to 15B. The capacity of PCV20 to elicit cross-reactive functional responses to 15C was explored in the Phase 3 trials.*

2. To describe the immune responses to the 20 serotypes induced by PCV20 in adults ≥18 years of age with underlying medical conditions or other factors that put them at increased risk for serious pneumococcal infection (e.g., asthma, diabetes mellitus, chronic lung disease, cigarette smoking)

    - Exploratory endpoint: Serotype-specific OPA titers 1 month after vaccination (for participants with an increased risk for serious pneumococcal infection)

    Reviewer Comment*: Exploratory objective 2 results are not included in this review, because the results are not considered clinically significant. Subjects with the noted risk factors are considered immunocompetent and are thus expected to elicit similar levels of serotype-specific OPA antibodies compared to adults without the noted risk factors.*

6.1.2 Design Overview

Study B7471007 was a Phase 3, randomized, double-blind, multicenter study conducted in the U.S. and Sweden. A total of 3,880 pneumococcal vaccine-naïve adults ≥18 years of age were to be enrolled into 1 of 3 age-based cohorts (Table 2). The randomization ratio was 1:1 in Cohort 1, and 3:1 in Cohorts 2 and 3. All subjects enrolled in Sweden were ≥65 years of age.

Table 2. Planned Enrollment and Vaccination[a], Study B7471007

Cohort Number	Age (Years)	Vaccination #1 Day 1	Vaccination #2 Day 28-42	Planned # of Subjects
1	≥60	PCV20	Saline	1500[b]
1	≥60	PCV13	PPSV23	1500[b]
2	50-59	PCV20	-	330
2	50-59	PCV13	-	110
3	18-49	PCV20	-	330
3	18-49	PCV13	-	110

[a] All injections were 0.5 mL and administered intramuscularly in the deltoid of the non-dominant arm.
[b] Enrollment in Cohort 1 was stratified by age, targeting 1,000 subjects 60-64 years of age and 500 subjects ≥65 years of age in each treatment group. Among ≥65-year-old subjects, enrollment targeted ~700 subjects 65-69 years, ~200 subjects 70-79 years and ~100 subjects ≥80 years of age.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Protocol Table 3, p27.

Vaccination 1 (PCV20 or PCV13) was administered in a double-blind fashion as the PCV20 and PCV13 vaccines were identical in appearance and the pre-filled syringes were packaged in blinded cartons. Vaccination 2 (PPSV23 or saline) was prepared by and administered by a third-party unblinded site staff member who did not participate in subject assessments, as saline and PPSV23 do not appear the same. Serology testing was also performed in a blinded fashion. All other study site staff and investigators as well as Wyeth were blinded until the last subject completed the final telephone call and the database was locked. Only one analysis was performed after final database lock; this final analysis included all planned safety and immunogenicity analyses.

The duration of subject participation was approximately 6 months after the first vaccination (PCV20 or PCV13) and included 3 study visits and 1 telephone contact as follows:

- Visit 1 (Day 1): Informed consent, Vaccination 1, blood draw for immunogenicity
- Visit 2 (Day 28 to 42 post-Vaccination 1): Vaccination 2, blood draw for immunogenicity
- Visit 3 (Day 28 to 42 post-Vaccination 2): blood draw for immunogenicity
- 6-Month Safety Telephone Contact (168-196 days after Vaccination 1)

6.1.3 Population

Individuals were eligible for enrollment if they met all of the study inclusion criteria and none of the exclusion criteria. Selected key inclusion and exclusion criteria are listed below. Vaccination was to be temporarily delayed for eligible subjects until 1) resolution of any febrile (body temperature ≥38.0°C) or other acute illness within 48 hours before study vaccination, 2) at least 14 days passed after receipt of any non-live vaccine or least 28 days passed after any live vaccine, and 3) at least 28 days passed since discontinuation of any short term (<14 days) systemic corticosteroid use. Immunogenicity blood draws planned at visits 1-3 were to be temporarily delayed as needed until at least 72 hours after any receipt of antibiotic therapy.

Key Inclusion Criteria

1. Adult males and females 18 years of age and older
   a. Cohort 1: 60 years of age and older
   b. Cohort 2: 50-59 years of age
   c. Cohort 3: 18-49 years of age
2. Adults determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study, including adults with preexisting stable disease, defined as disease not requiring significant change in therapy in the previous 6 weeks or hospitalization for worsening disease within 12 weeks before receipt of investigational product.

Key Exclusion Criteria

1. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.
2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of PCV20, PCV13, or any other diphtheria toxoid–containing vaccine or PPSV23.
3. Serious chronic disorder including metastatic malignancy, severe chronic obstructive pulmonary disease requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excluded the participant from participating in the study.
4. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the participant inappropriate for entry into this study.
5. History of microbiologically proven invasive disease caused by *S. pneumoniae.*
6. Participants who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw. If systemic corticosteroids had been administered short term (<14 days) for treatment of an acute illness, participants should not have been enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.
7. Participants with known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, generalized malignancy, human immunodeficiency virus infection, leukemia, lymphoma, or organ or bone marrow transplant.
8. Receipt of blood/plasma products or immunoglobulins from 60 days before investigational product administration or planned receipt through study participation.

6.1.4 Study Treatments or Agents Mandated by the Protocol

PCV20 and PCV13 vaccines were supplied as single-use prefilled syringes. PPSV23 and saline placebo were supplied as packaged vials. Each study treatment was to be administered intramuscularly in the deltoid muscle of the non-dominant arm.

PCV20 is a sterile liquid suspension for IM administration of capsular polysaccharide antigens of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F each individually conjugated to nontoxic variant of diphtheria toxin (CRM_{197}) as a carrier protein. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5 mL dose. The vaccine contains (b) (4) succinate buffer, (b) (4) sodium chloride, (b) (4) polysorbate 80, and 0.125 mg aluminum as aluminum phosphate, per 0.5 mL dose. Lot number: T82473.

PCV13 contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM_{197}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5 mL dose. The vaccine contains (b) (4) succinate buffer, (b) (4) sodium chloride, (b) (4) polysorbate 80, and 0.125 mg aluminum as aluminum phosphate, per 0.5 mL dose. The PCV13 polysaccharide intermediates and vaccine substances were manufactured according to the approved Prevnar 13 commercial

process, and the formulation and filling processes are similar; but they are performed at a different scale than the commercial process. Lot number: W73014.

PPSV23 is a clear, sterile solution consisting of a mixture of purified capsular polysaccharides from 23 serotypes of *S. pneumoniae*: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20 22F, 23F and 33F. The vaccine is formulated to contain 25 µg of each of the 23 purified polysaccharide serotypes per 0.5 mL dose of vaccine in an isotonic saline solution containing 0.25% phenol as a preservative. Lot numbers: R022111, R007722.

Placebo is a sterile normal saline solution for injection (0.9% sodium chloride injection). Lot number: AN-LDM.

Non-study Vaccines

The name and date of administration of any permitted non-study vaccinations were recorded in the case report form (CRF). Licensed inactivated influenza vaccine was permitted >14 days prior to or >14 days after study product injection. Receipt of any other licensed non-study vaccine (except pneumococcal vaccine which was prohibited in this study) was permitted after Visit 3 (Cohort 1 only) or after Visit 2 (Cohorts 2 and 3). Prophylactic antipyretics were permitted but not recommended on the day prior to or the day of investigational product administration.

6.1.6 Sites and Centers

Study B7471007 was conducted at a total of 61 sites; 54 sites in the U.S. and 7 sites in Sweden. The numbers of subjects randomized/enrolled were 3,730 and 172 in the U.S. and Sweden, respectively.

> ***Reviewer Comment:*** *All subjects who enrolled in Sweden in studies B7471007 and B7471006 were ≥65 years of age. CBER agreed to enrollment of subjects from European clinical study sites, as Wyeth foresaw difficulty in enrolling the targeted number of pneumococcal vaccine-naïve adults ≥65 years of age in the U.S., where ACIP recommendations for adults ≥65 years of age include routine vaccination with PPSV23 in addition to shared decision making for administration of PCV13 to persons ≥65 years of age.*

6.1.7 Surveillance/Monitoring

Safety Monitoring

Safety monitoring in study B7471007 included monitoring for the following:

1. Immediate adverse reactions within 30 minutes after each vaccination
2. Solicited[8] local reactions through 10 days[9] after Vaccination 1 (injection site erythema, edema and pain),
3. Solicited systemic adverse events and use of antipyretic/pain medication through 7 days[10] after Vaccination 1 (headache, tiredness, muscle pain, joint pain and fever),

[8] Subjects were given a digital thermometer, a measuring device and an electronic diary (e-diary) to record prompted local reactions and systemic adverse events daily in their e-diary. One measuring device unit = 0.5 cm (measuring range: 1 to 21+ units). The highest temperature for each day was to be recorded in the e-diary. In the event of fever on day 7, temperature was to be collected daily until resolution.
[9] Study days 1 through 10 (day 1 = day of vaccination)
[10] Study days 1 through 7 (day 1 = day of vaccination)

4. Unsolicited adverse events through 1 month after each vaccination, and
5. SAEs and newly diagnosed chronic medical conditions through 6 months after Vaccination 1.

Solicited local reactions and solicited systemic adverse events were graded according to a pre-specified toxicity grading scale (see Tables 15-20 in Section 6.1.12.2). Severity was not collected for use of antipyretic or pain medication. Grade 4 assessments were only to be made by the investigator and recorded as AEs in the CRF. The need for an unscheduled visit was considered for subjects with a ≥ grade 3 injection site reaction within 10 days post-vaccination or any grade 4 systemic reaction during 7 days post-vaccination.

Immunogenicity Monitoring

Blood samples for immunogenicity assessments were collected from all subjects prior to and 1 month after Vaccination 1. In Cohort 1 subjects only, blood samples for immunogenicity were also collected 1 month after Vaccination 2. OPA titers for all serotypes present in PCV20 were determined on all sera collected prior to and 1 month after Vaccination 1. OPA titers for the 7 additional serotypes only (8, 10A, 11A, 12F, 15B, 22F, and 33F) were determined on sera collected 1 month after Vaccination 2 in Cohort 1. In addition, OPA titers were tested for non-vaccine serotype 15C in a random subset of subjects.

6.1.8 Endpoints and Criteria for Study Success

Please see Section 6.1.1 of the clinical review.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations

- A total of 2,000 subjects 60-64 years of age were planned in Cohort 1 to ensure ~1,800 evaluable subjects in this age group and to provide the study with 72% power to demonstrate noninferiority in serotype-specific OPA GMT ratios for all 20 serotypes. Please refer to the statistical review for details regarding sample size calculations.
- A total of 440 subjects were planned in Cohorts 2 and 3 to ensure >90% power to demonstrate noninferiority in serotype-specific OPA GMT ratios between each of the younger age cohorts and the subjects 60-64 years of age from Cohort 1 (Cohort 1 subset).

Statistical Considerations

- For the primary study objective (primary analyses), calculation of OPA GMT ratios and CIs for each serotype used a linear regression model that included terms for age, corresponding baseline OPA titer, sex, smoking status, and vaccine group. The unadjusted serotype-specific OPA GMT ratio and CI were also calculated for each serotype.
- For the secondary study objective (secondary bridging analyses), calculation of OPA GMT ratios and CIs for each serotype used a regression model that included terms for the corresponding baseline OPA titer, sex, smoking status and cohort. Two separate regression models were fitted for comparing results from the younger cohort to results from Cohort 1. Unadjusted serotype-specific OPA GMT ratios and CIs were also calculated for each of the serotypes as a supportive approach.

- Missing assay results were not replaced or imputed.
- Serotype-specific OPA titers below the corresponding serotype-specific assay LLOQ were set to 0.5 x LLOQ for analysis (Source: STN 125731.1 module 5.3.5.1, Study B7471007 Statistical Analysis Plan).
    - The LLOQs by serotype are as follows:
        - Serotype 1: (b) (4)
        - Serotype 3:
        - Serotype 4:
        - Serotype 5:
        - Serotype 6A (b) (4)
        - Serotype 6B
        - Serotype 7F:
        - Serotype 8: (b) (4)
        - Serotype 9V: (b) (4)
        - Serotype 10A
        - Serotype 11A
        - Serotype 12F
        - Serotype 14:
        - Serotype 15B: (b) (4)
        - Serotype 18C:
        - Serotype 19A:
        - Serotype 19F:
        - Serotype 22F:
        - Serotype 23F:
        - Serotype 33F:
        - Serotype 15C:

Analysis Timing

A single final analysis conducted after the database lock included all planned safety and immunogenicity analyses.

Safety Analysis

The safety objectives were evaluated by descriptive summary statistics for each primary safety endpoint for each vaccine group and each cohort.

Analysis Populations

- The safety population included all subjects who received at least 1 dose of PCV20, PCV13, PPSV23, or saline and had safety follow-up. Subjects were included in the vaccine group corresponding to the vaccine actually received.

- Three evaluable immunogenicity populations were defined for the analysis of immunogenicity results. Subjects were included in the evaluable vaccine group corresponding to their randomized assignment.

  – Evaluable 13-matched immunogenicity population: primary analysis population for results of the 13-matched serotypes in Cohort 1.
  – Evaluable 7-additional immunogenicity population: primary analysis population for results of the 7 additional serotypes in Cohort 1.
  – Evaluable-20 immunogenicity population: primary analysis population for immunogenicity results in Cohorts 2 (50-59 years) and 3 (18-49 years); defined for

comparisons between the Cohort 1 subset (subjects 60-64 years of age) and either Cohort 2 or Cohort 3 subjects.

Evaluable 13-Matched Population Criteria

1. Received the assigned vaccination at Visit 1 (PCV20 or PCV13) as randomized
2. Enrolled in appropriate cohort based on age at Visit 1 (i.e., ≥60 years or age in Cohort 1)
3. Had Visit 2 blood draw within 27 to 49 days after Vaccination 1.
4. Had ≥1 valid and determinate OPA titer for any of the 13 matched serotypes at Visit 2
5. Had no major protocol deviations as determined by the clinician.

Evaluable 7-Additional Population Criteria

1. Received Vaccination 1 if randomized to the PCV20/saline group or received both vaccinations as randomized if randomized to the PCV13/PPSV23 group
2. Enrolled in appropriate cohort based on age on the day of first vaccination
3. Had either the Visit 2 blood draw within 27 to 49 days after Vaccination 1 (PCV20 for the PCV20/saline group or the Visit 3 blood draw within 27 to 49 days after Vaccination 2 (PPSV23) for the PCV13/PPSV23 group
4. Had ≥1 valid and determinate OPA titer for any of the 7 additional serotypes at either Visit 2 for the PCV20/saline group or Visit 3 for the PCV13/PPSV23 group.
5. Had no major protocol deviations as determined by the clinician.

Evaluable-20 Population Criteria

1. Received the assigned Vaccination at Visit 1 as randomized
2. Enrolled in appropriate cohort based on age on the day of first vaccination
3. Had Visit 2 blood draw within 27 to 49 days after Vaccination 1
4. Had ≥1 valid and determinate OPA titer for any of 20 serotypes for Visit 2
5. Had no major protocol deviations as determined by the clinician.

The all-available immunogenicity population included all subjects who received ≥1 dose of PCV20, PCV13, PPSV23, or saline and had ≥1 valid and determinate OPA titer after any vaccination. This population was the secondary analysis population for immunogenicity results. Subjects were included in all-available vaccine group corresponding to their randomized assignment.

- For cohort-specific analysis, the need for all-available analyses was assessed separately for each cohort. If there was <5% difference in sample size between the all-available and evaluable populations, then only the evaluable population was used for the immunogenicity analyses.
- For cross-cohort analysis where Cohort 2 or 3 was compared to the Cohort 1 subset (subjects 60-64 years of age), if either cohort in the comparison had <5% difference in sample size between the all-available and evaluable populations, analyses would be based on the evaluable populations only.

6.1.10 Study Population and Disposition

A total of 3009 subjects were randomized in Cohort 1; 2,997 received PCV20 or PCV13 and 2,835 (94.2%) completed the study (Table 8). A total of 445 subjects were randomized and vaccinated in Cohort 2, and 432 (97.1%) completed the study. In Cohort 3, a total of 448 subjects were randomized, 447 were vaccinated, and 423 (94.4%) completed the study.

6.1.10.1 Populations Enrolled/Analyzed

Section 6.1.9 defines this study's populations enrolled and analyzed. The proportions of subjects in Cohort 1 included in the evaluable 13-matched, evaluable 7-additional, and all-available immunogenicity analysis populations were similar in the PCV20/saline and PCV13/PPSV23 groups (Table 3). Similarly, the proportion of subjects in Cohorts 2 and 3 included in the evaluable-20 immunogenicity populations were similar in the PCV20/saline and PCV13/PPSV23 groups (Table 4). The most common reason for exclusion from each of the evaluable immunogenicity populations (13-matched, 7-additional, and evaluable-20) was not having blood collected within the pre-specified time window. No analyses in Cohorts 1, 2 or 3 were conducted using the all-available immunogenicity analysis population due to a ≤5% difference in sample size between the all-available population and each of the evaluable populations.

Table 3. Immunogenicity Analysis Populations, Cohort 1 (≥60 Years), Study B7471007

Group/Reason for Exclusion	PCV20/Saline n[a] (%)	PCV13/PPSV23 n[a] (%)	Total n[a] (%)
Randomized[b]	1514 (100.0)	1495 (100.0)	3009 (100.0)
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)
≥65 years of age	490 (32.4)	472 (31.6)	962 (32.0)
Subjects excluded[c] from evaluable 13-matched immunogenicity population	79 (5.2)	75 (5.0)	154 (5.1)
Didn't receive assigned Vaccination 1 as randomized	7 (0.5)	5 (0.3)	12 (0.4)
Didn't have Visit 2 (V2) blood collection within 27 to 49 days after Vaccination 1	66 (4.4)	60 (4.0)	126 (4.2)
Didn't have at least 1 valid OPA titer for any of the 13-matched serotypes at V2	48 (3.2)	43 (2.9)	91 (3.0)
Had any other major protocol deviations[d]	15 (1.0)	19 (1.3)	34 (1.1)
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)
≥65 years of age	488 (32.2)	466 (31.2)	954 (31.7)
Subjects excluded[c] from evaluable 7-additional immunogenicity population	81 (5.4)	112 (7.5)	193 (6.4)
Didn't receive Vaccination 1 if randomized to PCV20/saline group or both vaccinations as randomized if randomized to PCV13/PPSV23	7 (0.5)	50 (3.3)	57 (1.9)
Didn't have blood collected 27 to 49 days after Vaccination 1 for PCV20/saline group or after Vaccination 2 for PCV13/PPSV23 group	66 (4.4)	81 (5.4)	147 (4.9)
No valid and determinate OPA titer for any of 7 additional serotypes at V2 for PCV20/saline group or Visit 3 for PCV13/PPSV23 group	50 (3.3)	61 (4.1)	111 (3.7)
Had any other major protocol deviations[d]	15 (1.0)	34 (2.3)	49 (1.6)

Group/Reason for Exclusion	PCV20/Saline n[a] (%)	PCV13/PPSV23 n[a] (%)	Total n[a] (%)
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)
≥65 years of age	502 (33.2)	484 (32.4)	986 (32.8)
Subjects excluded[c] from all-available immunogenicity population	38 (2.5)	39 (2.6)	77 (2.6)
Did not receive ≥1 dose of study vaccine	7 (0.5)	5 (0.3)	12 (0.4)
Didn't have valid and determinate OPA titer after vaccination	38 (2.5)	39 (2.6)	77 (2.6)

Abbreviation: OPA = opsonophagocytic activity.
[a] n = Number of subjects with the specified characteristic.
[b] These values are the denominators for the percentage calculations.
[c] Subjects may have been excluded for more than 1 reason.
[d] Includes subjects who took prohibited concomitant medication or vaccine, who entered into study but did not meet eligibility criterion, and who were administered investigational product after a temperature excursion (n=13 at 1 site)
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Tables 8, p 53-54.

Table 4. PCV20 Vaccination in Cohort 1 Subset (60-64 Years), Cohort 2 and Cohort 3, Evaluable-20 Immunogenicity Populations, Study B7471007

Reason for Exclusion	Cohort 1 Subset PCV20/Saline Group (60-64 years) a[n] (%)	Cohort 2 PCV20 Group n[a] (%)	Cohort 3 PCV20 Group n[a] (%)
Randomized[b]	996 (100.0)	334 (100.0)	336 (100.0)
Evaluable-20 immunogenicity population	946 (95.0)	321 (96.1)	317 (94.3)
Subjects excluded[c] from evaluable-20 immunogenicity population	50 (5.0)	13 (3.9)	19 (5.7)
Didn't receive PCV20 vaccination as Randomized	3 (0.3)	0	1 (0.3)
Wasn't enrolled in appropriate cohort/stratum based on age on the day of first vaccination	0	0	1 (0.3)
Did not have Visit 2 blood collection within 27 to 49 days after PCV20 vaccination	41 (4.1)	11 (3.3)	16 (4.8)
Didn't have valid and determinate OPA titer for any of the 20 serotypes for Visit 2	29 (2.9)	3 (0.9)	12 (3.6)
Had any other major protocol deviations[d]	10 (1.0)	2 (0.6)	3 (0.9)

Abbreviation: OPA = opsonophagocytic activity.
[a] n = Number of subjects with the specified characteristic.
[b] These values are the denominators for the percentage calculations.
[c] Subjects may have been excluded for more than 1 reason.
[d] Includes subjects who took prohibited vaccine, who entered into the study but did not meet elig bility criterion, and who were enrolled into the incorrect cohort.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Tables 9, p 54-55.

6.1.10.1.1 Demographics

Table 5 summarizes baseline demographic characteristics and smoking history by study cohort and study group for the safety population (results were similar for each evaluable population; data not shown, Supplemental Tables 14.4 through 14.6). The two study groups within each cohort were similar with regard to baseline demographics and smoking history. Overall, the safety population included 58%-69% females, 81%-90% White, 6%-14% Black and <6% from other racial groups across all cohorts; 4%-11% were Hispanic/Latino; and 11%-20% were current smokers. Overall in Cohort 1, 66.2% were 60-64 years of age, 20.8% were 65-69 years of age, 10.6% were 70-79 years of age, and 2.3% were ≥80 years of age. The mean age of subjects was 65 years in Cohort 1, 55 years in Cohort 2, and 34 years in Cohort 3.

Table 5. Baseline Demographic Characteristics by Study Cohort and Study Group, Safety Population, Study B7471007

Characteristic	Cohort 1 (≥60 Years) PCV20/Saline N[a]=1507 n[b] (%)	Cohort 1 (≥60 Years) PCV13/PPSV23 N[a]=1490 n[b] (%)	Cohort 2 (50-59 Years) PCV20 N[a]=334 n[b] (%)	Cohort 2 (50-59 Years) PCV13 N[a]=111 n[a] (%)	Cohort 3 (18-49 Years) PCV20 N[a]=335 n[a] (%)	Cohort 3 (18-49 Years) PCV13 N[a]=112 n[a] (%)
Sex						
Male	610 (40.5)	611 (41.0)	139 (41.6)	42 (37.8)	121 (36.1)	35 (31.3)
Female	897 (59.5)	879 (59.0)	195 (58.4)	69 (62.2)	214 (63.9)	77 (68.8)
Race						
White	1295 (85.9)	1237 (83.0)	278 (83.2)	90 (81.1)	274 (81.8)	101 (90.2)
Black or African American	177 (11.7)	212 (14.2)	35 (10.5)	15 (13.5)	34 (10.1)	7 (6.3)
Asian	19 (1.3)	15 (1.0)	10 (3.0)	2 (1.8)	11 (3.3)	1 (0.9)
American Indian or Alaska Native	6 (0.4)	9 (0.6)	0 (0.0)	3 (2.7)	1 (0.3)	1 (0.9)
Native Hawaiian or other Pacific Islander	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	1 (0.9)
Multiracial	7 (0.5)	9 (0.6)	6 (1.8)	1 (0.9)	8 (2.4)	1 (0.9)
Not Reported	2 (0.1)	7 (0.5)	5 (1.5)	0 (0.0)	4 (1.2)	0 (0.0)
Ethnicity						
Hispanic/Latino	167 (11.1)	169 (11.3)	12 (3.6)	8 (7.2)	24 (7.2)	7 (6.3)
Non-Hispanic/non-Latino	1324 (87.9)	1308 (87.8)	319 (95.5))	101 (91.0)	300 (89.6)	102 (91.1)
Not reported	16 (1.1)	13 (0.9)	3 (0.9)	2 (1.8)	11 (3.3)	3 (2.7)
Age Group						
60-64 years	993 (65.9)	992 (66.6)	N/A	N/A	N/A	N/A
65-69 years	319 (21.2)	305 (20.5)	N/A	N/A	N/A	N/A
70-79 years	160 (10.6)	159 (10.7)	N/A	N/A	N/A	N/A
≥80 years	35 (2.3)	34 (2.3)	N/A	N/A	N/A	N/A
Age at Vaccination 1 (Years)						
Mean (SD)	64.6 (4.8)	64.6 (4.8)	54.9 (2.8)	55.0 (3.1)	34.0 (8.8)	33.9 (8.0)
Median (Min, Max)	63.0 (60, 91)	63.0 (60, 89)	55.0 (50, 59)	56.0 (48, 59)	34.0 (18, 60)	32.0 (19, 49)
Smoking History						
Current Smoker	170 (11.3)	192 (12.9)	52 (15.6)	17 (15.3)	49 (14.6)	22 (19.6)
Mean (SD) # Years Smoking	38.4 (15.4)	37.4 (14.4)	31.6 (11.4)	28.7 (13.5)	14.8 (8.9)	13.5 (9.0)
Ex-smoker	446 (29.6)	472 (31.7)	67 (20.1)	22 (19.8)	47 (14.0)	22 (19.6)
Mean (SD) # Years Since Quitting	23.5 (14.6)	24.7 (14.8)	18.5 (11.6)	18.8 (13.3)	8.1 (6.9)	6.8 (5.9)
Never Smoked	891 (59.1)	826 (55.4)	215 (64.4)	72 (64.9)	239 (71.3)	68 (60.7)

Note: N/A = not applicable. Note: Subject (b) (6) was incorrectly enrolled in Cohort 3 rather than in Cohort 1 and is included in the Cohort 3 data analysis. Subject (b) (6) was incorrectly enrolled in Cohort 2, rather than in Cohort 3 and is included in the Cohort 2 data analysis.

[a] N = number of subjects in the specified group or the total sample. This value is the denominator for the percentage calculations.

[b] n = Number of subjects with the specified characteristic.

Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Tables 10-12, p 56-60.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

At enrollment, approximately one-third of subjects had risk factors for serious pneumococcal disease, including smoking (12.9%), stable medical conditions of chronic cardiovascular disease (5.5%), chronic pulmonary disease including asthma (8.7%), chronic liver disease (0.4%), and diabetes mellitus (13.9%). (Data not shown. Integrated Summary of Safety Table 17 shows data for Study B7471007 Cohorts Pooled).

Table 6 presents the proportions of study subjects with one or more risk factors[6] for serious pneumococcal infections in the primary immunogenicity analysis populations. The proportion of subjects with underlying comorbidities were similar between the two Cohort 1 study groups and were generally similar across the smaller study groups in Cohorts 2 and 3 (PCV20 groups shown only in Table 6). The distributions of baseline comorbidities were consistent with those observed in the primary immunogenicity analysis populations.

Table 6. Subjects with Stable Underlying Comorbidities Known to Increase the Risk for Serious Pneumococcal Infection, Cohort 1, Evaluable 13-Matched Immunogenicity Population, and the Evaluable-20 Immunogenicity Population for Cohorts 2 and 3, Study B7471007

Comorbidity	Cohort 1 (≥60 Years) PCV20/ Saline N[a]=1435 n[b] (%)	Cohort 1 (≥60 Years) PCV13/ PPSV23 N[a]=1420 n[b] (%)	Cohort 2 (50-59 Years) PCV20 N[a]=321 n[b] (%)	Cohort 3 (18-49 Years) PCV20 N[a]=108 n[b] (%)
Subjects with ≥1 risk factor(s)[c]	465 (32.4)	516 (36.3)	104 (32.4)	79 (24.9)
Any selected medical history[d]	354 (24.7)	404 (28.5)	65 (20.2)	39 (12.3)
Chronic cardiovascular disease	71 (4.9)	109 (7.7)	12 (3.7)	3 (0.9)
Chronic liver disease	5 (0.3)	7 (0.5)	2 (0.6)	0 (0.0)
Chronic pulmonary disease	130 (9.1)	117 (8.2)	22 (6.9)	30 (9.5)
Diabetes mellitus	209 (14.6)	243 (17.1)	39 (12.1)	9 (2.8)
Current smoking	163 (11.4)	179 (12.6)	50 (15.6)	46 (14.5)

Note: MedDRA (v22.1) coding dictionary applied.
[a] N = Number of subjects in the specified group or the total sample. This value is in the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] Includes current smoking as a risk factor.
[d] Includes medical condition risk factors based on 2010 MMWR;59(34):1102-1106. Does not include current smokers.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Tables 14.7 - 14.9 on pages 141-147.

Reviewer Comment: *The at-risk conditions summarized in Table 6 above were based on the Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-valent Pneumococcal Polysaccharide Vaccine (PPSV23) (Nuorti and Whitney 2010). These include the following medical conditions in immunocompetent adults:*

- *Chronic heart disease (excluding hypertension and arrhythmias and including congestive heart failure and cardiomyopathies); this includes atherosclerotic cardiovascular disease, angina, congestive heart failure, and Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms relating to certain heart valve conditions (i.e., mitral valve incompetence, aortic valve incompetence, mitral valve disease and aortic valve disease). (Note: mitral valve prolapse was not included because Wyeth noted that, although it can progress to mitral regurgitation and heart failure, it can exist in a stable form without significant physiologic consequences; in addition, pulmonary valve incompetence in retrospect should have been added to this list, however the only study participant with pulmonary*

valve incompetence was already included in Table 6 due to concomitant mitral valve incompetence which was considered a risk condition).

- *Chronic lung disease (including chronic obstructive pulmonary disease, emphysema and asthma)*
- *Diabetes mellitus*
- *Cigarette smoking*

There were no subjects with cerebrospinal fluid leaks and cochlear implants; there were only a few subjects with alcoholism or chronic liver disease, as in most cases, such subjects would not meet eligibility criteria.

Table 7 presents select baseline comorbidities noted in the medical history (ongoing at the time of enrollment) for Cohort 1, 2, and 3 PCV20 group safety populations. Of note, pre-licensure PCV20 studies excluded persons with serious chronic disorders (e.g., severe chronic obstructive pulmonary disease, end-stage renal disease, clinically unstable cardiac disease) and persons with known or suspected immunodeficiency or other conditions associated with immunosuppression.

Table 7. Select Medical History (Ongoing) of Cohorts 1, 2, and 3, Safety Population, Study B7471007

Comorbidity	Cohort 1 (≥60 Years) PCV20/Saline N[a]=1507 n[b] (%)	Cohort 1 (≥60 Years) PCV13/PPSV23 N[a]=1490 n[b] (%)	Cohort 2 (50-59 Years) PCV20 N[a]=334 n[b] (%)	Cohort 2 (50-59 Years) PCV13 N[a]=111 n[a] (%)	Cohort 3 (18-49 Years) PCV20 N[a]=335 n[a] (%)	Cohort 3 (18-49 Years) PCV13 N[a]=112 n[a] (%)
Any medical history by MedDRA SOC/PT	1448 (96.1)	1438 (96.5)	310 (92.8)	105 (94.6)	261 (77.9)	93 (83.0)
Blood and lymphatic system disorders	41 (2.7)	41 (2.8)	7 (2.1)	2 (1.8)	8 (2.4)	1 (0.9)
Cardiac disorders[c]	134 (8.9)	147 (9.9)	16 (4.8)	1 (0.9)	6 (1.8)	2 (1.8)
Endocrine disorders	233 (15.5)	249 (16.7)	51 (15.3)	17 (15.3)	19 (5.7)	7 (6.3)
Gastrointestinal disorders	454 (30.1)	409 (27.4)	83 (24.9)	19 (17.1)	59 (17.6)	11 (9.8)
Hepatobiliary disorders	25 (1.7)	24 (1.6)	1 (0.3)	0 (0.0)	3 (0.9)	1 (0.9)
Immune system disorders[d]	621 (41.2)	593 (39.8)	130 (38.9)	46 (41.4)	107 (31.9)	46 (41.1)
Drug hypersensitivity	325 (21.6)	317 (21.3)	69 (20.7)	27 (24.3)	57 (17.0)	14 (12.5)
Infections and infestations	103 (6.8)	112 (7.5)	15 (4.5)	2 (1.8)	26 (7.8)	11 (9.8)
Metabolism and nutrition disorders	779 (51.7)	779 (52.3)	142 (42.5)	42 (37.8)	52 (15.5)	23 (20.5)
Hypercholesterolaemia	191 (12.7)	184 (12.3)	44 (13.2)	12 (10.8)	6 (1.8)	1 (0.9)
Hyperlipidemia	286 (19.0)	294 (19.7)	27 (8.1)	8 (7.2)	5 (1.5)	2 (1.8)
Obesity	147 (9.8)	148 (9.9)	22 (6.6)	8 (7.2)	22 (6.6)	12 (10.7)
Type 2 diabetes mellitus	214 (14.2)	243 (16.3)	38 (11.4)	12 (10.8)	9 (2.7)	3 (2.7)
Nervous system disorders	342 (22.7)	328 (22.0)	78 (23.4)	18 (16.2)	64 (19.1)	26 (23.2)
Renal and urinary disorders	138 (9.2)	120 (8.1)	19 (5.7)	5 (4.5)	9 (2.7)	4 (3.6)
Respiratory, thoracic and mediastinal Disorders	296 (19.6)	280 (18.8)	41 (12.3)	8 (7.2)	42 (12.5)	18 (16.1)
Asthma	89 (5.9)	80 (5.4)	16 (4.8)	4 (3.6)	23 (6.9)	11 (9.8)
Chronic obstructive pulmonary disease	41 (2.7)	35 (2.3)	3 (0.9)	0 (0.0)	1 (0.3)	0 (0.0)
Sleep apnoea syndrome	109 (7.2)	107 (7.2)	14 (4.2)	2 (1.8)	7 (2.1)	3 (2.7)
Vascular disorders	705 (46.8)	754 (50.6)	110 (32.9)	39 (35.1)	29 (8.7)	8 (7.1)
Hypertension	671 (44.5)	727 (48.8)	105 (31.4)	35 (31.5)	25 (7.5)	5 (4.5)

Note: MedDRA (v22.1) coding dictionary applied. SOC: System Organ Class. PT: Preferred Term.
Note: Select clinically-relevant and frequently reported PTs are listed in this table.
[a] N = Number of subjects in the specified group or the total sample. This value is in the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] This includes approximately 60 individual Preferred Terms encompassing valvular disease, arrhythmias, and other cardiac-related disease.
[d] This consisted of allergies, sensitivities, and sarcoidosis.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report, Tables 14.12-14.14, pages 150-283.

6.1.10.1.3 Subject Disposition

The dispositions of all randomized subjects (as described in Section 6.1.10) are summarized in Table 8. In Cohorts 1-3, subject disposition was similar in both study groups within each cohort and the most common reason for withdrawal in both study groups was being lost to follow-up. There was one death in a Cohort 1 subject due to a self-inflected gunshot wound in the PCV20/saline group that was considered unrelated to study treatment.

Table 8. Disposition of All Randomized Subjects, by Age Cohort and Study Group, Study B7471007

Cohort 1 (≥60 Years)	**PCV20/Saline n[a] (%)**	**PCV13/PPSV23 n[a] (%)**	**Total n[a] (%)**
Randomized[b]	1514 (100.0)	1495 (100.0)	3009 (100.0)
Not vaccinated	7 (0.5)	5 (0.3)	12 (0.4)
Vaccinated			
Vaccination 1	1507 (99.5)	1490 (99.7)	2997 (99.6)
Vaccination 2[c]	1461 (96.5)	1446 (96.7)	2907 (96.6)
Completed visit 3[d]	1441 (95.2)	1428 (95.5)	2869 (95.3)
Completed study	1418 (93.7)	1417 (94.8)	2835 (94.2)
Withdrawn from study	96 (6.3)	78 (5.2)	174 (5.8)
Reason for withdrawal			
Adverse event	11 (0.7)	8 (0.5)	19 (0.6)
Death[e]	1 (0.0)	0 (0.0)	1 (0.0)
Lost to follow-up	41 (2.7)	28 (1.9)	69 (2.3)
No longer meets eligibility criteria	3 (0.2)	9 (0.6)	12 (0.4)
Protocol deviation	21 (1.4)	13 (0.9)	34 (1.1)
Withdrawal by subject	19 (1.3)	20 (1.3)	39 (1.3)
Cohort 2 (50-59 Years)	**PCV20 n[a] (%)**	**PCV13 n[a] (%)**	**Total n[a] (%)**
Randomized[b]	334 (100.0)	111 (100.0)	445 (100.0)
Not vaccinated	0 (0.0)	0 (0.0)	0 (0.0)
Vaccinated			
Completed visit 2[f]	330 (98.8)	110 (99.1)	440 (98.9)
Completed study	323 (96.7)	109 (98.2)	432 (97.1)
Withdrawn from study	11 (3.3)	2 (1.8)	13 (2.9)
Reason for withdrawal			
Lost to follow-up	9 (2.7)	2 (1.8)	11 (2.5)
Protocol deviation	1 (0.3)	0 (0.0)	1 (0.2)
Withdrawal by subject	1 (0.3)	0 (0.0)	1 (0.2)
Cohort 3 (18-49 Years)	**PCV20 n[a] (%)**	**PCV13 n[a] (%)**	**Total n[a] (%)**
Randomized[b]	336 (100.0)	112 (100.0)	448 (100.0)
Not vaccinated	1 (0.3)	0 (0.0)	1 (0.2)
Vaccinated	335 (99.7)	112 (100.0)	447 (99.8)
Completed visit 2[f]	325 (96.7)	109 (97.3)	434 (96.9)
Completed study	319 (94.9)	104 (92.9)	423 (94.4)
Withdrawn from study	17 (5.1)	8 (7.1)	25 (5.6)

Reason for withdrawal			
Lost to follow-up	14 (4.2)	8 (7.1)	22 (4.9)
No longer meets eligibility criteria	1 (0.3)	0 (0.0)	1 (0.2)
Protocol deviation	1 (0.3)	0 (0.0)	1 (0.2)
Withdrawal by subject	1 (0.3)	0 (0.0)	1 (0.2)

[a] Number of subjects with the specified characteristics.
[b] These values are the denominators for the percentage calculations.
[c] Includes subject (b) (6) erroneously injected with a non-protocol defined investigational product at Vaccination #2.
[d] One-month after Vaccination #2.
[e] One-month after Vaccination #1
[f] One subject died of a self-inflicted gunshot wound (considered unrelated to study vaccination).
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Tables 5-7, p 48-50.

No concomitant vaccines were administered to any study subjects within the 14 days before or after investigational product administration (Visit 1 or 2 for Cohort 1; Visit 1 for Cohorts 2 and 3) (STN 125731.11).

6.1.11 Efficacy Analyses

The results from the unadjusted OPA GMT ratios and associated 95% CIs were consistent with the linear regression model-based OPA GMT ratio results for each of the 20 vaccine serotypes.

6.1.11.1 Analyses of Primary Endpoint(s)

Cohort 1 Primary Non-inferiority Analysis

PCV20 met the primary immunogenicity objective for the 13-matched vaccine serotypes (Table 9). One month post-vaccination, the OPA GMTs to each of the 13-matched vaccine serotypes induced by PCV20 were non-inferior to those induced by PCV13, as the lower bound of the 2-sided 95% CI for the primary analysis of the evaluable 13-matched immunogenicity population model-based OPA GMT ratios (PCV20/saline relative to PCV13/PPSV23) was >0.5 (2-fold non-inferiority margin).

Table 9. Pneumococcal Opsonophagocytic Activity GMTs and GMT Ratio for the PCV13 Serotypes at 1 Month Post-Vaccination 1, by Study Group, Cohort 1 (≥60 Years), Evaluable 13-Matched Immunogenicity Population, Study B7471007

Serotype	PCV20/ Saline Group n[a]	PCV20/ Saline Group GMT[b] (95% CI[b])	PCV13/ PPSV23 Group n[a]	PCV13/ PPSV23 Group GMT[b] (95% CI[b])	Comparison GMT Ratio[c] (95% CI[c])
1	1430	123 (112, 136)	1419	154 (140, 169)	0.80 (0.71, 0.90)
3	1415	41 (38, 44)	1411	48 (45, 51)	0.85 (0.78, 0.93)
4	1415	509 (457, 567)	1409	627 (564, 697)	0.81 (0.71, 0.93)
5	1418	92 (83, 101)	1395	110 (100, 120)	0.83 (0.74, 0.94)
6A	1403	889 (795, 994)	1390	1165 (1043, 1301)	0.76 (0.66, 0.88)
6B	1413	1115 (1003, 1240)	1401	1341 (1209, 1489)	0.83 (0.73, 0.95)
7F	1409	969 (887, 1058)	1391	1129 (1035, 1232)	0.86 (0.77, 0.96)
9V	1399	1456 (1318, 1608)	1391	1568 (1421, 1731)	0.93 (0.82, 1.05)
14	1418	747 (679, 821)	1408	747 (680, 820)	1.00 (0.89, 1.13)
18C	1420	1253 (1123, 1397)	143	1482 (1331, 1652)	0.85 (0.74, 0.97)
19A	1420	518 (472, 568)	1398	645 (589, 707)	0.80 (0.71, 0.90)

Serotype	PCV20/ Saline Group n[a]	PCV20/ Saline Group GMT[b] (95% CI[b])	PCV13/ PPSV23 Group n[a]	PCV13/ PPSV23 Group GMT[b] (95% CI[b])	Comparison GMT Ratio[c] (95% CI[c])
19F	1421	266 (240, 294)	1403	333 (302, 368)	0.80 (0.70, 0.91)
23F	1424	277 (243, 315)	1409	335 (294, 381)	0.83 (0.70, 0.97)

Note: The PCV20/saline group received PCV20 on study day 1 followed by Saline 1 month later. The PCV13/PPSV23 group received 13PnC on study day 1 followed by PPSV23 1 month later.
Note: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
[a] n = Number of subjects with valid and determinate OPA titers for the specified serotype.
[b] GMTs and 2-sided CIs were calculated by exponentiating the least squares means and the corresponding CIs based on analysis of log-transformed OPA titers using a regression model with vaccine group, sex, smoking status, age at vaccination in years (continuous), and baseline log transformed OPA titers.
[c] GMT ratios (ratio of GMTs PCV20/saline to PCV13/PPSV23) and 2-sided CIs were calculated by exponentiating the difference of least squares means and the corresponding CIs based on the same regression model as above.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Table 16, p 65-66.

Reviewer Comments:

- *Although the pre-specified 2-fold non-inferiority criterion was met by each the 13 serotypes shared between PCV20 and PCV13, the GMT ratios (ratio of PCV20 to PCV13) were numerically less than 1 for 12 of the 13 common serotypes. These data suggest that there is some interference in OPA antibody response due to the 7 additional serotypes included in PCV20, resulting in lower OPA titers elicited by PCV20 compared to PCV13 against 12 of the 13 common serotypes. This phenomenon was also observed in PCV13 infant studies for the additional serotypes relative to the 7-valent pneumococcal conjugate vaccine (see clinical review of STN 125324/0).*
- *A 2-fold non-inferiority margin was used in the evaluation of Prevnar, Prevnar 13 and other bacterial polysaccharide conjugate vaccines. In the infant pneumococcal conjugate vaccine programs, this margin was based on an IgG ELISA assay. Since OPA is an assay with greater variability, setting a more stringent criterion (e.g., 1.5-fold) would have been inconsistent and resulted in substantially larger sample sizes to demonstrate non-inferiority for 20 primary outcomes.*
- *Based on the data in Table 9, Prevnar 20 would have met a 1.5-fold non-inferiority criterion since the lower limit of the 95% CI for the GMT ratios was > 0.67 for each of the PCV13 serotypes. This, in addition to the supportive secondary endpoints, provides reassurance regarding PCV20 vaccine effectiveness.*

PCV20 met the primary immunogenicity objective for 6 of the 7 additional vaccine serotypes (Table 10). One month post-vaccination, the OPA GMTs for 6 of the 7 additional serotypes induced by PCV20 were non-inferior to those induced by PPSV23, as the lower bound of the 2-sided 95% CI for the model-based OPA GMT ratio (PCV20/saline relative to PCV13/PPSV23 group) exceeded CBER's agreed upon pre-specified non-inferiority margin of 0.5 (2-fold non-inferiority margin) for these six serotypes. The lower bound of the 95% CI for the model-based GMT ratio for serotype 8 was 0.49, which was outside the pre-specified non-inferiority criterion of 0.5.

Table 10. Pneumococcal Opsonophagocytic Activity GMTs and GMT Ratios for the 7 Additional Serotypes 1 Month Post-Vaccination, Cohort 1, Evaluable 7-Additional Immunogenicity Population, Study B7471007

Serotype	PCV20/ Saline Group n[a]	PCV20/Saline Group GMT[b] (95% CI[b])	PCV13/ PPSV23 Group n[a]	PCV13/PPSV23 Group GMT[b] (95% CI[b])	Comparison GMT Ratio[c] (95% CI[c])
8	1374	466 (423, 513)	1319	848 (769, 935)	0.55 (**0.49**, 0.62)
10A	1310	2008 (1808, 2229)	1263	1080 (972, 1200)	1.86 (1.63, 2.12)
11A	1198	4427 (3966, 4942)	1209[d]	2535 (2277, 2822)	1.75 (1.52, 2.01)
12F	1294	2539 (2255, 2858)	1222	1717 (1522, 1936)	1.48 (1.27, 1.72)
15B	1283	2398 (2091, 2751)	1249	769 (670, 882)	3.12 (2.62, 3.71)
22F	1274	3666 (3244, 4143)	1227	1846 (1637, 2083)	1.99 (1.70, 2.32)
33F	1157	5126 (4611, 5698)	1201	3721 (3356, 4125)	1.38 (1.21, 1.57)

Note: The PCV20/Saline group received PCV20 on study day 1 followed by Saline 1 month later. The PCV13/PPSV23 group received 13PnC on study day 1 followed by PPSV23 1 month later.
Note: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
[a] n = Number of subjects with valid and determinate OPA titers for the specified serotype.
[b] GMTs and 2-sided CIs were calculated by exponentiating the least squares means and the corresponding CIs based on analysis of log-transformed OPA titers using a regression model with vaccine group, sex, smoking status, age at vaccination in years (continuous), and baseline log transformed OPA titers.
[c] GMT ratios (GMTs PCV20/saline to PCV13/PPSV23) and 2-sided CIs were calculated by exponentiating the difference of least squares means and the corresponding CIs based on a regression model.
[d] There were a total of 1102 evaluable subjects at 1 month after the PCV13 dose (Visit 2) versus 1209 evaluable subjects at 1 month after the PPSV23 dose (Visit 3). Wyeth explains that this difference is accounted for by a modestly higher rate of subjects with indeterminate 11A assay results at Visit 2 (1 month after PCV13) compared to Visit 3 (1 month after the PPSV23 dose). The OPA assay by nature has a small proportion of indeterminate results that occur across all serotypes due to various immunologic and non-immunologic factors. This appears to be slightly more frequent with serotype 11A in unvaccinated persons. However, subjects at Visit 2 in the PCV13/PPSV23 group are unvaccinated with respect to the serotype 11A antigen and do not contribute to the primary analyses for serotype 11A. In addition, the majority of subjects with sera at Visit 2 in the PCV13/PPSV23 group (and thus contributing to the analyses of serotype 11A) had a valid result. This was therefore found to be acceptable by the statistical reviewers.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Table 17, p 68-69.

> ***Reviewer Comment:*** *Although the non-inferiority criterion for serotype 8 was not met (Table 8) and the percentage of subjects who achieved a ≥4-fold increase in anti-serotype 8 antibodies was lower in the PCV20 group compared to the PPSV23 active control (Table 14), it is important to note that a specific protective OPA antibody titer has not been established for any pneumococcal vaccine serotype. In addition, a substantial proportion of subjects in Cohort 1 achieved a ≥4-fold increase in anti-serotype 8 OPA antibody titers (77.8%), demonstrating that the vaccine elicits functional OPA antibody responses. Thus, it is reasonable to include serotype 8 in the Indications for Prevnar 20, because the vaccine elicits functional antibodies that will likely contribute to protection against IPD and pneumococcal pneumonia.*

6.1.11.2 Analyses of Secondary Endpoints

Cohort 2 Immunobridging Analyses

PCV20 met the secondary immunogenicity objective for each of the 20 vaccine serotypes based on comparisons of the serotype-specific OPA GMTs in subjects 50-59 years of age (Cohort 2) to those in subjects 60-64 years of age (Cohort 1 subset). The lower bound of the 2-sided 95% CI for the ratio (PCV20 in Cohort 2 relative to PCV20 in Cohort 1 subset) of the model-based OPA GMTs at 1 month post-vaccination exceeded 0.5 (the pre-specified 2-fold immune-bridging success criterion) for each of the 20 vaccine serotypes (Table 11).

Table 11. Comparisons of Pneumococcal Opsonophagocytic Activity GMTs 1 Month After PCV20 Vaccination in Cohort 2 (50-59 Years of Age) and Cohort 1 Subset (60-64 Years of Age), Evaluable-20 Immunogenicity Population, Study B7471007

Serotype	Cohort 2 50-59 Years n[a]	Cohort 2 50-59 Years GMT[b] (95% CI[b])	Cohort 1 Subset 60-64 Years n[a]	Cohort 1 Subset 60-64 Years GMT[b] (95% CI[b])	Comparison GMT ratio[c] (95% CI[c])
PCV13					
1	320	136 (113, 163)	941	132 (117, 148)	1.03 (0.84, 1.26)
3	318	43 (38, 49)	935	41 (38, 45)	1.06 (0.92, 1.22)
4	318	633 (514, 780)	931	578 (506, 661)	1.10 (0.87, 1.38)
5	313	85 (70, 102)	935	97 (86, 109)	0.88 (0.72, 1.07)
6A	318	1204 (968, 1497)	921	997 (867, 1148)	1.21 (0.95, 1.53)
6B	318	1503 (1228, 1839)	933	1199 (1054, 1363)	1.25 (1.00, 1.56)
7F	313	1047 (884, 1240)	924	1173 (1053, 1307)	0.89 (0.74, 1.07)
9V	312	1726 (1424, 2091)	922	1688 (1494, 1907)	1.02 (0.83, 1.26)
14	313	926 (762, 1126)	933	742 (656, 840)	1.25 (1.01, 1.54)
18C	315	1805 (1460, 2232)	937	1355 (1184, 1551)	1.33 (1.06, 1.68)
19A	318	618 (520, 736)	932	600 (538, 671)	1.03 (0.85, 1.25)
19F	320	287 (236, 348)	937	290 (256, 329)	0.99 (0.80, 1.22)
23F	319	549 (425, 709)	937	328 (278, 385.6)	1.68 (1.27, 2.22)
Additional					
8	314	487 (401, 592)	901	502 (443, 570)	0.97 (0.78, 1.20)
10A	296	2520 (2076, 3060)	857	2437 (2150, 2763)	1.03 (0.84, 1.28)
11A	271	6417 (5132, 8024)	796	5249 (4565, 6036)	1.22 (0.96, 1.56)
12F	292	3445 (2808, 4227)	855	3105 (2723, 3541)	1.11 (0.88, 1.39)
15B	284	3356 (2582, 4362)	830	2874 (2438, 3387)	1.17 (0.88, 1.56)
22F	284	3808 (2998, 4837)	835	4228 (3630, 4926)	0.90 (0.69, 1.17)
33F	266	5571 (4496, 6904)	765	5445 (4749, 6243)	1.02 (0.81, 1.30)

Note: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.

Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

[a] n = Number of subjects with a determinate OPA titer to the given serotype.

[b] GMTs and 2-sided CIs were calculated by exponentiating the least squares means and the corresponding CIs based on analysis of log-transformed OPA titers using a regression model with cohort, sex, smoking status, and baseline log transformed OPA titers.

[c] GMT ratios (ratio of Cohort 2 to Cohort 1 subset) and 2-sided CIs were calculated by exponentiating the difference of least squares means and the corresponding CIs based on the regression model described above.

Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Table 22, p 77.

Cohort 3 Immunobridging Analyses

PCV20 met the secondary immunogenicity objective for each of the 20 vaccine serotypes based on comparisons of the serotype-specific OPA GMTs in subjects 18-49 years of age (Cohort 2) to those in subjects 60-64 years of age (Cohort 1). The lower bound of the 2-sided 95% CI for the ratio (PCV20 in Cohort 3 relative to PCV20 in Cohort 1) of the model-based OPA GMTs at 1 month post-vaccination exceeded the pre-specified non-inferiority margin of 0.5 (2-fold non-inferiority margin) for each of the 20 vaccine serotypes (Table 12).

Table 12. Comparisons of Pneumococcal Opsonophagocytic Activity GMTs 1 Month After PCV20 Vaccination in Cohort 3 (18-49 Years of Age) and Cohort 1 Subset (60-64 Years of Age), Evaluable-20 Immunogenicity Population, Study B7471007

Serotype	Cohort 3 18-49 Years n[a]	Cohort 3 18-49 Years GMT[b] (95% CI[b])	Cohort 1 Subset 60-64 Years n[a]	Cohort 1 Subset 60-64 Years GMT[b] (95% CI[b])	Comparison GMT Ratio[c] (95% CI[c])
PCV13					
1	316	163 (135, 196)	941	132 (118, 148)	1.23 (1.01, 1.50)
3	316	42 (37, 48)	935	42 (39, 46)	1.00 (0.87, 1.16)
4	315	1967 (1600, 2418)	931	595 (523, 676)	3.31 (2.65, 4.13)
5	317	108 (89, 130)	935	97 (86, 109)	1.11 (0.91, 1.36)
6A	315	3931 (3176, 4864)	921	1023 (896, 1167)	3.84 (3.06, 4.83)
6B	314	4260 (3461, 5243)	933	1250 (1102, 1418)	3.41 (2.73, 4.26)
7F	311	1873 (1564, 2242)	924	1187 (1064, 1324)	1.58 (1.30, 1.91)
9V	315	6041 (4963, 7355)	922	1727 (1529, 1950)	3.50 (2.83, 4.33)
14	316	1848 (1515, 2256)	933	773 (685, 872)	2.39 (1.93, 2.96)
18C	312	4461 (3585, 5550)	937	1395 (1221, 1595)	3.20 (2.53, 4.04)
19A	312	1415 (1182, 1694)	932	611 (548, 682)	2.31 (1.91, 2.81)
19F	315	655 (538, 797)	937	301 (267, 340)	2.17 (1.76, 2.68)
23F	315	1559 (1208, 2012)	937	325 (277, 380)	4.80 (3.65, 6.32)
Additional					
8	306	867 (710, 1059)	901	508 (449, 575)	1.71 (1.38, 2.12)
10A	292	4157 (3411, 5067)	857	2570 (2274, 2904)	1.62 (1.31, 2.00)
11A	263	7169 (5736, 8961)	796	5420 (4738, 6200)	1.32 (1.04, 1.68)
12F	273	5875 (4720, 7314)	855	3075 (2698, 3504)	1.91 (1.51, 2.41)
15B	279	4601 (3488, 6069)	830	3019 (2563, 3556)	1.52 (1.13, 2.05)
22F	273	7568 (5927, 9663)	835	4483 (3863, 5202)	1.69 (1.30, 2.20)
33F	251	7977 (6342, 10034)	765	5693 (4970, 6522)	1.40 (1.10, 1.79)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.

Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

[a] n = Number of subjects with a determinate OPA titer to the given serotype.

[b] GMTs and 2-sided CIs were calculated by exponentiating the least squares means and the corresponding CIs based on analysis of log-transformed OPA titers using a regression model with cohort, sex, smoking status, and baseline log transformed OPA titers.

[c] GMT ratios (ratio of Cohort 3 to Cohort 1 subset) and 2-sided CIs were calculated by exponentiating the difference of least squares means and the corresponding CIs based on the regression model described above.

Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Table 25, p 84.

> **Re*viewer Comment*:** *For 19 of the 20 vaccine serotypes, adults 18-49 years of age responded with numerically higher OPA GMTs (GMT ratios ranging from 1.1 to 4.8) compared to adults 60-64 years of age. For serotype 3, the same OPA GMT point estimate was achieved across the two age groups.*

Descriptive Secondary Analyses (≥4-fold rise in OPA titers)

The following analyses were descriptive in nature with no hypothesis testing and no pre-specified success criteria.

Cohort 1 (≥60 years of age) Descriptive Analyses

For the PCV13 serotypes, the proportion of subjects achieving a ≥4-fold rise in serotype-specific OPA titers from pre- to 1 month after PCV20 was generally similar to or lower than the corresponding proportion following PCV13 (Table 13). There was one exception (serotype 14), as the proportion of subjects achieving ≥4-fold rise in anti-serotype 14 OPA antibodies was numerically higher following PCV20 compared to PCV13.

For the 7 additional serotypes, the proportion of subjects achieving a ≥4-fold rise in OPA titers from pre- to 1 month after PCV20 was generally higher than the corresponding proportion after PPSV23, except for serotype 8 (Table 14). After PPSV23, 86.8% achieved a ≥ 4-fold rise in OPA titers to serotype 8. After PCV20, 77.8% of subjects achieved a ≥4-fold rise in OPA titers to serotype 8.

Cohort 2 (50-59 years of age) Descriptive Analyses

The proportions of subjects achieving a ≥4-fold rise in OPA titers from pre- to 1 month post-vaccination with PCV20 were generally similar between Cohort 2 subjects (50-59 years of age) and Cohort 1 subset subjects (60-64 years of age) (Data not shown, Table 24 of Study B7471007 CSR).

Cohort 3 (18-49 years of age) Descriptive Analyses

The proportions of subjects achieving a ≥4-fold rise in OPA titers from pre- to 1 month post-vaccination with PCV20 were generally similar between Cohort 3 subjects 18-49 years of age and Cohort 1 subset subjects (60-64 years of age) (Data not shown, Table 27 of Study B7471007 CSR).

Table 13. Proportion of Subjects Achieving a ≥4-Fold Rise in Opsonophagocytic Activity Titers for the PCV13 Serotypes From Before Vaccination 1 to 1 Month After Vaccination 1, Cohort 1, Evaluable 13-Matched Immunogenicity Population, Study B7471007

Serotype	PCV20/ Saline Group N[a]	PCV20/ Saline Group n[b]	PCV20/Saline Group % (95% CI[c])	PCV13/ PPSV23 Group N[a]	PCV13/ PPSV23 Group n[b]	PCV13/PPSV23 Group % (95% CI[c])
PCV13						
1	1425	1027	72.1 (69.7, 74.4)	1418	1060	74.8 (72.4, 77.0)
3	1404	787	56.1 (53.4, 58.7)	1401	864	61.7 (59.1, 64.2)
4	1370	1035	75.5 (73.2, 77.8)	1374	1094	79.6 (77.4, 81.7)
5	1411	784	55.6 (52.9, 58.2)	1394	845	60.6 (58.0, 63.2)
6A	1382	1112	80.5 (78.3, 82.5)	1371	1152	84.0 (82.0, 85.9)
6B	1360	1029	75.7 (73.3, 77.9)	1360	1055	77.6 (75.3, 79.8)
7F	1367	981	71.8 (69.3, 74.1)	1355	979	72.3 (69.8, 74.6)
9V	1317	892	67.7 (65.1, 70.3)	1294	897	69.3 (66.7, 71.8)
14	1370	797	58.2 (55.5, 60.8)	1366	737	54.0 (51.3, 56.6)
18C	1407	1093	77.7 (75.4, 79.8)	1396	1111	79.6 (77.4, 81.7)
19A	1400	1031	73.6 (71.3, 75.9)	1379	1069	77.5 (75.2, 79.7)
19F	1405	894	63.6 (61.1, 66.2)	1397	935	66.9 (64.4, 69.4)
23F	1409	995	70.6 (68.2, 73.0)	1402	1043	74.4 (72.0, 76.7)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: The PCV20/saline group received PCV20 on study day 1 followed by saline 1 month later. The PCV13/PPSV23 group received PCV13 on study 1 followed by PPSV23 1 month later.
[a] n = Number of subjects with a valid and determinate assay result to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations.
[b] n = Number of subjects with a ≥4-fold rise in titers from before Vaccination 1 to 1 month after Vaccination 1 for the specified serotype.
[c] Exact 2-sided CI based on the Clopper and Pearson method.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Table 20, p 73.

Table 14. Proportion of Subjects Achieving a ≥4-Fold Rise in Opsonophagocytic Activity Titers for the 7 Additional Serotypes From Before Vaccination 1 to 1 Month After Vaccination 1, Cohort 1, Evaluable 7-Additional Immunogenicity Population, Study B7471007

Serotype	PCV20/ Saline Group N[a]	PCV20/ Saline Group n[b]	PCV20/ Saline Group % (95% CI[c])	PCV13/ PPSV23 Group N[a]	PCV13/ PPSV23 Group n[b]	PCV13/ PPSV23 Group % (95% CI[c])
8	1353	1053	77.8 (75.5, 80.0)	1293	1122	86.8 (84.8, 88.6)
10A	1208	912	75.5 (73.0, 77.9)	1164	764	65.6 (62.8, 68.4)
11A	973	576	59.2 (56.0, 62.3)	993	515	51.9 (48.7, 55.0)
12F	1226	1072	87.4 (85.5, 89.2)	1147	924	80.6 (78.1, 82.8)
15B	1228	955	77.8 (75.3, 80.1)	1178	752	63.8 (61.0, 66.6)
22F	1178	974	82.7 (80.4, 84.8)	1156	888	76.8 (74.3, 79.2)
33F	1020	613	60.1 (57.0, 63.1)	1080	599	55.5 (52.4, 58.5)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: For the PCV20/saline group, fold rise is calculated using assay results from before Vaccination 1 to 1 month after Vaccination 1; for subjects in the PCV13/PPSV23 group, fold rise is calculated using assay results from before Vaccination 1 to 1 month after Vaccination 2.
Note: The PCV20/saline group received PCV20 on study day 1 followed by saline 1 month later. The PCV13/PPSV23 group received PCV13 on study 1 followed by PPSV23 1 month later.
[a] N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations.
[b] n = Number of subjects with a ≥4-fold rise in titers from before Vaccination 1 to 1 month after vaccination for the specified serotype.
[c] Exact 2-sided CI based on the Clopper and Pearson method.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007 Clinical Study Report. Table 21, p 74.

> ***Reviewer Comment:*** *While serotype-specific OPA titers < LLOQ were replaced with 0.5xLLOQ for determination of the 4-fold rise calculations, CBER conducted additional analyses using LLOQ to replace titers < LLOQ in the calculation of 4-fold rise (i.e., 4xLLOQ). The results of these additional analyses were generally consistent with the original analyses.*

The proportions of participants achieving a ≥4-fold rise in OPA titers from before vaccination to 1 month after PCV20 were generally similar between Cohort 2 and Cohort 1 subset subjects (60-64 years of age) (Data not shown, CSR Table 24).

The proportions of participants achieving a ≥4-fold rise in OPA titers from before vaccination to 1 month after PCV20 were generally higher in Cohort 3 than in Cohort 1 for the 13 original serotypes (ranging from 56.7% for serotype 3 to 91.4% for serotype 4 in Cohort 3 participants) (Data not shown, CSR Table 27). For 6 of the 7 new serotypes, the proportions of subjects achieving a ≥4-fold rise in OPA titers from before vaccination to 1 month after PCV20 in Cohort 3 were similar to those in Cohort 1. For serotype 11A, the proportion was higher among Cohort 3 subjects (60.4%) than among Cohort 1 subjects (47.3%) (Data not shown, CSR Table 27).

> ***Reviewer Comment:*** *Among all study cohorts, ≥72% of subjects in both study groups achieved OPA titers ≥ LLOQ for each of the vaccine serotypes assessed, supporting the acceptability of the serotype-specific OPA assays. These data were provided in the following tables within the CSR: 14.25 (p366), 14.26 (p368), 14.38 (p387), 14.43 (p398), 14.52 (p419), 14.53 (p422), 14.58 (p432).*

The CBER statistical reviewer determined that the differences in the proportions of Cohort 1 subjects who achieved OPA titers ≥ LLOQ one month after PCV20 relative to one month after the active control (PCV13 for the 13 original serotypes and PPSV23 for the 7 new serotypes) would be expected to be greater than -10% (a commonly accepted margin of noninferiority).

6.1.11.3 Subpopulation Analyses

Descriptive subgroup analyses of the primary immunogenicity endpoint (OPA GMTs) for the primary and secondary objective were provided based on age, sex, race, and country subgroups. Since <6% of the study population comprised the "All Others" racial group (i.e., Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiracial or not reported), this review focuses on results pertaining to White and Black subjects.

Subpopulation Analyses by Age

In subgroup analyses of Cohort 1 by age (60-64, 65-69 70-79, ≥80 years), OPA GMTs generally decreased with increasing age in each of the immunogenicity analysis populations (evaluable-13, evaluable-7, and evaluable-20 populations) (Data not shown, CSR Tables 14.72, 14.76). Among PCV20 recipients, the OPA GMTs of subjects 70-79 years of age and ≥80 years of age were generally lower than those of younger subjects (18-49, 50-59 and 60-64 years) for all pneumococcal serotypes.

OPA GMTs also decreased with increasing age among PCV20 recipients across the age-based cohorts of subjects 18-49 years, 50-59 years and ≥60 years (see Tables 11 and 12).

Subpopulation Analyses by Sex

In Cohorts 1 and 2, serotype-specific OPA GMTs for the 20 vaccine serotypes were generally higher among females compared to males in each of the immunogenicity analysis populations (evaluable-13, evaluable-7, and evaluabe-20 populations) (Data not shown, CSR Tables 14.70, 14.74, and 14.109). In Cohort 3 (18-49 years), OPA GMTs appeared similar with between females and males (evaluable-20 population) (Data not shown, CSR Table 14.113).

Reviewer Comment: *The statistical reviewer confirmed that his analysis of OPA GMT ratios by sex would not result in different outcomes in males versus females with regards to the primary or secondary study objectives.*

Although the biologic basis for numerically higher immune responses post-vaccination among females compared to males in Cohorts 1 and 2 is unclear, hormonal and genetic differences between the sexes are possible contributing factors (Fathi et al. 2021; Fischinger et al. 2019).

In the adult PCV13 immunogenicity trials supporting accelerated approval, females generally achieved higher serotype-specific OPA GMTs compared to males in one Phase 3 study. However, in the subsequent confirmatory study, vaccine efficacy by sex was not consistent across the primary and secondary study objectives. Vaccine efficacy against vaccine-type IPD (secondary endpoint) was statistically significant among women but not men in study 6115A1-3006. However, vaccine efficacy against VT-CAP (primary endpoint) was similar between males and females, and vaccine efficacy against vaccine-type non-bacteremic CAP (a secondary endpoint) was statistically significant among males but not females.

Subpopulation Analyses by Race (White, Black and "All Others")

In Cohort 1, serotype-specific OPA GMTs for the 20 vaccine serotypes generally appeared similar between White and Black racial subgroups in Cohort 1 (evaluable-13 and evaluable 7 immunogenicity populations) (Data not shown, CSR, Tables 14.71, 14.75). No clear trends were observed in these Cohort 1 racial subgroups. In Cohorts 2 and 3, serotype-specific OPA GMTs for the 20 vaccine serotypes were generally lower among Black subjects compared to White subjects (evaluable-20 population) (Data not shown, CSR Tables 14.110 and 14.114).

Subpopulation Analyses by Country

Serotype-specific OPA GMTs for the 20 vaccine serotypes were generally similar between country subgroups, although lower GMTs were achieved in Sweden compared to the U.S. for several serotypes (Data not shown, CSR Tables 14.73, 14.77). The sample size of subjects enrolled in Sweden was small relative to the number of subjects enrolled in the U.S. (<5% of the total study population), which resulted in wider confidence intervals. This subgroup analysis was limited to adults ≥65 years of age in Cohort 1, because only subjects in this age group were enrolled in Sweden.

6.1.11.4 Dropouts and/or Discontinuations

Please see Section 6.1.10.1.3 for information on subject disposition, including withdrawals. Missing values were not imputed for subject who had missing blood draws.

6.1.11.5 Exploratory and Post Hoc Analyses

In exploratory analyses conducted in random subsets of subjects, PCV20 elicited functional OPA antibody responses to serotype 15C in each study cohort based on OPA GMTs and the proportion of subjects achieving a ≥4-fold rise in OPA titers (Data not shown, CSR Tables 32, 34, and 29-31).

- The serotype 15C OPA GMT at 1 month after PCV13 was 40.6[11] (95% CI 38.2, 43.2) in Cohort 1 (N=211) and at 1 month after PCV20 was:
  - 118 (95% CI 96, 146), in Cohort 1 (N=205);
  - 104 (95% CI (82, 130) in Cohort 2 (N=153); and
  - 139 (95% CI 107, 180) in Cohort 3 (N=144).
- The proportion of subjects achieving a ≥4-fold rise in 15C OPA titers from pre- to 1 month post-PCV13 was 1.9% (95% CI 0.5, 4.8) and from pre-to 1 month post-PCV20 was:
  - 34.8% (95% CI 28.3, 41.8) in Cohort 1 (N=204);
  - 33.3% (95% CI 25.9, 41.5) in Cohort 2 (N=150); and
  - 37.3% (95% CI 29.4, 45.8) in Cohort 3 (N=142).

Reviewer Comment: *Although PCV20 vaccine elicits functional antibodies to non-vaccine serotype 15C, results from this exploratory analysis are not adequate to support definitive conclusions about effectiveness of PCV20 to prevent serotype 15C IPD or pneumonia due to cross-protection.*

[11] This is below the 15C assay LLOQ.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses were descriptive. Please see Section 6.1.7 for details regarding safety surveillance/monitoring, Section 6.1.1 for a listing of safety endpoints, and Section 6.1.9 for details regarding the safety analysis population.

For solicited local and systemic adverse reactions, if any data were reported for local reactions within 10 days after vaccination or systemic reactions within 7 days after vaccination, then the e-diary was considered transmitted. Daily transmission of e-diary data during the entire e-diary collection period was ≥91.5% for each day in Cohort 1, ≥88.3% for each day in Cohort 2, and ≥85.1% for each day in Cohort 3 (Data not shown, CSR Tables 13-15). These daily e-diary transmission rates in Cohorts 1, 2 and 3 were similar in the PCV20 and PCV13 study groups each day. However, in Cohort 3, transmission rates on days 5, 7, 8 and 9 were lower in the PCV20 group (86.0%-89.3%) compared to the PCV13 group (92.0%-93.8%). Transmission rates for all 10 days was 71%-72% in Cohort 1 and 70%-72% in Cohort 2; these rates were similar in the two study groups. The transmission rate for all 10 days was lower in the PCV20 group (49.0%) than the PCV13 group (65.2%).

> ***Reviewer Comment:*** *Although there was a lower transmission rate for all 10 days post-vaccination among PCV20 recipients in Cohort 3, the daily transmission rates were generally similar between the PCV20 and PCV13 study groups. Therefore, e-diary data were considered adequate to assess reactogenicity in each study cohort.*

6.1.12.2 Overview of Adverse Events

Solicited Local Injection Site Adverse Reactions

The proportions of subjects within each study cohort reporting solicited local injection site reactions within 10 days after Vaccination 1 by maximum severity were similar between the two study groups (Tables 15-17). The most frequently reported local adverse reaction was injection site pain (55.4%, 72.5%, 81.2% among PCV20 recipients in Cohorts 1, 2, and 3 respectively). Most local reactions were mild or moderate in severity. Rates of solicited local injection site reactions were highest in the oldest cohort (Cohort 1) and lowest in the youngest cohort (Cohort 3).

Within each study cohort, the mean day of onset and mean duration of solicited local reactions were also similar across the two study groups after Vaccination 1 (Data not shown, CSR Tables 14.121-14.126). The mean day of onset of these local reactions across study cohorts was between Days 1-2 (SD ~1 day) to Days 2.5-3.5 (SD ~1-2 days) (Day 1 = day of vaccination). The mean duration of these local reactions across study cohorts was between 2 days (SD ~2 days) to 3 days (SD ~1.5-2.5 days).

Table 15. Local Reactions, by Maximum Severity, Within 10 Days After Vaccination 1, Cohort 1 (≥60 years), Safety Population, Study B7471007

Local Reaction	PCV20/Saline Group N[a]=1505 n[b] (%)	PCV13/PPSV23 Group N[a]=1483 n[b] (%)
Any local reaction[c]	864 (57.4)	830 (56.0)
Pain at injection site[d]		
Any	834 (55.4)	803 (54.1)
Mild	682 (45.3)	662 (44.6)
Moderate	149 (9.9)	136 (9.2)
Severe	3 (0.2)	5 (0.3)
Swelling[e]		
Any (>2.0 cm)	113 (7.5)	118 (8.0)
Mild	72 (4.8)	72 (4.9)
Moderate	36 (2.4)	42 (2.8)
Severe	5 (0.3)	4 (0.3)
Redness[e]		
Any (>2.0 cm)	110 (7.3)	92 (6.2)
Mild	56 (3.7)	56 (3.8)
Moderate	42 (2.8)	33 (2.2)
Severe	12 (0.8)	3 (0.2)

[a] N = number of subjects with any e-diary data reported after Vaccination 1. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] Any local reaction = any pain at injection site, any swelling >2.0 cm, or any redness >2.0 cm during Day 1 to Day 10 after Vaccination 1.
[d] Absent: none; Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity. Prevention of daily activity may include missed days of work or school or other incapacitation and includes use of narcotics for analgesia. Any = mild, moderate or severe.
[e] Absent: 0 to ≤2.0; Mild: >2.0 to 5.0 cm; Moderate: >5.0 to 10.0 cm; Severe: >10.0 cm. Any = mild, moderate or severe.
Note: There were no Grade 4 injection site reactions reported in this study. Grade 4 erythema and Grade 4 edema were defined as necrosis or exfoliative dermatitis. Grade 4 injection site pain was defined as an ER visit or hospitalization.
Source: STN 125731/0.1 module 5.3.5.1, B7471007 Clinical Study Report. Table 35, p 104.

Table 16. Local Reactions, by Maximum Severity, Within 10 Days After Vaccination, Cohort 2 (50-59 Years), Safety Population, Study B7471007

Local Reaction	PCV20 Group N[a]=331 n[b] (%)	PCV13 Group N[a]=111 n[b] (%)
Any local reaction[c]	241 (72.8)	78 (70.3)
Pain at injection site[d]		
Any	240 (72.5)	77 (69.4)
Mild	177 (53.5)	58 (52.3)
Moderate	59 (17.8)	18 (16.2)
Severe	4 (1.2)	1 (0.9)
Swelling[e]		
Any (>2.0 cm)	29 (8.8)	12 (10.8)
Mild	19 (5.7)	8 (7.2)
Moderate	10 (3.0)	4 (3.6)
Severe	0 (0.0)	0 (0.0)

Local Reaction	PCV20 Group N[a]=331 n[b] (%)	PCV13 Group N[a]=111 n[b] (%)
Redness[e]		
Any (>2.0 cm)	27 (8.2)	6 (5.4)
Mild	17 (5.1)	3 (2.7)
Moderate	9 (2.7)	3 (2.7)
Severe	1 (0.3)	0 (0.0)

[a] N = number of subjects with any e-diary data reported after Vaccination. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] Any local reaction = any pain at injection site, any swelling >2.0 cm, or any redness >2.0 cm during Day 1 to Day 10 after Vaccination 1.
[d] Absent: none; Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity. Prevention of daily activity may include missed days of work or school or other incapacitation and includes use of narcotics for analgesia. Any = mild, moderate or severe.
[e] Absent: 0 to ≤2.0; Mild: >2.0 to 5.0 cm; Moderate: >5.0 to 10.0 cm; Severe: >10.0 cm. Any = mild, moderate or severe.
Note: There were no Grade 4 injection site reactions reported in this study. Grade 4 erythema and Grade 4 edema were defined as necrosis or exfoliative dermatitis. Grade 4 injection site pain was defined as an ER visit or hospitalization.
Source: STN 125731/0.1 module 5.3.5.1, B7471007 Clinical Study Report. Table 36, p 105.

Table 17. Local Reactions, by Maximum Severity, Within 10 Days After Vaccination, Cohort 3 (18-49 Years), Safety Population, Study B7471007

Local Reaction	PCV20 Group N[a]=335 n[b] (%)	PCV13 Group N[a]=112 n[b] (%)
Any local reaction[c]	272 (81.2)	92 (82.1)
Pain at Injection Site[d]		
Any	272 (81.2)	92 (82.1)
Mild	143 (42.7)	59 (52.7)
Moderate	128 (38.2)	32 (28.6)
Severe	1 (0.3)	1 (0.9)
Swelling[e]		
Any (>2.0 cm)	39 (11.6)	14 (12.5)
Mild	24 (7.2)	10 (8.9)
Moderate	15 (4.5)	4 (3.6)
Severe	0 (0.0)	0 (0.0)
Redness[e]		
Any (>2.0 cm)	30 (9.0)	11 (9.8)
Mild	10 (3.0)	6 (5.4)
Moderate	18 (5.4)	5 (4.5)
Severe	2 (0.6)	0 (0.0)

[a] N = number of subjects with any e-diary data reported after Vaccination. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] Any local reaction = any pain at injection site, any swelling >2.0 cm, or any redness >2.0 cm during Day 1 to Day 10 after Vaccination 1.
[d] Absent: none; Mild: does not interfere with activity; Moderate: interferes with activity; Severe: prevents daily activity. Prevention of daily activity may include missed days of work or school or other incapacitation and includes use of narcotics for analgesia. Any = mild, moderate or severe.
[e] Absent: 0 to ≤2.0; Mild: >2.0 to 5.0 cm; Moderate: >5.0 to 10.0 cm; Severe: >10.0 cm. Any = mild, moderate or severe.
Note: There were no Grade 4 injection site reactions reported in this study. Grade 4 erythema and Grade 4 edema were defined as necrosis or exfoliative dermatitis. Grade 4 injection site pain was defined as an ER visit or hospitalization.
Source: STN 125731/0.1 module 5.3.5.1, B7471007 Clinical Study Report. Table 37, p 106-107.

Solicited Systemic Adverse Reactions

The proportions of subjects within each study cohort reporting solicited systemic adverse reactions within 10 days after Vaccination 1 by maximum severity were similar between the two study groups (Tables 18-20). The most frequently reported systemic adverse reaction was muscle pain (39.1%, 49.8%, and 66.6% among PCV20 recipients in Cohorts 1, 2, and 3 respectively). Most systemic adverse reactions were mild or moderate in severity. Rates of solicited systemic reactions were highest among the older cohort (Cohort 1) and lowest in the youngest cohort (Cohort 3).

Within each study cohort, the mean day of onset and mean duration of solicited systemic adverse reactions were also similar across the two study groups after Vaccination 1 (Data not shown, CSR Tables 14.34 - 14.35 and 14.37 - 14.40). The mean day of onset of these systemic reactions across study cohorts was between Day 1.5 (SD ~1 day) and Days 3-4 (SD ~2 days) (Day 1 = day of vaccination). The mean duration of these reactions across study cohorts was between 1-2 days (SD ~0-2 days) and 3.5-4.0 days (SD ~3-6 days).

Table 18. Systemic Adverse Reactions, by Maximum Severity, Within 7 Days After Vaccination 1, Cohort 1 (≥60 Years), Safety Population, Study B7471007

Local Reaction	PCV20/Saline Group N[a]=1505 n[b] (%)	PCV13/PPSV23 Group N[a]=1483 n[b] (%)
Any Systemic Adverse Reaction[c]	831 (55.2)	822 (55.4)
Muscle Pain[d]		
Any	588 (39.1)	533 (37.3)
Mild	435 (28.9)	398 (26.8)
Moderate	147 (9.8)	148 (10.0)
Severe	6 (0.4)	7 (0.5)
Fatigue[d]		
Any	454 (30.2)	455 (30.7)
Mild	243 (16.1)	260 (17.5)
Moderate	193 (12.8)	177 (11.9)
Severe	18 (1.2)	18 (1.2)
Headache[d]		
Any	324 (21.5)	345 (23.3)
Mild	233 (15.5)	252 (17.0)
Moderate	81 (5.4)	88 (5.9)
Severe	10 (0.7)	5 (0.3)
Joint Pain[d]		
Any	190 (12.6)	203 (13.7)
Mild	104 (6.9)	106 (7.1)
Moderate	81 (5.4)	94 (6.3)
Severe	5 (0.3)	3 (0.2)

Local Reaction	PCV20/Saline Group N[a]=1505 n[b] (%)	PCV13/PPSV23 Group N[a]=1483 n[b] (%)
Fever		
≥38.0°C	14 (0.9)	12 (0.8)
≥38.0°C to 38.4°C	4 (0.3)	6 (0.4)
>38.4°C to 38.9°C	4 (0.3)	3 (0.2)
>38.9°C to 40.0°C	1 (0.0)	0 (0.0)
>40.0°C	5 (0.3)	3 (0.2)
Use of antipyretic or pain medication[e]	278 (18.5)	303 (20.4)

[a] N = number of subjects with any e-diary data reported after Vaccination 1. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] Any systemic event = any fever ≥38.0°C, any fatigue, any headache, any joint pain, or any muscle pain during Day 1 to Day 7 after vaccination.
[d] Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity. Prevention of daily activity may include missed days of work or school or other incapacitation and includes use of narcotics for analgesia. Any = mild, moderate or severe.
[e] Use of antipyretic or pain medication was recorded as "yes" or "no."
Note: There were no Grade 4 solicited reactions reported in this cohort other than fever. Grade 4 reactions were defined as an ER visit or hospitalization. Grade 4 fever was defined as a temperature >40.0oC.
Note: Twelve subjects in Cohort 1 (5 in the PCV20/saline group and 7 in the PCV13/PPSV23 group) were confirmed by the study site to have entered Grade 4 fever in error and were excluded from Table 18. These subjects confirmed that they experienced no reaction or fever of any severity at the specified timepoints.
Source: STN 125731/0.1 module 5.3.5.1, B7471007 Clinical Study Report. Table 38, p 108-109.

Table 19. Systemic Adverse Reactions, by Maximum Severity, Within 7 Days After Vaccination 1, Cohort 2 (50-59 Years), Safety Population, Study B7471007

Local Reaction	PCV20/Saline Group N[a]=331 n[b] (%)	PCV13/PPSV23 Group N[a]=111 n[b] (%)
Any Systemic Adverse Reaction[c]	230 (69.5)	75 (67.6)
Muscle Pain[d]		
Any	165 (49.8)	55 (49.5)
Mild	112 (33.8)	35 (31.5)
Moderate	51 (15.4)	19 (17.1)
Severe	2 (0.6)	1 (0.9)
Fatigue[d]		
Any	130 (39.3)	40 (36.0)
Mild	70 (21.1)	20 (18.0)
Moderate	57 (17.2)	17 (15.3)
Severe	3 (0.9)	3 (2.7)
Headache[d]		
Any	107 (32.3)	40 (36.0)
Mild	68 (20.5)	24 (21.6)
Moderate	36 (10.9)	15 (13.5)
Severe	3 (0.9)	1 (0.9)
Joint Pain[d]		
Any	51 (15.4)	23 (20.7)
Mild	35 (10.6)	14 (12.6)
Moderate	16 (4.8)	8 (7.2)
Severe	0 (0.0)	1 (0.9)
Fever		
≥38.0°C	5 (1.5)	1 (0.9)
≥38.0°C to 38.4°C	2 (0.6)	1 (0.9)
>38.4°C to 38.9°C	1 (0.3)	0 (0.0)
>38.9°C to 40.0°C	1 (0.3)	0 (0.0)
>40.0°C	1 (0.3)	0 (0.0)

Local Reaction	PCV20/Saline Group N[a]=331 n[b] (%)	PCV13/PPSV23 Group N[a]=111 n[b] (%)
Use of antipyretic or pain medication[e]	81 (24.5)	31 (27.9)

[a] N = number of subjects with any e-diary data reported after Vaccination 1. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] Any systemic event = any fever ≥38.0°C, any fatigue, any headache, any joint pain, or any muscle pain during Day 1 to Day 7 after vaccination.
[d] Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity. Prevention of daily activity may include missed days of work or school or other incapacitation and includes use of narcotics for analgesia. Any = mild, moderate or severe.
[e] Use of antipyretic or pain medication was recorded as "yes" or "no."
Note: There were no Grade 4 solicited reactions reported in this cohort other than fever. Grade 4 reactions were defined as an ER visit or hospitalization. Grade 4 fever was defined as a temperature >40.0°C.
Source: STN 125731/0.1 module 5.3.5.1, B7471007 Clinical Study Report. Table 39, p 110.

Table 20. Systemic Adverse Reactions, by Maximum Severity, Within 7 Days After Vaccination 1, Cohort 3 (18-49 Years), Safety Population, Study B7471007

Local Reaction	PCV20/Saline Group N[a] =335 n[b] (%)	PCV13/PPSV23 Group N[a]=112 n[b] (%)
Any Systemic Adverse Reaction[c]	266 (79.4)	93 (83.0)
Muscle Pain[d]		
Any	223 (66.6)	83 (74.1)
Mild	122 (36.4)	47 (42.0)
Moderate	97 (29.0)	35 (31.3)
Severe	4 (1.2)	1 (0.9)
Fatigue[d]		
Any	143 (42.7)	49 (43.8)
Mild	63 (18.8)	23 (20.5)
Moderate	74 (22.1)	22 (19.6)
Severe	6 (1.8)	4 (3.6)
Headache[d]		
Any	130 (38.8)	38 (33.9)
Mild	72 (21.5)	18 (16.1)
Moderate	49 (14.6)	19 (17.0)
Severe	9 (2.7)	1 (0.9)
Joint Pain[d]		
Any	45 (13.4)	20 (17.9)
Mild	21 (6.3)	10 (8.9)
Moderate	24 (7.2)	9 (8.0)
Severe	0 (0.0)	1 (0.9)
Fever		
≥38.0°C	4 (1.2)	2 (1.8)
≥38.0°C to 38.4°C	2 (0.6)	0 (0.0)
>38.4°C to 38.9°C	1 (0.3)	0 (0.0)
>38.9°C to 40.0°C	1 (0.3)	2 (1.8)
>40.0°C	0 (0.0)	0 (0.0)

Local Reaction	PCV20/Saline Group N[a] =335 n[b] (%)	PCV13/PPSV23 Group N[a]=112 n[b] (%)
Use of antipyretic or pain medication[e]	86 (25.7)	26 (23.2)

[a] N = number of subjects with any e-diary data reported after Vaccination 1. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] Any systemic event = any fever ≥38.0°C, any fatigue, any headache, any joint pain, or any muscle pain during Day 1 to Day 7 after vaccination.
[d] Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity. Prevention of daily activity may include missed days of work or school or other incapacitation and includes use of narcotics for analgesia. Any = mild, moderate or severe.
[e] Use of antipyretic or pain medication was recorded as "yes" or "no."
Note: There were no Grade 4 solicited reactions reported in this cohort. Grade 4 reactions were defined as an ER visit or hospitalization. Grade 4 fever was defined as a temperature >40.0ºC.
Note: Two subjects in Cohort 3 (both in the PCV20/saline group) were confirmed by the study site to have entered Grade 4 fever in error and were excluded from Table 20. These subjects confirmed that they experienced no reaction or fever of any severity at the specified timepoints.
Source: STN 125731/0.1 module 5.3.5.1, B7471007 Clinical Study Report. Table 40, p 112.

Unsolicited Adverse Events (AEs) Reported Through 30 Days Post-Vaccination

Cohort 1 Safety Population

In the Cohort 1 safety population, a similar and low proportion of subjects in the PCV20/saline group (9.8%) and the PCV13/PPSV23 group (11.1%) reported at least one unsolicited AE within 1 month after Vaccination 1 (Data not shown, Table 14.149). Most unsolicited AEs were mild or moderate in severity. Severe AEs were reported by 12 subjects (0.8%) in each of the two study groups within the Cohort 1 safety population (Data not shown, CSR Table 14.159). Among Cohort 1 subjects, the most frequently reported unsolicited AEs after Vaccination 1 occurring in a higher proportion of PCV20 recipients compared to PCV13 recipients are as follows:

- upper respiratory tract infection (0.8% after PCV20, 0.5% after PCV13);
- arthralgia (0.4% after PCV20, 0.1% after PCV13);
- bronchitis (0.3% after PCV20, 0.2% after PCV13); and
- viral infection (0.3% after PCV20, 0% after PCV13).

There was a minor imbalance in the rates of subjects reporting Preferred Terms within the System Organ Class (SOC) of *Cardiac disorders* through 1 month after Vaccination 1, with 7 subjects (0.46%) in the PCV20/saline group and 2 subjects (0.13%) in the PCV13/PPSV23 group reporting AEs including coronary artery disease, atrial fibrillation, bradycardia, palpitations, and myocardial infarction. In the PCV20/saline group, 7 subjects reported one or more of the following cardiac events: atrial fibrillation (n=2), bradycardia (n=1), coronary artery disease (n=3), myocardial infarction (n=1), and palpitations (n=1). In the PCV13/PPSV23, the following cardiac events were reported by one subject each: palpitations and silent myocardial infarction.

Cohort 2 Safety Population

In the Cohort 2 safety population, a similar and low proportion of subjects in the PCV20 group (10.2%) and PCV13 group (8.1%) reported at least 1 unsolicited AE within 1 month after Vaccination (Data not shown, CSR, Table 14.152). Severe AEs were reported by 2 subjects (0.6%) in the PCV20 group and 1 subject (0.9%) in the PCV13 group (Data not shown, CSR Table 14.161). Unsolicited AEs reported most frequently after vaccination in a higher proportion of PCV20 recipients compared to PCV13 recipients in Cohort 2 are as follows:

- fall (1.2% after PCV20, 0% after PCV13);
- bronchitis (0.9% after PCV20, 0% after PCV13);

- nasopharyngitis (0.6% after PCV20, 0% after PCV13);
- arthralgia (0.6% after PCV20, 0% after PCV13); and
- nephrolithiasis (0.6% after PCV20, 0% after PCV13).

There were no Preferred Terms reported for the SOC *Cardiac disorders* in Cohort 2.

Cohort 3 Safety Population

In the Cohort 3 safety population, a similar proportion of subjects in the PCV20 group (15.2%) and PCV13 group (11.6%) reported at least 1 unsolicited AE within 1 month after vaccination (Data not shown, CSR, Table 14.153). Severe AEs were reported by 5 subjects (1.5%) in the PCV20 group and 2 subjects (1.8%) in the PCV13 group (Data not shown, CSR Table 14.162). The unsolicited AEs reported most frequently after vaccination in a higher proportion of PCV20 recipients compared to PCV13 recipients in Cohort 3 are as follows:

- upper respiratory tract infection (2.1% after PCV20, 0.9% after PCV13);
- influenza (2.1% after PCV20, 0.9% after PCV13);
- pharyngitis streptococcal (0.6% after PCV20, 0% after PCV13);
- cough (0.6% after PCV20, 0% after PCV13);
- nasal congestion (0.6% after PCV20, 0% after PCV13);
- respiratory disorder (0.6% after PCV20, 0% after PCV13); and
- pain in extremity (0.6% after PCV20, 0% after PCV13).

One subject (0.3%) in the PCV20 group was reported to have an acute myocardial infarction and coronary artery disease.

Newly Diagnosed Chronic Medical Conditions *(Section 12.5.4 page 128)*
Within Cohort 1, a similar proportion of subjects in the PCV20/saline group (2.3%) and the PCV13/PPSV23 group (2.3%) reported a newly diagnosed chronic medical condition (NDCMC) within 6 months post-vaccination (Data not shown, CSR Table 14.176). Overall, NDCMCs were most frequently reported within the SOC *Musculoskeletal and connective tissue disorders*. Three subjects (0.2%) in the PCV20/saline group and 1 subject in the PCV13/PPSV23 group reported NDCMCs within the SOC *Cardiac disorders*.

Within Cohort 2, 5 subjects (1.5%) in the PCV20 group and 1 subject (0.9%) in the PCV13 reported a NDCMC (Data not shown, CSR Table 14.178). NDCMCs in the PCV20 group were classified as type 2 diabetes mellitus (n=2), hypertension (n=2), and peripheral venous disease (n=1). NDCMCs in the PCV13 group were classified as type 2 diabetes mellitus (n=1).

Within Cohort 3, 5 subjects (1.5%) in the PCV20 group and 2 subjects (1.8%) in the PCV13 group reported a NDCMC (Data not shown, CSR Table 14.180). NDCMCs in the PCV20 group were classified as coronary artery disease, type 2 diabetes mellitus, rheumatoid arthritis, breast cancer, and migraine; in the PCV13 group, NDCMCs were classified as diabetic retinopathy, type 2 diabetes mellitus, and headache.

Immediate Adverse Reactions *(Data not shown, Tables 14.155, 14.157, 14.158)*
Within 30 minutes after Vaccination 1, three Cohort 1 subjects (0.2%) in each study group reported adverse reactions. These included injection site pain and swelling, joint swelling, musculoskeletal stiffness, and somnolence. In the Cohort 2 and Cohort 3 safety populations, 1 subject in each cohort experienced an adverse reaction (headache and dizziness, respectively) in the 30 minutes immediately following vaccination.

Other Significant Adverse Events
Two Cohort 3 participants (18-49 years of age) who had documented negative urine pregnancy tests at enrollment became pregnant during the study. The pregnancies were reported 71 and 116 days after vaccination with PCV20. Both participants gave birth to healthy male infants at 39 weeks of gestation with no reported pregnancy complications.

Safety Analyses by Subgroups

Since <6% of the study population were included in "All Others" racial groups (i.e., Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Multiracial or not reported), this review focuses on results pertaining to White and Black subjects.

Subgroup Analyses by Age (Cohort 1 Only)

There was a general trend toward decreased rates of injection site reactions with age (Data not shown, CSR Table 14.129). With the exception of fever, rates of systemic adverse reactions (including use of antipyretic or pain medication) decreased with increasing age; the fever rate was highest in adults ≥80 years) (Data not shown, CSR Table 14.144).

Subgroup Analyses by Sex

- Local reactions: In Cohort 1, prompted local injection site reactions within 7 days after Vaccination 1 (Data not shown, CSR Table 14.127) were generally reported by a higher proportion of females in Cohort 1 compared to males. In Cohorts 2 and 3, the proportions of females and males reporting prompted local injection site reactions after Vaccination 1 were generally similar (Data not shown, CSR, Tables 14.130 and 14.132).

- Systemic reactions: In Cohort 1, prompted systemic reactions and antipyretic or pain medication use within 10 days after Vaccination 1 were generally reported by a higher proportion of females compared to males (Data not shown, CSR Table 14.142) In Cohorts 2 and 3, a higher proportion of females generally reported fatigue, headache, muscle pain (cohort 2 only) and use of antipyretic or pain medication after Vaccination 1, whereas the proportions of females and males reporting other prompted systemic events (muscle pain (Cohort 3 only), joint pain and fever) were generally similar (Data not shown, CSR Tables 14.145 and 14.147).

Reviewer Comment**:** *Although the biologic basis for the noted higher rates of reactogenicity among females compared to males is unclear, these findings are consistent with the literature on differences between males and females with respect to reactogenicity following preventive vaccines (Klein and Pekosz 2014).*

Subgroup Analyses by Race (White, Black, and "All Others")

- In Cohort 1, a numerically lower proportion of Black subjects reported injection site redness and pain compared to White subjects (rates of swelling were similar) (Data not shown, CSR Table 14.128). In Cohort 2, a numerically lower proportion of Black subjects reported injection site pain compared to White subjects (Data not shown, CSR Table 14.131). In Cohort 3, a numerically lower proportion of Black reported prompted local injection site reactions compared to White subjects (Data not shown, CSR Table 14.133).

- There were no clear trends in the rates of solicited adverse reactions reported among subjects by race (Data not shown, CSR Tables 14.143, 14.146, 14.148).

Similar trends as described above were generally observed in analyses of unsolicited AEs by age, sex and race.

> ***Reviewer Comment:*** *This study was conducted in the U.S. and Sweden. Subgroup analyses were not provided by country. Since less than 0.5% of the total study population was enrolled in Sweden (172/3902), CBER did not consider such subgroup analyses by country would have been helpful.*

6.1.12.3 Deaths

There was one death in this study in a Cohort 1 PCV20/saline recipient aged 60 years with a medical history of suicide attempts resulting in hospitalization (1974, 1985, and 2006) and depression since 2006. The subject's death was due to a self-inflicted gunshot wound to the head 48 days after receipt of Vaccination 2 (saline). This death was not considered related to the investigational product.

6.1.12.4 Nonfatal Serious Adverse Events

Overall, there were no serious adverse events (SAEs) that were considered by the investigator to be related to the study vaccine.

The proportions of subjects in the Cohort 1 safety population reporting at least 1 serious adverse event (SAE) within 6 months post-Vaccination 1 were similar in the PCV20/saline group (2.4% (36/1507)) and in the PCV13/PPSV23 group (1.9% (29/1490)) (Data not shown, CSR Table 46). There were no meaningful imbalances in rates of SAEs based on reported preferred terms (PTs) or systemic organ classes (SOCs), including no imbalance overall in cardiovascular serious adverse events. No SAEs were considered by the study investigator to be related to the study vaccination.

Within 1 month after Vaccination 1, 0.5% of subjects in each of the study group of the Cohort 1 safety population reported at least 1 SAE (Data not shown, CSR Table 14.170). No consistent imbalances were noted in the rates of subjects reporting individual Preferred Terms within the SOC *Cardiac disorders* or in the overall rates of all reported PTs within *Cardiac disorders* at 1 month post-Vaccination 1 (Data not shown, CSR Table 14.149).

In the Cohort 2 safety population, the proportions of subjects reporting at least 1 SAE within 6 months post-vaccination were low and similar in the PCV20 group (0.3%) and the PCV13 group (0.9%) (Data not shown, CSR Table 47). One subject in the PCV20 group reported two SAEs (nephrolithiasis and ureteric obstruction) and 1 subject in the PCV13 group reported one SAE (skin bacterial infection). Each of these SAEs occurred within 1 month post-vaccination. None of the reported SAEs in Cohort 2 were considered by the investigator to be related to the study vaccination.

In the Cohort 3 safety population, the proportions of subjects reporting at least 1 SAE within 6 months post-vaccination were low and similar in the PCV20 group (0.6%) and the PCV13 (0.9%) (Data not shown, CSR Table 48). Within the PCV20 group, 1 subject reported an acute myocardial infarction within 1 month post-vaccination, and one subject reported a pulmonary embolism within 6 months post-vaccination. In the PCV13 group, 1 subject reported herpes

simplex meningitis within 6 months post-vaccination. None of the SAEs reported in Cohort 3 were considered by the investigator to be related to study vaccination.

Serious Adverse Event Narratives

Narratives were provided for 2 subjects (both in Cohort 1) who reported SAEs and were discontinued for safety-related reasons.

- Subject (b) (6) : A 65-year-old black female from the U.S. with pertinent medical history of hypertension (since 2007) presented to the Emergency Room on Day 14 after receipt of PCV20 with chest pain and was subsequently hospitalized. On Day 15, the subject underwent a cardiac catheterization to treat severe 3-vessel coronary artery disease. On Day 17, the subject underwent a triple bypass surgery. The subject was withdrawn from further vaccination on Study Day 50 because of ongoing coronary artery disease and completed safety follow-up on Day 169. The investigator considered that there was no reasonable possibility that the CAD was related to the study vaccine, but rather was related to underlying cardiac disease.

- Subject (b) (6) : An 84-year-old while male from the U.S. with a pertinent medical history of left knee meniscus damage (in 2002) and arthroscopy (unreported date), left knee meniscus injury and repair (2010), arthritis (since 2010), left knee sprain (2019), and left knee pain (since April 2019), received Vaccination 1 (PCV13). Twenty days post-vaccination, the subject was diagnosed with a severe muscle rupture (torn left quadricep muscle). The subject's ongoing history of left knee pain since April 2019 worsened to the point that he sought medical attention. The subject refused to continue in the safety follow-up phase and subsequently withdrew on Day 169 due to the muscle rupture. The investigator considered that there was no reasonable possibility that the torn left quadricep muscle was related to the study vaccine but rather to the prior noted injury.

6.1.12.7 Dropouts and/or Discontinuations

A total of 20 subjects in Cohort 1 (12 subjects in the PCV20/saline group (including 1 death) and 8 subjects in the PCV13/PPSV23 group) were withdrawn prior from further vaccination due to an AE or SAE (Table 8), and narratives were provided for these subjects (CSR, pages 822-916). No subjects in Cohort 2 or Cohort 3 were withdrawn due to an adverse event. The narratives for the 17 subjects withdrawn early due to an AE are described below, and the narratives for the remaining 3 subjects withdrawn early due to a SAE or death are summarized above in Sections 6.1.12.3 and 6.1.12.4.

- Subject (b) (6) : On study Day 8 after receipt of PCV20, an 80-year-old White U.S. female subject with a history of coronary artery disease and hypercholesterolemia (treated with lovastatin) developed mild angioedema. Wyeth did not have details regarding the body location(s) affected in the clinical presentation upon request. On Day 24, lovastatin was discontinued and on the same day, the angioedema resolved. The subject was discontinued from further vaccination per her request due to the adverse event. The angioedema was considered by the investigator to be related to concomitant drug treatment (lovastatin).

Reviewer Comment: *Angioedema was temporally associated with PCV20 administration. However, this reviewer agrees that this event is more likely related to concomitant administration of lovastatin based on the persistent nature of the event (lasting 22 days) and the resolution of the mild angioedema following lovastatin discontinuation. Angioedema is listed as a known adverse reaction reported during post-approval use of lovastatin. Although PCV20 cannot be ruled out as a cause of this event (i.e., non-IgE mediated mast cell degranulation resulting from an inflammatory response to PCV20 [delayed angioedema]), this reviewer agrees that PCV20 is a less likely cause of the noted adverse event.*

- Subject (b) (6) : On study Day 22 after receipt of PCV13, a 79-year-old White U.S. female with a history of hypertonic bladder developed moderate cystitis. On Day 29, the cystitis resolved. This AE was considered related to the pre-existing hypertonic bladder.

- Subject (b) (6) : On study Day 1 within 5 hours after receipt of PCV13, a 64-year-old White U.S. female subject experienced mild injection site pain and mild myalgia which resolved on Days 2 and 3, respectively. The subject also reported mild fatigue (Day 2 only) and mild myalgia (Day 1 only). The reported injection site pain and myalgia were considered related to the study vaccine.

- Subject (b) (6) : On Day 1, ~12 hours after receipt of PCV20, a 64-year-old White U.S. female with a medical history of hypothyroidism, Raynaud's disease and taking concomitant levothyroxine (0.1 mg) reported moderate anxiety and palpitations which resolved on Days 7 and 3, respectively. The investigator considered there was a reasonable possibility that the anxiety and palpitations were possibly related to the study vaccine.

- Subject (b) (6) : On Day 1 ~9 hours after receipt of PCV20, a 62-year-old White U.S. female subject with a medical history of rosacea, paresthesia, hypertension (taking lisinopril), and tension headaches and on hormonal therapy for menopausal symptoms reported moderate injection site pruritis and swelling which resolved on Days 6 and 8, respectively. The investigator considered there was a reasonable possibility that these AEs were related to study vaccination.

- Subject (b) (6) : On Day 31 after receipt of PCV20, a 65-year-old White U.S. male subject with no pertinent medical history reported severe presyncope at the time of blood sample collection for Visit 2. The investigator considered the AE to be related to a vasovagal reflex-vasomotor reaction after blood was drawn by venipuncture.

- Subject (b) (6) : On Day 2 after receipt of PCV20, a 72-year-old multiracial U.S. male subject with a medical history pertinent for drug hypersensitivity (penicillin) and food allergy (chocolate) reported moderate pruritis and mild abnormal feeling in the head which resolved on Day 17 and Day 8, respectively. The subject also reported moderate rash on Day 6 through Day 9. The investigator considered there to be a reasonable possibility that the AEs on Day 2 were related to the study product.

- Subject (b) (6) : On day 2 after receipt of PCV13, a 62-year-old White U.S. male subject with a history of hypertension reported a moderate headache which resolved on Day 17. The subject also reported moderate fatigue on Days 2 through 17, moderate myalgia from Days 1-2, and moderate arthralgia on days 2017. The subject used an antipyretic/pain medication on Days 2, 4, 5, 6, and 7. The subject was withdrawn on Day 99 due to the headache, and the investigator considered headache to be related to study vaccination.

- Subject (b) (6) : On Day 5 after receipt of PCV20, a 64-year-old black U.S. male subject with no pertinent medical history reported severe injection site swelling which resolved on Day 6. The subject also reported moderate injection site redness on Day 2 only and mild injection site pain on Days 1-4. The subject was withdrawn due to the injection site swelling on Day 64. The investigator considered there was a reasonable possibility that the injection site swelling was related to the study product.

- Subject (b) (6) : On Day 16 after receipt of PCV20, a 63-year-old White U.S. female subject with a history of atopic dermatitis reported moderate worsening of atopic dermatitis which resolved on Day 49. The investigator considered there no reasonable possibility that the worsening atopic dermatitis was related to the study product but rather to the pre-existing condition.

- Subject (b) (6) : On Day 26 after receipt of PCV13, a 63-year old White U.S male subject with no pertinent medical history reported a mild lower respiratory tract infection. The subject withdrew consent and safety follow-up on Day 42 due to this AE. The investigator considered there was no reasonable possibility that the AE was related to the study product but rather to community exposure.

- Subject (b) (6) : On Day 2 after receipt of PCV13, a 67-year-old White U.S. male subject with no pertinent medical history reported mild injection site pain from Days 2-4, severe injection site redness on Days 2-6, and mild fever on Day 2 only. The subject used an antipyretic/pain medication on day 2 only. The investigator considered there was a reasonable possibility that the injection site pain and redness were related to the study product.

- Subject (b) (6) : On Day 37 after receipt of PCV20, a 61-year-old black male U.S. subject with a medical history of ongoing seasonal allergies (receiving allergy shots) reported mild hypersensitivity due to seasonal allergens and received a steroid injection the same day. The investigator considered there to be no reasonable possibility that hypersensitivity occurring 36 days post-vaccination was related to the study product but rather to seasonal allergies.

- Subject (b) (6) : On Day 1 ~5 hours before receipt of PCV20, an 83-year-old male U.S. subject with a history of osteoarthritis of the right should and right hand (on methotrexate) reported arthritis. The subject started treatment with prednisone on Day 2. The investigator considered the AE related to the underlying medical history.

- Subject (b) (6) : On Day 6 after receipt of PCV13, a 65-year-old White male U.S. subject with a BMI of 41.1 and a medical history of being a former cigarette smoker (1975-2004), dyslipidemia, deep vein thrombosis, peripheral venous

disease and hypertension reported severe bronchial hyperreactivity which resolved on Day 33. The subject's concomitant medications included simvastatin, warfarin, lisinopril, omega-3 fatty acids and ibuprofen. The event was not considered serious. The investigator considered there was a reasonable possibility that the AE was related to the study product.

- Subject (b) (6) : On day 2 after receipt of PCV13, a 73-year-old White U.S. female subject with a history of chronic obstructive pulmonary disease (COPD) reported severe exacerbation of COPD. The investigator considered that the AE was related to the medical history of COPD.

- Subject (b) (6) : On day 2 after receipt of PCV20, a 63-year old White U.S. female with no pertinent medical history reported severe injection site erythema which resolved on Day 10. The subject also reported moderate injection site swelling from Days 6-8 and mild injection site pain on Days 2-6. Mild fever was recorded on Day 2 only. The subject was withdrawn due to the injection site erythema, which the investigator considered related to the study product.

Reviewer Comment*: Of the 20 AEs/SAEs that led to withdrawal, 10 were viewed by the study investigator to be attributed to an alternative etiology. The investigator considered the remaining 10 AEs/SAEs to be possibly related to the study vaccine; these included injection site reactions (pain, pruritis, erythema and swelling), myalgia, moderate anxiety, palpitations, pruritis, feeling abnormal, headache and bronchial hyperreactivity. The clinical reviewer agrees with the assessments of the investigators as noted above.*

6.1.13 Study Summary and Conclusions

The effectiveness of Prevnar 20 (PCV20) was demonstrated in persons 60 years of age and older by demonstrating immunologic noninferiority of the serotype-specific OPA antibody responses induced by PCV20 compared to the corresponding serotypes-specific OPA antibody responses induced by a licensed pneumococcal conjugate vaccine. For the original 13 serotypes, the OPA antibody responses induced by PCV20 were compared to those induced by Prevnar 13. For the 7 new serotypes, OPA antibody responses induced by PCV20 were compared to those induced by Pneumovax 23. The pre-specified 2-fold non-inferiority criterion (a lower limit of the 95% CI for the GMT ratio ($GMT_{PCV20}/GMT_{active\ control}$) >0.5) was met for each serotype, except for serotype 8 (LL =0.49). In supportive secondary analyses, 77.8% of subjects ≥60 years of age achieved a ≥4-fold increase in anti-serotype 8 OPA titers.

The effectiveness of Prevnar 20 in younger adults 18-49 years of age and 50-59 years of age was demonstrated by immunobridging to the established effectiveness in the 60-64-year-old adult age group (Cohort 1 Subset).

Overall, the safety profile of Prevnar 20 in adults was generally consistent with the known safety profile of U.S.-licensed Prevnar 13 (the active control for safety). No safety concerns were identified.

6.2 Study B7471008

Study B7471008 was designed to provide clinical data supporting manufacturing consistency. This study was conducted between February 14, 2019 and April 6, 2020 and enrolled a total of 1,708 subjects across all vaccine groups. The clinical study report was dated June 30, 2020.

6.2.1 Objectives

Primary Safety Objective: To demonstrate the safety profile of PCV20.

- 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 NDCMCs within 6 months after vaccination.

Primary Immunogenicity Objective: To demonstrate that the immune responses to 20 serotypes induced by PCV20 were equivalent across 3 lots.

- Primary endpoint: serotype-specific OPA titers 1 month after vaccination
- Equivalence criterion: The serotype-specific OPA GMT ratio and 2-sided 95% CI for each pair of lot comparisons (Lot 1/Lot 2, Lot 1/Lot 3, Lot 2/Lot 3) were calculated. Using a 2-fold equivalence margin, lot consistency was declared for a given serotype if each of the 3 pairwise CIs for that serotype was contained in the interval (0.5, 2.0). Overall lot consistency was declared if the 3 lots met the criteria for all 20 serotypes. Note: this requires a total of 60 comparisons (3 pairwise between-lot comparisons for each of the 20 serotypes).

Secondary Immunogenicity Objective: To describe the immune response to PCV20

- Secondary endpoints:
  - Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
  - ≥4-fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
  - Serotype-specific OPA titers ≥ LLOQ 1 month after vaccination.

Reviewer Comment*: This review focuses on the primary endpoint only, as the primary objective was met for each vaccine serotype, and the supportive secondary endpoints are less informative for the purposes of lot-to-lot consistency.*

Exploratory Immunogenicity Objective: To further describe the immune response induced by PCV20

- Exploratory endpoints:
  - ≥4-fold rise in pneumococcal serotype 15C OPA titer from before to 1 month after vaccination.
  - Pneumococcal serotype 15C OPA titer ≥ LLOQ 1 month after vaccination.
  - Pneumococcal serotype 15C OPA titer 1 month after vaccination.
  - Fold rise in pneumococcal serotype 15C OPA titer from before to 1 month after vaccination.

6.2.2 Design Overview

Study B7471008 was a Phase 3, randomized, double-blind, multicenter study with a 4-arm parallel design conducted in the U.S. A total of ~1,610 adults 18-49 years of age with no history of pneumococcal vaccination were planned to be enrolled and randomized (via site-based randomization) into 1 of 4 groups in a 2:2:2:1 ratio to receive one of three lots of PCV20 or PCV13 (Table 21). The PCV13 group was a control for safety only, but sera were assayed to

maintain blinding and for descriptive purposes. Adults 18-49 years of age with no history of pneumococcal vaccination were selected as the study population because they have lower variability in immune response than potentially previously vaccinated older populations, thus facilitating interpretation of immunogenicity results for lot consistency.

Investigational product was administered in a double-blind fashion as the appearance of PCV20 and PCV13 were identical pre-filled syringes packaged in blinded cartons. Laboratory personnel performing immunogenicity assays were blinded throughout clinical testing. Wyeth personnel directly involved with evaluating participant data and investigator site staff were blinded until the database was locked and unblinded for the final analyses of all safety and immunogenicity data.

The duration of subject participation was approximately 6 months post-vaccination and included the 2 study visits and 1 telephone contact listed below. Please see Section 6.2.7 for details regarding safety and immunogenicity monitoring.

- Visit 1 (Day 1): Informed consent, Vaccination 1, Blood draw for immunogenicity
- Visit 2 (Day 28 to 42 post-vaccination): Blood draw for immunogenicity and collection of safety data
- 6-Month Safety Telephone Contact (168 to 196 days post-vaccination)

Table 21. Enrollment and Vaccination, Study B7471008

Vaccine Group	Planned # of Participants
PCV20 Lot 1	460
PCV20 Lot 2	460
PCV20 Lot 3	460
PCV13	230

Source: STN 125731/0.1 module 5.3.5.1, Study B7471007, Clinical Study Report, Table 3, p20.

6.2.3 Population

Individuals were eligible for enrollment if they met all study inclusion criteria and none of the exclusion criteria. With one exception (age), inclusion criteria and exclusion criteria for study B7471008 were identical to those described for study B7471007 (see Section 6.1.3). The one exception was that study B7471008 inclusion criteria required subject age to be ≥18 years and <50 years at the time of enrollment. Criteria for temporarily delaying vaccination at visit 1 or delaying the immunogenicity blood draw at visits 1 and 2 were also identical to those described for study B7471007 (see Section 6.1.3).

6.2.4 Study Treatments or Agents Mandated by the Protocol

A 0.5 mL dose of 3 lots of PCV20 vaccine or PCV13 vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm at Visit 1 based on randomization. The study vaccines were identical in appearance and supplied as single-use prefilled syringes. Please see Section 6.1.4 for detailed descriptions of the PCV20 and PCV13 vaccines' composition. The PCV20 lot numbers used in this study included the following: W73014 (lot 1), X29529 (lot 2), X29567-1 (lot 3). The PCV13 lot number used in this study was T82473.

Non-study Vaccines

The name and date of administration of any permitted non-study vaccinations were recorded in the CRF. Licensed inactivated influenza vaccine was permitted >14 days prior to or >14 days after study product injection. Receipt of any other licensed non-study vaccine (except pneumococcal vaccine which was prohibited in this study) was permitted after Visit 2.

Prophylactic antipyretics were permitted but not recommended on the day prior to or the day of investigational product administration.

6.2.6 Sites and Centers

Study B7471008 was conducted at 21 sites in the U.S.

6.2.7 Surveillance/Monitoring

Safety Monitoring

Safety monitoring, adverse reaction grading, and procedures for unscheduled visits in study B7471008 were identical to those specified for study B7471007. Please see Section 6.1.7 for details. MedDRA version 22.1 coding dictionary was applied in study B7471008.

Immunogenicity Monitoring

Blood samples for immunogenicity were collected from all subjects prior to and 1 month after vaccination. OPA titers for all serotypes present in PCV20 were determined on all sera collected. In addition, OPA titers were tested for non-vaccine serotype 15C in a random subset of patients.

6.2.8 Endpoints and Criteria for Study Success

Please see Section 6.2.1 of the clinical review.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations

- A total of 1,610 subjects (460 in each of the three PCV20 lot groups and 230 in the PCV13 control group) was planned to ensure 1,449 evaluable subjects (414 in each of the three PCV20 lot groups and 207 in the PCV13 group).
- A δ[12] of 0.2 was used in the power calculation, corresponding to an assumption that the true GMT ratio of any lot to another lot is between 0.82 and 1.22.
- Based on the stated assumptions, the planned sample size provided the study with an overall power of 89.8% for declaring overall equivalence of the 3 lots of PCV20 vaccine.

Statistical Considerations

- For each serotype, a linear regression model that included terms for age, corresponding baseline OPA titer, sex, smoking status, and PCV20 lot was used as the primary approach to calculate serotype-specific OPA GMT ratio and CI for each pair of lot comparisons. The unadjusted serotype-specific OPA GMT ratio and CI were also calculated for each of the serotypes.
- Missing assay results will not be replaced or imputed.
- Serotype-specific OPA titers below the corresponding serotype-specific assay LLOQ were set to 0.5 x LLOQ for analysis.

[12] δ is the true maximum difference in the serotype-specific OPA titers between any 2 lots.

Analysis Timing

One analysis was performed after the complete study data were available and the database was locked.

Safety Analysis

The safety objective was evaluated by descriptive summary statistics for each primary safety endpoint for each study group.

Analysis Populations

- The safety population included all subjects who received at least 1 dose of any PCV20 lot or PCV13 and had safety follow-up after vaccination. Subjects were included in the vaccine group corresponding to the vaccine actually received.

- The evaluable immunogenicity population was the primary analysis population for the immunogenicity results. Participants were included in the vaccine group as randomized in the analysis. Criteria for inclusion in this population are as follows:
  - Received randomized vaccine,
  - Had Visit 2 blood draw within 27 to 49 days after study vaccination,
  - Had ≥1 valid and determinate OPA titer for any serotype at Visit 2, and
  - Had no other major protocol deviations as determined by the clinician.
- The all-available immunogenicity population was the secondary analysis population for immunogenicity results. Participants were included in the vaccine group as randomized in the analysis. The criteria for inclusion in this population were receipt of PCV20 (from any lot) or PCV13 and at least 1 valid and determinate OPA titer after vaccination.

- Analysis of immunogenicity data based on the all-available immunogenicity population was to be performed only if there was 10% or more difference in sample size between the evaluable immunogenicity population and the all-available immunogenicity population.

6.2.10 Study Population and Disposition

Of the 1,710 randomized subjects, 1,708 were vaccinated with either PCV20 (lot 1, 2 or 3) or PCV13, and 1,635 (95.6%) completed the study.

6.2.10.1 Populations Enrolled/Analyzed

Section 6.2.9 defines this study's populations enrolled and analyzed.

The proportion of subjects included in the evaluable immunogenicity population and all-available immunogenicity population were similar across all study groups. The most common reason for exclusion from the evaluable immunogenicity population was not having a blood draw within the pre-specified time window.

No analysis was performed on the all-available immunogenicity population because the difference between the evaluable and all-available populations was <10%.

Table 22. Evaluable and All-Available Immunogenicity Populations, Study B7471008

Disposition	PCV20 Lot 1 n[b] (%)	PCV20 Lot 2 n[b] (%)	PCV20 Lot 3 n[b] (%)	Pooled n[b] (%)	PCV13 n[b] (%)
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)
Subjects excluded from evaluable immunogenicity population	26 (5.3)	17 (3.5)	30 (6.2)	73 (5.0)	13 (5.3)
Didn't receive the vaccine as randomized	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
Didn't have Visit 2 blood sample collected within 27 to 49 days after vaccination	24 (4.9)	15 (3.1)	27 (5.6)	66 (4.5)	10 (4.1)
No valid and determinate OPA titer after vaccination	15 (3.1)	9 (1.8)	16 (3.3)	40 (2.7)	7 (2.9)
Had any other major protocol deviations[d]	1 (0.2)	3 (0.6)	3 (0.6)	7 (0.5)	2 (0.8)
All-available immunogenicity population	474 (96.9)	481 (98.2)	470 (96.7)	1425 (97.3)	238 (97.1)
Subjects excluded from all-available immunogenicity population	15 (3.1)	9 (1.8)	16 (3.3)	40 (2.7)	7 (2.9)
Did not receive ≥1 dose of investigational product	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)
No valid and determinate OPA titer after vaccination	15 (3.1)	9 (1.8)	16 (3.3)	40 (2.7)	7 (2.9)

[a] n = Number of subjects with the specified characteristic.
[b] These values are the denominators for the percentage calculations.
[c] Subjects may have been excluded for more than 1 reason.
[d] Four subject received vaccines within a prohibited time frame (i.e., 1 subject received Tdap within 14 days before vaccination and 3 participants received tetanus, human papillomavirus vaccine, Tdap vaccines (1 each) between vaccination and 1 month post-vaccination. Five subjects were enrolled but later found to have not met elig bility criteria (2 previously received pneumococcal vaccine, 1 had a medical history of asplenia, 1 had an ongoing history of leukopenia, and 1 met 3 criteria (unwilling to comply with visits and study procedures and had multiple suspected chronic medical conditions including rheumatoid arthritis, which required the use of systemic steroids).
Source: STN 125731/0.1 module 5.3.5.1, Study B7471007, Clinical Study Report, Table 6, p28.

6.2.10.1.1 Demographics

Table 23 summarizes baseline demographic characteristics and smoking history for the safety population. The four study groups were similar with regard to baseline demographics and smoking history. Overall, the safety population included 65.3% females, 72.7% White, 18.5% Black, 3.5% Asian, 2.2% multiracial, 1.3% American Indian or Alaska Native, 1.5% not reported and 0.4% Native Hawaiian or other Pacific Islander; 11.2% were Hispanic/Latino; 20.8% were current smokers, 17.2% were ex-smokers, and 62% never smoked. Overall, the mean age was 35.3 years (standard deviation 9.0 years).

Demographic characteristics and smoking history for the evaluable immunogenicity population were similar to those for the safety population.

Table 23. Demographic Characteristics and Smoking History, Safety Population, Study B7471008

Characteristic	PCV20 Lot 1 N[a]=488 n[b] (%)	PCV20 Lot 2 N[a]=489 n[b] (%)	PCV20 Lot 3 N[a]=486 n[b] (%)	Pooled N[a]=1463 n[b] (%)	PCV13 N[a]=245 n[b] (%)	Total N[a]=1708 n[b] (%)
Sex						
Male	157 (32.2)	173 (35.4)	162 (33.3)	492 (33.6)	101 (41.2)	593 (34.7)
Female	331 (67.8)	316 (64.6)	324 (66.7)	971 (66.4)	144 (58.8)	1115 (65.3)
Race						
White	367 (75.2)	351 (71.8)	350 (72.0)	1068 (73.0)	173 (70.6)	1241 (72.7)
Black or African American	87 (17.8)	88 (18.0)	97 (20.0)	272 (18.6)	44 (18.0)	316 (18.5)
Asian	13 (2.7)	17 (3.5)	17 (3.5)	47 (3.2)	12 (4.9)	59 (3.5)
American Indian or Alaska Native	5 (1.0)	9 (1.8)	5 (1.0)	19 (1.3)	4 (1.6)	23 (1.3)
Native Hawaiian or other Pacific Islander	2 (0.4)	1 (0.2)	1 (0.2)	4 (0.3)	2 (0.8)	6 (0.4)
Multiracial	6 (1.2)	13 (2.7)	13 (2.7)	32 (2.2)	5 (2.0)	37 (2.2)
Not Reported	8 (1.6)	10 (2.0)	3 (0.6)	21 (1.4))	5 (2.0	26 (1.5)
Ethnicity						
Hispanic/Latino	48 (9.8)	58 (11.9)	56 (11.5)	162 (11.1)	29 (11.8)	191 (11.2)
Non-Hispanic/non-Latino	434 (88.9)	427 (87.3)	427 (87.9)	1288 (88.0)	215 (87.8)	1503 (88.0)
Not reported	6 (1.2)	4 (0.8)	3 (0.6)	13 (0.9)	1 (0.4)	14 (0.8)
Age at Vaccination (Years)						
Mean (SD)	35.6 (9.17)	35.7 (9.03)	34.9 (9.05)	35.4 (9.08)	35.0 (8.70)	35.3 (9.03)
Median (Min, Max)	37.0 (18, 49)	36.0 (18, 49)	35.0 (18, 49)	36.0 (18, 49)	35.0 (18, 49)	36.0 (18, 49)
Smoking History						
Current Smoker	100 (20.5)	101 (20.7)	102 (21.0)	303 (20.7)	53 (21.6)	356 (20.8)
Mean (SD) # Years Smoking	16.6 (9.88)	14.6 (9.07)	15.1 (8.97)	15.4 (9.32)	16.2 (9.30)	15.6 (9.31)
Ex-smoker						
Mean (SD) # Years Since Quitting	7.5 (8.36)	8.6 (7.53)	7.5 (7.31)	7.8 (7.71)	6.6 (7.12)	7.7 (7.63)
Never Smoked	308 (63.1)	307 (62.8))	295 (60.7	910 (62.2)	149 (60.8)	1059 (62.0)

[a] N = number of subjects in the specified group or the total sample. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471008. Clinical Study Report, Table 7, p30-31.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 24 presents select baseline comorbidities noted in the medical history in the safety population. The proportion of subjects with any medical history was similar across study groups (overall 83.6%). A numerically higher proportion of PCV13 recipients reported a medical history within the SOC *Cardiac disorders* (4.1%) compared to the pooled PCV20 group (1.7%). However, the proportion of subjects with a cardiac medical condition was low across all study groups.

Table 24. Medical History, Safety Population, Study B7471008

Comorbidity	PCV20 Lot 1 N[a]=488 n[b] (%)	PCV20 Lot 2 N[a]=489 n[b] (%)	PCV20 Lot 3 N[a]=486 n[b] (%)	Pooled PCV20 N[a]=1463 n[b] (%)	PCV13 N[a]=245 n[b] (%)	Total N[a]=1708 n[b] (%)
Any medical history by MedDRA SOC/PT	419 (85.9)	408 (83.4)	402 (82.7)	1229 (84.0)	199 (81.2)	1428 (83.6)
Blood and lymphatic system disorders	12 (2.5)	18 (3.7)	18 (3.7)	48 (3.3)	6 (2.4)	54 (3.2)
Cardiac disorders	8 (1.6)	8 (1.6)	9 (1.9)	25 (1.7)	10 (4.1)	35 (2.0)
Endocrine disorders	22 (4.5)	23 (4.7)	31 (6.4)	76 (5.2)	10 (4.1)	86 (5.0)
Gastrointestinal disorders	73 (15.0)	74 (15.1)	80 (16.5)	227 (15.5)	28 (11.4)	255 (14.9)
Hepatobiliary disorders	23 (4.7)	18 (3.7)	31 (6.4)	72 (4.9)	10 (4.1)	82 (4.8)
Immune system disorders	182 (37.3)	168 (34.4)	177 (36.4)	527 (36.0)	79 (32.2)	606 (35.5)
Drug hypersensitivity	91 (18.6)	90 (18.4)	80 (16.5)	261 (17.8)	41 (16.7)	302 (17.7)
Infections and infestations	64 (13.1)	54 (11.0)	56 (11.5)	174 (11.9)	27 (11.0)	201 (11.8)
Metabolism and nutrition disorders	92 (18.9)	85 (17.4)	103 (21.2)	280 (19.1)	54 (22.0)	334 (19.6)
Hypercholesterolaemia	10 (2.0)	9 (1.8)	13 (2.7)	32 (2.2)	5 (2.0)	37 (2.2)
Hyperlipidemia	10 (2.0)	6 (1.2)	10 (2.1)	26 (1.8)	5 (2.0)	31 (1.8)
Obesity	41 (8.4)	48 (9.8)	61 (12.6)	150 (10.3)	30 (12.2)	180 (10.5)
Type 2 diabetes mellitus	11 (2.3)	12 (2.5)	8 (1.6)	31 (2.1)	3 (1.2)	34 (2.0)
Nervous system disorders	115 (23.6)	97 (19.8)	101 (20.8)	313 (21.4)	51 (20.8)	364 (21.3)
Renal and urinary disorders	16 (3.3)	15 (3.1)	18 (3.7)	49 (3.3)	8 (3.3)	57 (3.3)
Respiratory, thoracic and mediastinal disorders	71 (14.5)	74 (15.1)	55 (11.3)	200 (13.7)	26 (10.6)	226 (13.2)
Asthma	39 (8.0)	40 (8.2)	32 (6.6)	111 (7.6)	14 (5.7)	125 (7.3)
Sleep apnoea syndrome	8 (1.6)	8 (1.6)	9 (1.9)	25 (1.7)	4 (1.6)	29 (1.7)
Vascular disorders	43 (8.8)	52 (10.6)	47 (9.7)	142 (9.7)	19 (7.8)	161 (9.4)
Hypertension	36 (7.4)	48 (9.8)	36 (7.4)	120 (8.2)	16 (6.5)	136 (8.0)

Note: MedDRA (v22.1) coding dictionary applied.
[a] N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471008. Clinical Study Report, Table 14.2, p70-107.

6.2.10.1.3 Subject Disposition

The disposition of all randomized subjects (as described in Section 6.2.10) are summarized in Table 25. Subject disposition was similar across the 4 study groups; the most common reason for withdrawal in all study groups was being lost to follow-up (overall 3.7%).

Table 25. Disposition of All Randomized Subjects, Study B7471008

Disposition	PCV20 Lot 1 N[a]=488 n[b] (%)	PCV20 Lot 2 N[a]=489 n[b] (%)	PCV20 Lot 3 N[a]=486 n[b] (%)	Pooled N[a]=1463 n[b] (%)	PCV13 N[a]=245 n[b] (%)	Total N[a]=1708 n[b] (%)
Randomized[b]	489 (100.0)	490 (100.0)	486 (100.0)	1465 (100.0)	245 (100.0)	1710 (100.0)
Not vaccinated	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Vaccinated	488 (99.8)	489 (99.8)	486 (100.0)	1463 (99.9)	245 (100.0)	1708 (99.9)
Completed 1-month follow-up after Vaccination 2	477 (97.5)	483 (98.6)	472 (97.1)	1432 (97.7)	241 (98.4)	1673 (97.8)
Completed Study	465 (95.1)	475 (96.9)	460 (94.7)	1400 (95.6)	235 (95.9)	1635 (95.6)
Withdrawn from study	24 (4.9)	15 (3.1)	26 (5.3)	65 (4.4)	10 (4.1)	75 (4.4)
Reason for withdrawal						
Lost to follow-up	22 (4.5)	12 (2.4)	23 (4.7)	57 (3.9)	7 (2.9)	64 (3.7)
No longer meets eligibility criteria	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.1)	3 (1.2)	5 (0.3)
Protocol deviation	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
Withdrawal by subject	2 (0.4)	0 (0.0)	2 (0.4)	4 (0.3)	0 (0.0)	4 (0.2)

[a] n = Number of subjects with the specified characteristic.
[b] These values are the denominators for the percentage calculations.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471008. Clinical Study Report, Table 5, p26.

6.2.11 Efficacy Analyses

The results from the unadjusted OPA GMT ratios and associated 95% CIs were consistent with the model-based OPA GMT ratio results for each of the 20 vaccine serotypes.

6.2.11.1 Analyses of Primary Endpoint(s)

Lot Equivalence – Pneumococcal OPA GMTs and GMT Ratios

The study's primary objective was met, demonstrating that the serotype-specific OPA GMTs for the 20 vaccine serotypes in PCV20 induced by each of three manufacturing scale lots of PCV20 were equivalent based on a 2-fold equivalence margin. The 2-sided 95% CI for the model-based estimate of serotype-specific OPA GMT ratios at 1 month post-vaccination for each pair of lot comparisons were contained in the pre-specified interval (0.5, 2.0) for each of the 20 serotypes in PCV20 (Table 26).

Table 26. Pneumococcal Opsonophagocytic Activity GMTs and GMT Ratios 1 Month After Vaccination, Linear Regression Model, Evaluable Immunogenicity Population, Study B7471008

Serotype	PCV20 Lot 1 n[a]	PCV20 Lot 1 GMT (95% CI)[b]	PCV20 Lot 2 n[a]	PCV20 Lot 2 GMT (95% CI)[b]	PCV20 Lot 3 n[a]	PCV20 Lot 3 GMT (95% CI)[b]	Lot 1 to 2 Comparison GMT Ratio (95% CI)[c]	Lot 1 to 2 Comparison GMT Ratio (95% CI)[c]	Lot 1 to 2 Comparison GMT Ratio (95% CI)[c]
PCV13 Serotypes									
1	462	200 (174, 230)	470	175 (153, 201)	454	165 (143, 189)	1.14 (0.95, 1.37)	1.21 (1.01, 1.46)	1.06 (0.89, 1.28)
3	458	47 (43, 52)	469	47 (42, 52)	451	43 (39, 48)	1.01 (0.88, 1.16)	1.10 (0.96, 1.26)	1.09 (0.95, 1.24)
4	455	1500 (1288, 1746)	468	1568 (1350, 1821)	451	1506 (1294, 1751)	0.96 (0.78, 1.17)	1.00 (0.82, 1.22)	1.04 (0.85, 1.27)
5	457	126 (109, 146)	466	136 (117, 157)	450	117 (101, 135)	0.93 (0.77, 1.12)	1.08 (0.89, 1.31)	1.16 (0.96, 1.41)
6A	454	4654 (4033, 5371)	468	3748 (3256, 4315)	446	3330 (2885, 3845)	1.24 (1.03, 1.50)	1.40 (1.16, 1.69)	1.13 (0.93, 1.36)
6B	458	4403 (3833, 5059)	469	4350 (3796, 4984)	453	3907 (3401, 4488)	1.01 (0.85, 1.21)	1.13 (0.94, 1.35)	1.11 (0.93, 1.33)
7F	452	1821 (1589, 2087)	464	1866 (1630, 2136)	441	1876 (1633, 2155)	0.98 (0.82, 1.17)	0.97 (0.81, 1.16)	0.99 (0.83, 1.19)
9V	454	5120 (4465, 5873)	467	4604 (4024, 5268)	446	4922 (4292, 5643)	1.11 (0.93, 1.33)	1.04 (0.87, 1.25)	0.94 (0.78, 1.12)
14	455	2240 (1965, 554)	467	2091 (1840, 2377)	450	2002 (1760, 2277)	1.07 (0.90, 1.27)	1.12 (0.94, 1.33)	1.04 (0.88, 1.24)
18C	455	3904 (3340, 4563)	465	4451 (3818, 5188)	449	4222 (3616, 4929)	0.88 (0.72, 1.07)	0.92 (0.75, 1.13)	1.05 (0.86, 1.29)
19A	451	1458 (1288, 1651)	465	1528 (1353, 1726)	450	1434 (1268, 1623)	0.95 (0.81, 1.12)	1.02 (0.86, 1.20)	1.07 (0.91, 1.25)
19F	455	525 (451, 610)	466	529 (456, 615)	452	549 (472, 638)	0.99 (0.81, 1.21)	0.96 (0.78, 1.17)	0.96 (0.79, 1.17)
23F	459	1416 (1182, 1696)	471	1548 (1295, 1849)	454	1435 (1198, 1718)	0.92 (0.72, 1.16)	0.99 (0.78, 1.25)	1.08 (0.85, 1.37)

Serotype	PCV20 Lot 1 n[a]	PCV20 Lot 1 GMT (95% CI)[b]	PCV20 Lot 2 n[a]	PCV20 Lot 2 GMT (95% CI)[b]	PCV20 Lot 3 n[a]	PCV20 Lot 3 GMT (95% CI)[b]	Lot 1 to 2 Comparison GMT Ratio (95% CI)[c]	Lot 1 to 2 Comparison GMT Ratio (95% CI)[c]	Lot 1 to 2 Comparison GMT Ratio (95% CI)[c]
New Serotypes									
8	435	1595 (1403, 1814)	448	1346 (1186, 1528)	436	1624 (1430, 1845)	1.19 (1.00, 1.40)	0.98 (0.83, 1.16)	0.83 (0.70, 0.98)
10A	399	6328 (5408, 7405)	418	5693 (4890, 6627)	410	5962 (5121, 6941)	1.11 (0.91, 1.36)	1.06 (0.87, 1.30)	0.95 (0.78, 1.17)
11A	394	8656 (7308, 10253)	399	6729 (5693, 7952)	399	8720 (7409, 10264)	1.29 (1.03, 1.60)	0.99 (0.80, 1.24)	0.77 (0.62, 0.96)
12F	418	8563 (7322, 10015)	418	7908 (6765, 9243)	411	7412 (6332, 8677)	1.08 (0.88, 1.33)	1.16 (0.94, 1.42)	1.07 (0.87, 1.31)
15B	392	7343 (6108, 8827)	426	6357 (5325, 7589)	402	7019 (5854, 8416)	1.16 (0.91, 1.46)	1.05 (0.82, 1.33)	0.91 (0.71, 1.15)
22F	367	12508 (10318, 15161)	392	11213 (9337, 13467)	384	12729 (10572, 15326)	1.12 (0.87, 1.43)	0.98 (0.77, 1.26)	0.88 (0.69, 1.12)
33F	391	10746 (9042, 12771)	401	10328 (8737, 12209)	409	10418 (8815, 12313)	1.04 (0.83, 1.30)	1.03 (0.82, 1.29)	0.99 (0.79, 1.24)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; CIs: confidence intervals; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
[a] n = Number of subjects with valid and determinate OPA titers for the specified serotype.
[b] GMTs and 2-sided CIs were calculated by exponentiating the least squares means and the corresponding CIs based on the same regression model as above.
[c] GMT ratios for each pair of lot comparisons and 2-sided CIs were calculated by exponentiating the difference in least squares means and the corresponding CIs based on the analysis of log-transformed OPA titers using a regression model with PCV20 lot, sex, smoking status, age at vaccination in years (continuous), and baseline log-transformed OPA titers.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471008. Clinical Study Report, Table 9, p36-38.

6.2.11.2 Analyses of Secondary Endpoints

This review focuses on the primary endpoint only, as the primary objective was met for each vaccine serotype, and the supportive secondary endpoints are less informative for the purposes of lot-to-lot consistency.

6.2.11.3 Subpopulation Analyses

Subgroup analyses of the primary immunogenicity endpoint (OPA GMTs) were provided based on sex and race.

Subpopulation Analyses by Sex

Serotype-specific OPA GMTs were generally similar between males and females for the 20 vaccine serotypes (Data not shown, CSR Table 14.9).

Subpopulation Analyses by Race

No clear trend in serotype-specific OPA GMTs were identified among White, Black or other racial groups combined for the 20 vaccine serotypes

6.2.11.4 Dropouts and/or Discontinuations

Please see Section 6.2.10.1.3 for information on subject disposition, including withdrawals. Missing values were not imputed for subjects who had missing blood draws.

6.2.11.5 Exploratory and Post Hoc Analyses

In exploratory analyses, PCV20 elicited functional OPA titers to serotype 15C (Data not shown, CSR Tables 10 and 11). In a random subset of subjects for whom serotype 15C OPA was measured, 44.4% (2-sided 95% CI of 35.9% to 53.2%, n=60) achieved a ≥4-fold rise in 15C OPA titers from before vaccination to 1 month after vaccination with PCV20. The OPA GMT achieved by PCV20 recipients (pooled) at 1 month post-vaccination was 150.5 (95% CI 117.6, 192.5, n=138). The proportion of participants with 15C OPA titers ≥ LLOQ 1 month after vaccination with PCV20 was 55.1% (2-sided 95% CI of 46.4% to 63.5%, n=76). The serotype 15C LLOQ is (b) (4). There was no response to serotype 15C after vaccination with PCV13, which does not contain 15B conjugate.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety analyses were descriptive. Please see Section 6.2.7 for details regarding safety surveillance/monitoring, Section 6.2.1 for a listing of safety endpoints, and Section 6.2.9 for details regarding the safety analysis population.

E-diary transmission rates were similar across all study groups for each day for the entire 10-day period (Data not shown, CSR Table 8). Daily e-diary transmission rates ranged from 83.8% to 86.9%; transmission rates during the 10-day reporting period ranged from 49.2% to 53.5%.

6.2.12.2 Overview of Adverse Events

Solicited Local Injection Site Adverse Events

The proportions of subjects reporting local injection site reactions were generally similar, although reactogenicity rates were generally highest among PCV20 lot 1 recipients followed by PCV20 lot 2 recipients and generally lowest among PCV20 lot 3 recipients. A similar trend across the PCV20 lot groups was not evident in the immunogenicity data presented in Table 26, which is reassuring. Injection site reaction rates in the pooled PCV20 group and the 13vPnC group were generally similar.

Most local adverse reactions were mild or moderate in severity. The mean onset day and mean duration of injection site reactions were similar across PCV20 lots. When PCV20 data were pooled, the mean onset day was 2.5 days for redness, 2.0 days for swelling and 1.0 day for pain. The mean duration of injection site reactions for the PCV20 groups when pooled was 2.8 days for redness, 2.1 days for swelling and 2.5 for pain (Data not shown, CSR Tables 14.19 and 14.20).

Table 27. Local Reactions, by Maximum Severity, Within 10 Days After Vaccination, Safety Population, Study B7471008

Local Reaction	PCV20 Lot 1 N[a]=486 n[b] (%)	PCV20 Lot 2 N[a]=489 n[b] (%)	PCV20 Lot 3 N[a]=481 n[b] (%)	Pooled PCV20 N =1456 n[b] (%)	PCV13 N[a]=243 n[b] (%)	Pooled PCV20 vs PCV13 Difference (95% CI)[c]
Any local reaction[d]	403 (82.9)	386 (78.9)	364 (75.7)	1153 (79.2)	184 (75.7)	3.5 (-2.0, 9.6)
Pain at injection site[f]						
Any	402 (82.7)	386 (78.9)	358 (74.4)	1146 (78.7)	184 (75.7)	3.0 (-2.4, 9.1)
Mild	262 (53.9)	253 (51.7)	213 (44.3)	728 (50.0)	113 (46.5)	3.5 (-3.3, 10.2)
Moderate	135 (27.8)	128 (26.2)	138 (28.7)	401 (27.5)	67 (27.6)	-0.0 (-6.4, 5.7)
Severe	5 (1.0)	5 (1.0)	7 (1.5)	17 (1.2)	4 (1.6)	-0.5 (-3.0, 0.8)
Swelling[g]						
Any (>2.0 cm)	52 (10.7)	39 (8.0)	33 (6.9)	124 (8.5)	21 (8.6)	-0.1 (-4.5, 3.2)
Mild	35 (7.2)	26 (5.3)	18 (3.7)	79 (5.4)	13 (5.3)	0.1 (-3.6, 2.6)
Moderate	16 (3.3)	12 (2.5)	14 (2.9)	42 (2.9)	8 (3.3)	-0.4 (-3.6, 1.5)
Severe	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)	0 (0.0)	0.2 (-1.4, 0.6)
Redness[g]						
Any (>2.0 cm)	30 (6.2)	39 (8.0)	33 (6.9)	102 (7.0)	15 (6.2)	0.8 (-3.1, 3.7)
Mild	18 (3.7)	19 (3.9)	20 (4.2)	57 (3.9)	8 (3.3)	0.6 (-2.6, 2.6)
Moderate	11 (2.3)	17 (3.5)	10 (2.1)	38 (2.6)	7 (2.9)	-0.3 (-3.3, 1.5)
Severe	1 (0.2)	3 (0.6)	3 (0.6)	7 (0.5)	0 (0.0)	0.5 (-1.1, 1.0)

[a] N = number of subjects with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions (pooled PCV20 – PCV13) expressed as a percentage.
[d] Any local reaction = any injection site pain, any swelling >2.0 cm, or any redness >2.0 cm during Days 1 to 10 post-vaccination.
[f] Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity. Any = mild, moderate or severe.
[g] Mild is >2.0 to 5.0 cm, moderate is >5.0 to 10.0 cm, severe is >10.0 cm. Any = mild, moderate or severe.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471008. Clinical Study Report, Table 12, p47-48.

Solicited Systemic Adverse Reactions

The proportions of subjects reporting systemic reactions overall and by maximum severity were similar across each of the PCV20 lots and between the pooled group of PCV20 recipients

compared to the PCV13 control group (Table 28). The most frequently reported systemic reaction across all vaccine groups was muscle pain. Most systemic reactions across all study groups were mild or moderate in severity. The proportions of subjects reporting antipyretic or pain medication was similar across all vaccine groups.

The mean onset day and mean duration of systemic reactions were similar across PCV20 lots and between the pooled PCV20 group and the PCV13 control group. When PCV20 data were pooled, the mean onset day was Day 1.5 (muscle pain), Day 2.1 (fatigue), Day 2.6 (headache and joint pain) and Day 3.3 (fever). The mean duration of systemic reactions for the PCV20 groups when pooled was 3.3 days for fatigue, 2.7 days for headache, 2.5 days for muscle pain and joint pain and 1.2 days for fever (Data not shown, CSR Tables 14.21 and 14.22).

Table 28. Systemic Reactions, by Maximum Severity, Within 7 Days After Vaccination, Safety Population, Study B7471008

Local Reaction	PCV20 Lot 1 N[a]=486 n[b] (%)	PCV20 Lot 2 N[a]=489 n[b] (%)	PCV20 Lot 3 N[a]=481 n[b] (%)	Pooled PCV20 N[a]=1456 n[b] (%)	PCV13 N[a]=243 n[b] (%)	Pooled PCV20 vs PCV13 Difference (95% CI)[c]
Any Systemic Adverse Reaction[d]	370 (76.1)	366 (74.8)	375 (78.0)	1111 (76.3)	176 (72.4)	3.9 (-1.8, 10.2)
Muscle Pain[e]						
Any	301 (61.9)	299 (61.1)	304 (63.2)	904 (62.1)	147 (60.5)	1.6 (-4.9, 8.3)
Mild	189 (38.9)	193 (39.5)	178 (37.0)	560 (38.5)	94 (38.7)	-0.2 (-6.9, 6.2)
Moderate	109 (22.4)	98 (20.0)	121 (25.2)	328 (22.5)	48 (19.8)	2.8 (-3.1, 7.8)
Severe	3 (0.6)	8 (1.6)	5 (1.0)	16 (1.1)	5 (2.1)	-1.0 (-3.7, 0.4)
Fatigue[e]						
Any	229 (47.1)	222 (45.4)	242 (50.3)	693 (47.6)	106 (43.6)	4.0 (-2.8, 10.6)
Mild	108 (22.2)	127 (26.0)	124 (25.8)	359 (24.7)	59 (24.3)	0.4 (-5.8, 5.9)
Moderate	111 (22.8)	88 (18.0)	110 (22.9)	309 (21.2)	43 (17.7)	3.5 (-2.1, 8.4)
Severe	10 (2.1)	7 (1.4)	8 (1.7)	25 (1.7)	4 (1.6)	0.1 (-2.5, 1.4)
Headache[e]						
Any	179 (36.8)	169 (34.6)	179 (37.2)	527 (36.2)	92 (37.9)	-1.7 (-8.4, 4.7)
Mild	118 (24.3)	112 (22.9)	99 (20.6)	329 (22.6)	66 (27.2)	-4.6 (-10.8, 1.1)
Moderate	55 (11.3)	52 (10.6)	68 (14.1)	175 (12.0)	24 (9.9)	2.1 (-2.5, 5.8)
Severe	6 (1.2)	5 (1.0)	12 (2.5)	23 (1.6)	2 (0.8)	0.8 (-1.4, 1.8)
Joint Pain[e]						
Any	90 (18.5)	78 (16.0)	77 (16.0)	245 (16.8)	34 (14.0)	2.8 (-2.4, 7.2)
Mild	52 (10.7)	44 (9.0)	49 (10.2)	19 (7.8)	19 (7.8)	2.1 (-2.2, 5.4)
Moderate	36 (7.4)	30 (6.1)	28 (5.8)	94 (6.5)	13 (5.3)	1.1 (-2.6, 3.7)
Severe	2 (0.4)	4 (0.8)	0 (0.0)	6 (0.4)	2 (0.8)	0.4 (-2.6, 0.4)
Fever						
≥38.0°C	8 (1.6)	4 (0.8)	6 (1.2)	18 (1.2)	2 (0.8)	0.4 (-1.7, 1.4)
≥38.0°C to 38.4°C	4 (0.8)	2 (0.4)	5 (1.0)	11 (0.8)	1 (0.4)	0.3 (-1.6, 1.1)
>38.4°C to 38.9°C	2 (0.4)	1 (0.2)	1 (0.2)	4 (0.3)	1 (0.4)	-0.1 (-2.0, 0.4)
>38.9°C to 40.0°C	2 (0.4)	1 (0.2)	0 (0.0)	3 (0.2)	0 (0.0)	0.2 (-1.4, 0.6)
>40.0°C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (-1.6, 0.3)

Local Reaction	PCV20 Lot 1 N[a]=486 n[b] (%)	PCV20 Lot 2 N[a]=489 n[b] (%)	PCV20 Lot 3 N[a]=481 n[b] (%)	Pooled PCV20 N[a]=1456 n[b] (%)	PCV13 N[a]=243 n[b] (%)	Pooled PCV20 vs PCV13 Difference (95% CI)[c]
Use of antipyretic or pain medication[f]	109 (22.4)	96 (19.6)	115 (23.9)	320 (22.0)	44 (18.1)	3.9 (-1.8, 8.8)

[a] N = number of subjects with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
[b] n = Number of subjects with the specified characteristic.
[c] 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions (pooled PCV20 – PCV13) expressed as a percentage.
[d] Any systemic event = any fever ≥38.0°C, any fatigue, any headache, any joint pain, or any muscle pain during Day 1 to Day 7 after vaccination.
[e] Mild = does not interfere with activity, moderate = some interference with activity, severe = prevents daily activity. Any = mild, moderate or severe.
[f] Severity was not collected for use of antipyretic or pain medication. The numbers in the table reflect yes responses (i.e., number of events reported).
Note: One participant entered a fever of 41.1°C that was confirmed by the investigator site to be in error (no fever occurred). This has been corrected in Table 28.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471008. Clinical Study Report, Table 13, p50-52.

Unsolicited Adverse Events (AEs) Reported Through 30 Days Post-Vaccination

Similar and low proportions of subjects across each of the 3 manufacturing scale lots of PCV20 (5.9%-7.4%) and in the pooled PCV20 (6.8%) and PCV13 (5.3%) groups reported at least 1 unsolicited AE within 1 month after vaccination (Data not shown, CSR Table 14.24). Most unsolicited AEs were mild or moderate in severity. Severe AEs were reported by 7 subjects in the PCV20 pooled group and 2 subjects (0.8%) in the PCV13 group (Data not shown, CSR Table 14.26). There were no clear imbalances in rates of adverse reactions by the reported MedDRA Preferred Terms. The most frequently reported unsolicited AEs after vaccination that were reported by a numerically higher proportion of PCV20 recipients in the pooled PCV20 group versus the PCV13 group were within the SOC *Infections and infestations* (3.1% in the pooled PCV20 group and 1.6% in the PCV13 group).

At least one unsolicited AE that was considered related to the study product was reported by 0.3% (5 subjects) in the pooled PCV20 group and 0.8% (2 subjects) in the PCV13 group. These included reports of nausea, chills, injection site bruising, discoloration, induration or pain, musculoskeletal pain, neck pain, pain in extremity, migraine, anxiety and pruritis (Data not shown, CSR Table 14).

Newly Diagnosed Chronic Medical Conditions

Two percent or less of subjects in any vaccine group reported at least 1 NDCMC within 6 months after vaccination. None of the NDCMCs reported were considered by the investigator to be related to the study vaccine (Data not shown, CSR Tables 16 and 14.36).

Reviewer Comment*: One PCV20 lot 1 recipient was noted in the CSR to have been newly diagnosed with supraventricular extrasystoles. This subject (subject* (b) (6) *) was a 33-year old, White, non-Hispanic, non-smoking female with a history of palpitations occurring throughout her life. The subject, who was also noted to be pregnant at about 11 weeks post-vaccination, reported that the palpitations started occurring more frequently prior to her pregnancy. A heart monitor was used to evaluate the palpitations, and the monitor showed only occasional premature atrial contractions. The subject was diagnosed with an NDCMC of premature atrial contractions 10 weeks after receipt of PCV20. The event was reported as mild in severity, ongoing, not serious and not related to investigational product; the investigator noted that event represents an early heartbeat seen in 99% of adult heart monitors. The subject gave birth to a full-term male infant approximately one year post-vaccination (5.69 lb, 41.5 cm, head circumference 31 cm, Apgar score within 1 min was 8, within 5 min was 9); the estimated gestational age was 39 weeks, 2 days. The infant was considered small for gestational age. No other AEs or SAEs were reported for this participant. The subject confirmed that the reported palpitations decreased in frequency after her pregnancy. This reviewer agrees that the premature atrial contractions reported in this subject are more likely related to pregnancy rather than the study vaccination.*

Immediate Adverse Reactions

Two subjects (0.1%) in the pooled PCV20 group and no subjects in the PCV13 group reported an immediate adverse reaction within 30 minutes after vaccination. These subjects each reported nausea and vomiting due to residual anxiety from the blood draws.

Other Significant AEs

Six subjects who had documented negative urine pregnancy tests at enrollment became pregnant during the study (5 PCV20 recipients and 1 PCV13 recipient). Four events had an outcome of full-term live birth, 1 event had an unknown outcome, and 1 event had an outcome of spontaneous abortion (the latter involved a PCV13 recipient).

Two of these subjects (both PCV20 recipients) had estimated conception dates before vaccination (Day 4 and Day 19) and were reported at Visit 2 (1 month after vaccination). The subject with the estimated conception date 4 days prior to vaccination gave live birth to a full-term male infant at an estimated 39 weeks gestation. The pregnancy outcome of the subject with an estimated conception date 19 days prior to vaccination could not be determined, as the site informed Wyeth that the subject's telephone number was disconnected (subject (b) (6)).

Of the remaining 4 pregnancies, the estimated conception dates were after vaccination (Day 41, 78, 80 and 126); 2 were reported at the 6-month safety telephone call and 2 had unknown report dates. Three of these subjects (each PCV20) gave live birth to full term infants. The fourth subject was the PCV13 recipient with the pregnancy outcome of spontaneous abortion; the estimated conception date was ~4 months after vaccination). This subject reported being in a motor vehicle accident 187 days after vaccination; the reported spontaneous abortion occurred 196 days after vaccination (subject (b) (6) . The investigator considered there was not a reasonable possibility that the event was related to the study treatment, but rather to have more likely been triggered by the motor vehicle accident and associated fetal genetic anomaly, likely due to trisomy 21 (based on post-fetal demise screening).

Safety Analyses by Subgroups

Subgroup Analyses by Sex

A numerically higher proportion of females reported prompted local injection site reactions (pain, redness and swelling) within 10 days after vaccination compared to males (Data not shown, CSR Table 14.27). A numerically higher proportion of females reported fatigue, headache, muscle pain and use of antipyretic or pain medication within 7 days after vaccination compared to males (Data not shown, CSR 14.29). Rates of joint pain were similar between males and females. Rates of fever were too low to identify clear trends.

Subgroup Analyses by Race

A numerically lower proportion of Black subjects reported prompted local injection site reactions (pain, redness and swelling) within 10 days after vaccination compared to White and all other racial groups combined (subjects in the following racial groups were combined in one “All others” group due to low numbers: Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiracial or not reported) (Data not shown, CSR Table 14.28). Subjects in the combined racial groups reported similar rates of redness and swelling and numerically lower rates of injection site pain compared to White subjects. A numerically lower proportion of Black subjects reported fatigue, headache, muscle pain and use of antipyretic or pain medication within 7 days after vaccination compared to White subjects (Data not shown, CSR Table 14.30). Rates of joint pain were similar with clear trend across racial groups evaluated. No clear trend was observed among subjects in the combined racial groups.

Similar trends as described above were generally observed in analyses of unsolicited AEs by sex and race.

6.2.12.3 Deaths

No deaths were reported during study B7471008.

6.2.12.4 Nonfatal Serious Adverse Events

A total of 10 subjects (0.7%) in the PCV20 groups reported a serious adverse event within 6 months after vaccination (0.4% each in the lot 1 and lot 2 groups and 1.2% in the lot 3 group). No SAEs were reported by subjects in the PCV13 group in the same time period. No reported SAEs were considered by the investigator to be related to the study vaccine.

6.2.12.7 Dropouts and/or Discontinuations

No subjects were withdrawn during this study for safety-related reasons.

6.2.13 Study Summary and Conclusions

Study B7471008 was designed to provide clinical data supporting manufacturing consistency and additional safety data in the U.S. Pneumococcal vaccine-naïve adults 18-49 years of age received 1 of 3 manufacturing scale lots of PCV20 or PCV13 control. The primary objective was met, demonstrating that the immune responses induced by PCV20 at 1 month post-vaccination to the 20 serotypes in the vaccine were equivalent across 3 manufacturing scale lots. The safety profile of PCV20 among participants who received each manufacturing scale lot was comparable to the safety profile of U.S.-licensed Prevnar 13 (the active control in this study), and there were no important differences observed in safety outcomes among the three different manufacturing scale lots.

6.3 Study B7471006

Study B7471006 was an open-label Phase 3 study designed to describe the safety and immunogenicity of PCV20 administered to adults ≥65 years of age who have been previously vaccinated with PPSV23 (Cohort A), PCV13 (Cohort B), or PCV13 followed by PPSV23 (Cohort C). Cohort A and B participants were randomized 2:1 to receive PCV20 or a licensed pneumococcal vaccine that they had not previously received (PCV13 in Cohort A and PPSV23 in Cohort B) that served as active controls for safety assessments. All Cohort C participants received PCV20. The study was conducted between February 12, 2019 and May 29, 2020 and enrolled a total of 875 subjects. The clinical study report was dated July 25, 2020.

> ***Reviewer Comment****: Although Wyeth considered this study to be Phase 3, the analyses were descriptive only and there were no pre-specified success criteria for OPA assessments. Wyeth's intention with this study was to generate descriptive data that would help inform efforts to immunize individuals who have previously received PPSV23 and/or to inform efforts to immunize against the 7 additional serotypes in those previously vaccinated with PCV13.*
>
> *Pneumococcal vaccination recommendations have evolved over the years, and current recommendations differ across countries. In the U.S., from August 2014 through May 2019, the ACIP recommended vaccination of immunocompetent adults ≥65 years of age with PCV13 followed by PPSV23 a year later (see Section 2.3 and 2.6 for more information on ACIP recommendations on pneumococcal vaccination of adults).*

6.3.1 Objectives

Primary Safety Objective: To describe the safety profile of PCV20.

- 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 NDCMCs within 6 months after vaccination.

Primary Immunogenicity Objective: To describe the immune responses to PCV20 in adults previously vaccinated with PPSV23, previously vaccinated with PCV13, or previously vaccinated with both PCV13 and PPSV23.

- Primary immunogenicity endpoint: pneumococcal serotype-specific OPA titers 1 month after vaccination

Secondary Immunogenicity Objective: To further describe the immune responses to PCV20 in adults previously vaccinated with PPSV23, previously vaccinated with PCV13, or previously vaccinated with both PCV13 and PPSV23.

- Secondary endpoints:
  - Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
  - ≥4-Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
  - Serotype-specific OPA titers ≥ LLOQ 1 month after vaccination.

Exploratory Immunogenicity Objective: To further describe the immune responses induced by PCV20.

- Exploratory endpoints:
  - ≥4-Fold rise in pneumococcal serotype 15C OPA titers from before to 1 month after vaccination.
  - Pneumococcal serotype 15C OPA titer ≥ LLOQ 1 month after vaccination.
  - Pneumococcal serotype 15C OPA titer 1 month after vaccination.
  - Fold rise in pneumococcal serotype 15C OPA titer from before to 1 month after vaccination.

6.3.2 Design Overview

Study B7471006 was a Phase 3, randomized, open-label, multicenter descriptive safety and immunogenicity study conducted in the U.S. and Sweden (Table 29). Approximately 875 adults ≥65 years of age were targeted to be enrolled into 3 different cohorts based on their prior pneumococcal vaccination history.

Table 29. Vaccine Assignment, Study B7471006

Cohort	Prior Vaccination History	Vaccine Assignment	Sample Size
A	Received PPSV23 ≥1 to ≤5 years previously, but had not been vaccinated with PCV13	Randomized 2:1 to receive PCV20 or PCV13	PCV20: 250 PCV13: 125
B	Received PCV13 ≥6 months previously[a], but had not been vaccinated with PPSV23	Randomized 2:1 to receive PCV20 or PPSV23	PCV20: 250 PPSV23: 125
C	Previously received PCV13 followed by PPSV23 (PPSV23 must have been given ≥1 year prior to study enrollment)	PCV20	PCV20: 125

[a] Although the upper limit on the interval for prior PCV13 vaccination was not specified, the U.S. ACIP recommendation for PCV13 in all adults ≥65 years of age was issued in September 2014 (5 years before enrollment into study B7471006). Therefore, the PCV13 dose was likely to have been given no more than 5 years prior to study start.
Source: STN 125731/0.1 module 5.3.5.1, Study B7471006 Protocol Table 1, p22.

Participants in Cohort A were enrolled at both U.S. and Swedish sites, while participants in Cohorts B and C were enrolled only at U.S. sites, where a routine recommendation for administration of PCV13 followed by PPSV23 one (1) year later for all adults ≥65 years of age was in place between June 2014 and June 2019.

The PCV13 arm in Cohort A and the PPSV23 arm in Cohort B served as control groups for safety assessments of PCV20 in those cohorts. Blood was collected from all groups[13]; however, OPA titers were determined for the PCV20 groups only.

The duration of subject participation was approximately 6 months after vaccination and included the 2 study visits and 1 telephone contact listed below. Please see Section 6.3.7 for details regarding safety and immunogenicity monitoring.

- Visit 1 (Day 1): Informed consent and vaccination with either PCV20 or a control vaccine (PCV13 control in Cohort A and PPSV23 control in Cohort B)
- Visit 2 (Day 28 to 42 post-vaccination): Blood draw for immunogenicity and collection of safety data

[13] In the control groups, blood was collected for future vaccine research.

- 6-Month Safety Telephone Contact (168 to 196 days post-vaccination)

6.3.3 Population

Individuals were eligible for enrollment if they met all study inclusion criteria and none of the exclusion criteria. With two exceptions (age and prior pneumococcal vaccination history), inclusion criteria and exclusion criteria for study B7471006 were identical to those described for study B7471007 (see Section 6.1.3). The one exception was that study B7471006 inclusion criteria required subjects to be ≥65 years at the time of enrollment and meet one of the following criteria:

- Vaccination with PPSV23 ≥1 year and ≤5 years prior to vaccination in the study, and no prior PCV13 vaccination (Cohort A).
- Vaccination with PCV13 ≥6 months prior to vaccination in the study, and no prior PPSV23 vaccination (Cohort B).
- Vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to vaccination in the study) (Cohort C).

Criteria for temporarily delaying vaccination at visit 1 or delaying the immunogenicity blood draw at visits 1 and 2 were also identical to those described for study B7471007 (see Section 6.1.3).

6.3.4 Study Treatments or Agents Mandated by the Protocol

A 0.5 mL dose of PCV20, PCV13 or PPSV23 vaccines were administered intramuscularly in the deltoid muscle of the non-dominant arm at Visit 1 based on cohort and randomization. Please refer to Section 6.1.4 for detailed descriptions of each vaccine's composition. The vaccine lot numbers are as follows: PCV20 lot number X29567-2; PCV13 lot number T82473; PPSV23 lot number R012501.

Non-study Vaccines

The name and date of administration of any permitted non-study vaccinations were recorded in the CRF. Licensed inactivated influenza vaccine was permitted >14 days prior to or >14 days after study product injection. Receipt of any other licensed non-study vaccine (except pneumococcal vaccine which was prohibited in this study) was permitted after Visit 2.

6.3.6 Sites and Centers

Study B7471006 was conducted at 33 sites in the U.S. and 8 sites in Sweden. A total of 133 subjects were randomized/enrolled in Sweden and 742 subjects were randomized/enrolled in the U.S.

6.3.7 Surveillance/Monitoring

Safety Monitoring

Safety monitoring, adverse reaction grading, and procedures for unscheduled visits in study B7471008 were identical to those specified for study B7471007. Please see Section 6.1.7 for details. MedDRA version 22.1 coding dictionary was also applied in study B7471006.

Immunogenicity Monitoring

Blood samples were collected from all subjects prior to and 1 month after vaccination. However, OPA titers (for all serotypes present in PCV20 in addition to non-vaccine serotype 15C) were only determined for sera collected from subjects in the PCV20 study groups. The PCV13 arm in

Cohort A and the PPSV23 arm in Cohort B served as control groups only for safety assessments.

6.3.8 Endpoints and Criteria for Study Success

See Section 6.3.1 of this clinical review.

6.3.9 Statistical Considerations & Statistical Analysis Plan

No hypothesis testing between vaccine groups was performed, and no formal statistical decision rules were applied in this study. For immunogenicity results of serotype-specific OPA titers, GMTs and GMFRs were computed along with associated 95% CIs. Missing assay results were not imputed. OPA titers < LLOQ were set to 0.5 × LLOQ for analysis.

Analysis Populations

- The safety population included all subjects who received at least 1 dose of PCV20 or PCV13 and had safety follow-up after vaccination. Subjects were included in the vaccine group corresponding to the vaccine actually received.

- The evaluable immunogenicity population was the primary analysis population for the immunogenicity results. Participants were included in the vaccine group as randomized in the analysis. Criteria for inclusion in this population are as follows:
  - Received PCV20,
  - Was enrolled in appropriate cohort based on prior pneumococcal vaccination history,
  - Had Visit 2 blood draw within 27 to 49 days after study vaccination,
  - Had ≥1 valid and determinate OPA titer for any serotype at Visit 2, and
  - Had no other major protocol deviations as determined by the clinician.

- The all-available immunogenicity population was the secondary analysis population for immunogenicity results. Participants were included in the vaccine group as randomized in the analysis. The criterion for inclusion in this population was that the participant had to have received PCV20 and had at least 1 valid and determinate OPA titer 1 month after vaccination.

- Analysis of immunogenicity data based on the all-available immunogenicity population was to be performed only if there was 10% or more difference in sample size between the evaluable immunogenicity population and the all-available immunogenicity population.

6.3.10 Study Population and Disposition

A total of 873 subjects were vaccinated in study B7471006; 375 subjects in Cohort A (prior PPSV23 only), 373 in Cohort B, and 125 in Cohort C (prior PCV13 and PPSV23). Two subjects enrolled and randomized to Cohort B were not vaccinated. Of all randomized subjects, 98.4%, 99.2% and 100% in Cohorts A, B, and C, respectively, completed the study.

6.3.10.1 Populations Enrolled/Analyzed

Section 6.3.9 of this clinical review defines this study's populations enrolled and analyzed.

Among subjects randomized to receive PCV20 in Cohorts A and B and among subjects in Cohort C, a similar proportion were included in the evaluable and all-available immunogenicity populations across the study cohorts (Table 30). Approximately 3% or less of subjects were excluded from the evaluable immunogenicity population and ≤1.6% of subjects were excluded from the all-available population. The most common reasons for exclusion from these immunogenicity analysis populations were not having a blood sample collected within the pre-specified time frame and not having a valid and determinate OPA titer after vaccination.

No immunogenicity analyses were performed using the all-available immunogenicity population, as there was <10% difference in sample sizes between the evaluable and all-available immunogenicity populations for each cohort.

Table 30. Evaluable and All-Available Immunogenicity Populations, Study B7471006

Study Cohorts[a]	Cohort A PCV20 n[b] (%)	Cohort B PCV20 n[b] (%)	Cohort C PCV20 n[b] (%)
Randomized[c]	253 (100.0)	248 (100.0)	125 (100.0)
Evaluable Immunogenicity Population	247 (97.6)	243 (98.0)	121 (96.8)
Subjects excluded from evaluable immunogenicity population[d]	6 (2.4)	5 (2.0)	4 (3.2)
Reason for exclusion			
Did not receive PCV20 as randomized	0 (0.0)	2 (0.8)	0 (0.0)
Did not have Visit 2 blood sample collection within 27 to 49 days after vaccination	5 (2.0)	5 (2.0)	1 (0.8)
Did not have valid and determinate OPA titer after vaccination	4 (1.6)	4 (1.6)	1 (0.8)
Had any other major protocol deviations[e]	1 (0.4)	1 (0.4)	2 (1.6)
All-Available Immunogenicity Population	249 (98.4)	244 (98.4)	124 (99.2)
Subjects excluded from all-available immunogenicity population[d]	4 (1.6)	4 (1.6)	1 (0.8)
Reason for exclusion			
Did not receive at least 1 dose of investigational product	0 (0.0)	2 (0.8)	0 (0.0)
Did not have valid and determinate OPA titer after any vaccination	4 (1.6)	4 (1.6)	1 (0.8)

Abbreviation: OPA = opsonophagocytic activity.
Note: There are no immunogenicity results for the control groups PCV13 (Cohort A) and PPSV23 (Cohort B). Cohort C was a single arm cohort.
[a] Cohort A: vaccination with PPSV23 ≥1 year and ≤5 years prior to enrollment, and no prior PCV13 vaccination
Cohort B: vaccination with PCV13 ≥6 months prior to enrollment, and no prior PPSV23 vaccination
Cohort C: vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to enrollment)
[b] n = Number of subjects with the specified characteristic.
[c] These values are the denominators for the percentage calculations.
[d] Subjects may have been excluded for more than 1 reason.
[e] One Cohort A subject who was vaccinated with PCV20 was later determined to have received PPSV23 >5 years prior to randomization. One Cohort B subject who was vaccinated with PCV20 was later determined to have received PPSV23 followed by PCV13 prior to randomization. Two Cohort C subjects who were vaccinated with PCV20 were later determined to have received PPSV23 <1 year prior to being enrolled in the study.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471006. Clinical Study Report, Table 5, p30.

6.3.10.1.1 Demographics

Study groups across cohorts were similar with respect to baseline demographics and smoking history (Table 31). Overall, approximately 44%-48% were males, 90%-94% were White, 3%-7% were Black, and 0.8%-3.3% were among one of the other racial groups (Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, Multiracial or not reported). In Cohort A, 35.5% of the participants were enrolled in Sweden. The mean or median number of years since the prior pneumococcal vaccination was not summarized in the clinical study report.

Table 31. Demographic Characteristics and Smoking History, Safety Population, Study B7471006

Study Group[a]	Cohort A PCV20 N[b]=253 n[c] (%)	Cohort A PCV13 N[b]=122 n[c] (%)	Cohort A Total N[b]=375 n[c] (%)	Cohort B PCV20 N[b]=246 n[c] (%)	Cohort B PPSV23 N[b]=127 n[c] (%)	Cohort B Total N[b]=373 n[c] (%)	Cohort C PCV20 N[b]=125 n[c] (%)
Sex							
Male	113 (44.7)	58 (47.5)	171 (45.6)	108 (43.9)	59 (46.5)	167 (44.8)	60 (48.0)
Female	140 (55.3)	64 (52.5)	204 (54.4)	138 (56.1)	68 (53.5)	206 (55.2)	65 (52.0)
Race							
White	236 (93.3)	110 (90.2)	346 (92.3)	226 (91.9)	118 (92.9)	344 (92.2)	117 (93.6)
Black or African American	15 (5.9)	8 (6.6)	23 (6.1)	14 (5.7)	6 (4.7)	20 (5.4)	4 (3.2)
Asian	1 (0.4)	2 (1.6)	3 (0.8)	0 (0.0)	2 (1.6)	2 (0.5)	0 (0.0)
American Indian or Alaska Native	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 1 (0.8)	0 (0.0)	1 (0.3)	1 (0.4)	1 (0.8)	2 (0.5)	0 (0.0)
Multiracial	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)	3 (2.4)
Not reported	0 (0.0)	1 (0.8)	1 (0.3)	3 (1.2)	0 (0.0)	3 (0.8)	1 (0.8)
Ethnicity							
Hispanic/Latino	4 (1.6)	3 (2.5)	7 (1.9)	6 (2.4)	1 (0.8)	7 (1.9)	2 (1.6)
Non-Hispanic/non-Latino	247 (97.6)	117 (95.9)	364 (97.1)	231 (93.9)	122 (96.1)	353 (94.6)	113 (90.4)
Not reported	2 (0.8)	2 (1.6)	4 (1.1)	9 (3.7)	4 (3.1)	13 (3.5)	10 (8.0)
Country							
U.S.	163 (64.4)	79 (64.8)	242 (64.5)	246 (100.0)	127 (100.0)	373 (100.0)	125 (100.0)
Sweden	90 (35.6)	43 (35.2)	133 (35.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age group							
65-69 years	143 (56.5)	63 (51.6)	206 (54.9)	136 (55.3)	72 (56.7)	208 (55.8)	70 (56.0)
70-79 years	105 (41.5)	57 (46.7)	162 (43.2)	86 (35.0)	43 (33.9)	129 (34.6)	47 (37.6)
≥80 years	5 (2.0)	2 (1.6)	7 (1.9)	24 (9.8)	12 (9.4)	36 (9.7)	8 (6.4)
Age at vaccination (Years)							
Mean (SD)	69.6 (3.88)	70.2 (4.09)	69.8 (3.96)	70.7 (5.71)	70.6 (5.73)	70.7 (5.71)	70.8 (4.26)
Median (min, max)	69.0 (65, 84	69.0 (65, 80)	69.0 (65, 84)	68.0 (65, 92)	68.0 (65, 92)	68.0 (65, 81)	69.0 (65, 90)
Smoking history							
Current smoker	24 (9.5)	7 (5.7)	31 (8.3)	13 (5.3)	6 (4.7)	19 (5.1)	5 (4.0)
Mean (SD) # years smoking	46.2 (13.68)	39.6 (18.13)	44.7 (14.74)	37.5 (16.86)	47.5 (6.23)	40.6 (14.94)	50.9 (7.02)
Ex-smoker	94 (37.2)	43 (35.2)	137 (36.5)	95 (38.6)	36 (28.3)	131 (35.1)	43 (34.4)
Mean (SD) # years since quitting	24.7 (14.31)	26.0 (14.93)	25.1 (14.46)	27.8 (15.58)	30.8 (14.70)	28.6 (15.35)	33.4 (15.44)
Never smoked	135 (53.4)	72 (59.0)	207 (55.2)	138 (56.1)	85 (66.9)	223 (59.8)	77 (61.6)

[a] Cohort A: vaccination with PPSV23 ≥1 year and ≤5 years prior to enrollment, and no prior PCV13 vaccination; Cohort B: vaccination with PCV13 ≥6 months prior to enrollment, and no prior PPSV23 vaccination; Cohort C: vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to enrollment)
[b] N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[c] n = Number of subjects with the specified characteristic.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471006. Clinical Study Report, Table 6, p31-32.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 32 presents select baseline comorbidities noted in the medical history in the safety population. The proportion of subjects with any medical history was similar across study groups (overall 93%-100%). The proportion of subjects reporting a medical history in each System Organ Class was generally highest in Cohort C (prior PCV13 and PPSV23).

Table 32. Medical History by Study Cohorts[a], Safety Population, Study B7471006

Comorbidity	Cohort A PCV20 N[b]=253 n[c] (%)	Cohort A PCV13 N[b]=122 n[c] (%)	Cohort B PCV20 N[b]=246 n[c] (%)	Cohort B PPSV23 N[b]=127 n[c] (%)	Cohort C PCV20 N[b]=125 n[c] (%)
Any medical history by MedDRA SOC/PT	241 (95.3)	114 (93.4)	246 (100.0)	127 (100.0)	125 (100.0)
Blood and lymphatic system disorders	7 (2.8)	4 (3.3)	6 (2.4)	5 (3.9)	9 (7.2)
Cardiac disorders	56 (22.1)	24 (19.7)	40 (16.3)	27 (21.3)	32 (25.6)
Endocrine disorders	43 (17.0)	21 (17.2)	68 (27.6)	29 (22.8)	25 (20.0)
Gastrointestinal disorders	76 (30.0)	46 (37.7)	90 (36.6)	61 (48.0)	67 (53.6)
Hepatobiliary disorders	16 (6.3)	7 (5.7)	22 (8.9)	15 (11.8)	8 (6.4)
Immune system disorders	65 (25.7)	34 (27.9)	110 (44.7)	49 (38.6)	48 (38.4)
Drug hypersensitivity	40 (15.8)	16 (13.1)	59 (24.0)	35 (27.6)	33 (26.4)
Infections and infestations	37 (14.6)	22 (18.0)	51 (20.7)	30 (23.6)	19 (15.2)
Metabolism and nutrition disorders	146 (57.7)	70 (57.4)	169 (68.7)	72 (56.7)	96 (76.8)
Hypercholesterolaemia	49 (19.4)	18 (14.8)	59 (24.0)	27 (21.3)	33 (26.4)
Hyperlipidemia	58 (22.9)	27 (22.1)	79 (32.1)	34 (26.8)	41 (32.8)
Obesity	22 (8.7)	10 (8.2)	27 (11.0)	11 (8.7)	21 (16.8)
Type 2 diabetes mellitus	39 (15.4)	17 (13.9)	37 (15.0)	20 (15.7)	23 (18.4)
Nervous system disorders	61 (24.1)	26 (21.3)	66 (26.8)	25 (19.7)	34 (27.2)
Renal and urinary disorders	23 (9.1)	16 (13.1)	39 (15.9)	15 (11.8)	27 (21.6)
Respiratory, thoracic and mediastinal disorders	78 (30.8)	35 (28.7)	52 (21.1)	27 (21.3)	41 (32.8)
Asthma	24 (9.5)	10 (8.2)	15 (6.1)	8 (6.3)	10 (8.0)
Chronic obstructive pulmonary disease	23 (9.1)	9 (7.4)	8 (3.3)	6 (4.7)	7 (5.6)
Sleep apnoea syndrome	24 (9.5)	8 (6.6)	15 (6.1)	6 (4.7)	16 (12.8)
Vascular disorders	151 (59.7)	72 (59.0)	141 (57.3)	76 (59.8)	76 (60.8)
Hypertension	131 (51.8)	58 (47.5)	132 (53.7)	66 (52.0)	64 (51.2)

Note: MedDRA (v22.1) coding dictionary applied.
[a] Cohort A: vaccination with PPSV23 ≥1 year and ≤5 years prior to enrollment, and no prior PCV13 vaccination
Cohort B: vaccination with PCV13 ≥6 months prior to enrollment, and no prior PPSV23 vaccination
Cohort C: vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to enrollment)
[b] N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[c] n = Number of subjects with the specified characteristic.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471006. Clinical Study Report, Table 14.1, p65-95.

6.3.10.1.3 Subject Disposition

The disposition of all randomized subjects (as described in Section 6.3.10) are summarized in Table 33. Overall, 98%-100% of subjects completed the study.

Table 33. Disposition, All Randomized Subjects, Study B7471006

Disposition	Cohort A PCV20 n[a] (%)	Cohort A PCV13 n[a] (%)	Cohort A Total n[a] (%)	Cohort B PCV20 n[a] (%)	Cohort B PPSV23 n[a] (%)	Cohort B Total n[a] (%)	Cohort C PCV20 n[a] (%)
Randomized	253 (100.0)	122 (100.0)	375 (100.0)	248 (100.0)	127 (100.0)	375 (100.0)	125 (100.0)
Not Vaccinated	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.5)	0 (0.0)
Vaccinated	253 (100.0)	122 (100.0)	375 (100.0)	246 (99.2)	127 (100.0)	373 (99.5)	125 (100.0)
Completed 1month follow-up after vaccination	251 (99.2)	120 (98.4)	371 (98.9)	245 (98.8)	127 (100.0)	372 (99.2)	125 (100.0)
Completed study	250 (98.8)	119 (97.5)	369 (98.4)	245 (98.8)	126 (99.2)	371 (98.9)	125 (100.0)
Withdrawn from study	3 (1.2)	3 (2.5)	6 (1.6)	3 (1.2)	1 (0.8)	4 (1.1)	0 (0.0)
Reason for withdrawal							
Lost to follow-up	1 (0.4)	1 (0.8)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No longer meets eligibility criteria	0 (0.0)	1 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	1 (0.4)	1 (0.8)	2 (0.5)	2 (0.8)	0 (0.0)	2 (0.5)	0 (0.0)
Withdrawal by subject	1 (0.4)	0 (0.0)	1 (0.3)	1 (0.4)	1 (0.8)	2 (0.5)	0 (0.0)

Note: Cohort A: vaccination with PPSV23 ≥1 year and ≤5 years prior to enrollment, and no prior PCV13 vaccination
Note: Cohort B: vaccination with PCV13 ≥6 months prior to enrollment, and no prior PPSV23 vaccination
Note: Cohort C: vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to enrollment)
[a] n = Number of subjects with the specified characteristic.
[b] These values are the denominators for the percentage calculations.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471006. Clinical Study Report, Table 4, p27-28.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

Immune responses to all 20 vaccine serotypes were observed 1 month after PCV20 based on OPA GMTs in all 3 cohorts, regardless of prior pneumococcal vaccination (Table 34).

At baseline (prior to study vaccination), OPA GMTs for the PCV13 serotypes were generally highest in Cohort C (prior PCV13 and PPSV23), followed by Cohort B (prior PCV13 only) (Data not shown, CSR, Table 8). Baseline GMTs were lowest in Cohort A (prior PPSV23 only).

At baseline, OPA GMTs for the 7 additional serotypes were generally highest in participants with prior PCV13 and PPSV23, followed by participants with prior PPSV23 only (Data not shown, CSR Table 8). Baseline GMTs were lowest in participants with prior PCV13 only.

> ***Reviewer Comment:*** *The baseline OPA GMTs for the 7 new serotypes were generally highest among participants with prior PCV13 and PPSV23. Given that PCV13 does not contain these 7 new serotypes, participants with prior PCV13 and PPSV23 may have had higher baseline OPA GMTs compared to participants with prior PPSV23 alone due to timing of the prior PPSV23 dose. Participants with prior PCV13 and PPSV23 (who had to have their PPSV23 dose at least 1 year prior to vaccination) may have had a shorter interval between their PPSV23 dose and PCV20 study vaccination compared to participants with prior PPSV23 only (who had to have their PPSV23 dose 1 to 5 years prior to study enrollment).*

At 1 month after PCV20 vaccination, OPA GMTs for most of the PCV13 serotypes were generally higher in participants with prior PCV13 only or prior PCV13 and PPSV23 (ranging from 54 (serotype 3) to 4157 (serotype 22F) among participants with prior PCV13 only and ranging from 39 (serotype 3) to 2718 (serotype 22F) among participants with prior PCV13 and PPSV23) (Table 34). At 1-month post-PCV20, OPA GMTs for the PCV13 serotypes were lowest in participants with prior PPSV23 only, ranging from 31 (serotype 3) to 2026 (serotype 33F).

At 1 month after PCV20 vaccination, OPA GMTs for the 7 new serotypes were generally highest in participants with prior PCV13 only. The OPA GMTs for the 7 new serotypes were the lowest in participants with prior PPSV23 only. OPA GMTs in participants with prior PCV13 and PPSV23 fell in between the OPA GMTs achieved by the other two study cohorts (Table 34).

Table 34. Pneumococcal Opsonophagocytic Activity GMTs, Evaluable Immunogenicity Population, Study B7471006

Serotype	Cohort A[a] (prior PPSV23) PCV20 n[b]	Cohort A[a] (prior PPSV23) PCV20 GMT (95% CI)[c]	Cohort B[a] (prior PCV13) PCV20 n[b]	Cohort B[a] (prior PCV13) PCV20 GMT (95% CI)[c]	Cohort C[a] (prior PCV13 and PPSV23) PCV20 n[b]	Cohort C[s] (prior PCV13 and PPSV23) PCV20 GMT (95% CI)[c]
PCV13 Serotypes						
1	246	51 (42, 62)	243	115 (96, 138)	120	82 (61, 110)
3	243	31 (27, 36)	242	54 (47, 63)	119	39 (32, 48)
4	236	150 (118, 190)	241	335 (274, 410)	116	194 (143, 262)
5	244	63 (53, 75)	243	87 (73, 104)	120	84 (65, 108)
6A	242	749 (577, 972)	241	1081 (880, 1327)	121	1085 (797, 1478)
6B	243	727 (574, 922)	241	1159 (951, 1414)	121	1033 (755, 1415)
7F	240	378 (316, 452)	243	555 (467, 661)	120	346 (277, 432)
9V	241	550 (454, 667)	237	1085 (894, 1318)	117	723 (558, 938)
14	240	391 (315, 486)	242	665 (554, 798)	119	581 (434, 777)
18C	245	552 (445, 684)	240	846 (693, 1033)	120	621 (470, 821)
19A	242	239 (198, 288)	242	365 (303, 440)	120	341 (264, 440)
19F	244	159 (131, 192)	242	242 (199, 294)	118	218 (168, 282)
23F	245	152 (115, 199)	243	450 (358, 566)	120	293 (204, 421)
New Serotypes						
8	230	212 (172, 261)	226	603 (483, 753)	109	294 (220, 392)
10A	219	1012 (807, 1270)	210	2005 (1586, 2536)	110	1580 (1176, 2124)
11A	216	1473 (1192, 1820)	206	1908 (1542, 2362)	102	1567 (1141, 2151)
12F	224	1055 (822, 1353)	214	1763 (1372, 2267)	110	1401 (1002, 1960)
15B	225	647 (491, 853)	201	1480 (1093, 2003)	110	1067 (721, 1578)
22F	218	1773 (1355, 2320)	206	4157 (3244, 5326)	108	2718 (1978, 3733)
33F	216	2026 (1684, 2437)	208	3175 (2579, 3908)	103	2183 (1639, 2908)

Abbreviations: GMT = geometric mean titer; LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
[a] Cohort A: vaccination with PPSV23 ≥1 year and ≤5 years prior to enrollment, and no prior PCV13 vaccination
Cohort B: vaccination with PCV13 ≥6 months prior to enrollment, and no prior PPSV23 vaccination
Cohort C: vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to enrollment)
[b] n = Number of subjects with valid and determinate assay results for the given serotype at the specified time point.
[c] GMTs and 2-sided CIs calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on Student t distr bution).
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471006. Clinical Study Report, Table 8, p35-36.

6.3.11.2 Analyses of Secondary Endpoints

Proportion of Participants Achieving a ≥4-Fold Rise in Pneumococcal OPA

For most of the PCV13 serotypes, the proportions of participants who achieved a ≥4-fold rise in OPA titers from before to 1 month after PCV20 were generally similar in Cohort B (prior PCV13 only) and Cohort A (prior PPSV23 only). The proportions of participants who achieved a ≥4-fold rise in OPA titers from before to 1 month after PCV20 were lowest in Cohort C (prior PCV13 and PPSV23) (Table 35).

For the 7 additional serotypes, the proportions of participants with a ≥4-fold rise in OPA titers from before to 1 month after PCV20 were highest in Cohort B (prior PCV13 only); Cohort B participants were naïve to these vaccine serotypes prior to receiving PCV20 (Table 35). The proportions of participants with a ≥4-fold rise in OPA titers from before to 1 month after PCV20 were similar in Cohorts A (prior PPSV23 only) and C (prior PCV13 and PPSC23).

Table 35. Proportion of Subjects Achieving a ≥4-Fold Rise in Pneumococcal OPA Titers From Before Vaccination to 1 Month After Vaccination, Evaluable Immunogenicity Population, Study B7471006

	Cohort A[a] (prior PPSV23)	Cohort A[a] (prior PPSV23)	Cohort A[a] (prior PPSV23)	Cohort B[a] (prior PCV13)	Cohort B[a] (prior PCV13)	Cohort B[a] (prior PCV13)	Cohort C[a] (prior PCV13 and PPSV23)	Cohort C[a] (prior PCV13 and PPSV23)	Cohort C[a] (prior PCV13 and PPSV23)
Serotype	**PCV20 N[b]**	**PCV20 n[c]**	**PCV20 % (95% CI)[d]**	**PCV20 N[b]**	**PCV20 n[c]**	**PCV20 % (95% CI)[d]**	**PCV20 N[b]**	**PCV20 n[c]**	**PCV20 % (95% CI)[d]**
PCV13 Serotypes									
1	245	56	22.9 (17.8, 28.6)	243	98	40.3 (34.1, 46.8)	120	25	20.8 (14.0, 29.2)
3	243	72	29.6 (24.0, 35.8)	240	99	41.3 (35.0, 47.8)	119	22	18.5 (12.0, 26.6)
4	231	95	41.1 (34.7, 47.8)	235	97	41.3 (34.9, 47.9)	115	29	25.2 (17.6, 34.2)
5	241	62	25.7 (20.3, 31.7)	243	66	27.2 (21.7, 33.2)	120	19	15.8 (9.8, 23.6)
6A	239	147	61.5 (55.0, 67.7)	234	132	56.4 (49.8, 62.9)	118	53	44.9 (35.7, 54.3)
6B	238	127	53.4 (46.8, 59.8)	238	131	55.0 (48.5, 61.5)	119	42	35.3 (26.8, 44.6)
7F	233	61	26.2 (20.7, 32.3)	241	73	30.3 (24.6, 36.5)	119	17	14.3 (8.5, 21.9)
9V	226	64	28.3 (22.5, 34.7)	228	82	36.0 (29.7, 42.6)	114	23	20.2 (13.2, 28.7)
14	236	37	15.7 (11.3, 21.0)	237	59	24.9 (19.5, 30.9)	119	19	16.0 (9.9, 23.8)
18C	245	72	29.4 (23.8, 35.5)	240	92	38.3 (32.2, 44.8)	119	21	17.6 (11.3, 25.7)
19A	239	71	29.7 (24.0, 35.9)	239	70	29.3 (23.6, 35.5)	117	18	15.4 (9.4, 23.2)
19F	243	71	29.2 (23.6, 35.4)	241	79	32.8 (26.9, 39.1)	118	20	16.9 (10.7, 25.0)
23F	242	120	49.6 (43.1, 56.1)	242	142	58.7 (52.2, 64.9)	119	51	42.9 (33.8, 52.3)
New Serotypes									
8	223	89	39.9 (33.4, 46.7)	219	159	72.6 (66.2, 78.4)	101	31	30.7 (21.9, 40.7)
10A	198	90	45.5 (38.4, 52.7)	199	141	70.9 (64.0, 77.1)	109	48	44.0 (34.5, 53.9)
11A	184	56	30.4 (23.9, 37.6)	183	100	54.6 (47.1, 62.0)	91	32	35.2 (25.4, 45.9)
12F	208	107	51.4 (44.4, 58.4)	200	153	76.5 (70.0, 82.2)	103	42	40.8 (31.2, 50.9)
15B	211	79	37.4 (30.9, 44.3)	184	122	66.3 (59.0, 73.1)	99	38	38.4 (28.8, 48.7)
22F	207	118	57.0 (50.0, 63.8)	191	159	83.2 (77.2, 88.2)	104	57	54.8 (44.7, 64.6)
33F	203	38	18.7 (13.6, 24.8)	196	105	53.6 (46.3, 60.7)	99	19	19.2 (12.0, 28.3)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity. Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
[a] Cohort A: vaccination with PPSV23 ≥1 year and ≤5 years prior to enrollment, and no prior PCV13 vaccination; Cohort B: vaccination with PCV13 ≥6 months prior to enrollment, and no prior PPSV23 vaccination; Cohort C: vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to enrollment)
[b] N = number of subjects with valid and determinate assay results to the specified serotype from both before and 1 month after vaccination blood sample collections. These values are the denominators for the percentage calculations. [c] n = Number of subjects with a ≥4-fold rise in titers from before vaccination to 1 month after vaccination for the specified serotype.
[d] Exact 2-sided CI based on the Clopper and Pearson method. Source: STN 1259731/0.1, module 5.3.5.1, Study B7471006. Clinical Study Report, Table 10, p40-41.

6.3.11.3 Subpopulation Analyses

OPA GMTs before and 1 month after PCV20 by sex were presented in the study CSR (Data not shown, CSR Table 14.4). Serotype-specific OPA GMTs measured 1 month after PCV20 were generally higher among females compared to males in the evaluable immunogenicity populations for each study cohort.

6.3.11.4 Dropouts and/or Discontinuations

See Section 6.3.10.1.3 for information on subject disposition, including withdrawals. Missing values were not imputed for subjects who had missing blood draws.

6.3.11.5 Exploratory and Post Hoc Analyses

In exploratory analyses, the proportion of subjects achieving a ≥4-fold rise in serotype 15C OPA titers from before to 1 month after vaccination was 9.0% (95% CI 5.6, 13.5) in Cohort A, 19.5% (95% CI 14.4, 25.5) in Cohort B, and 11.7% (95% CI 6.2, 19.5) in Cohort C.

However, due to the substantial proportion of subjects with OPA titers < LLOQ, exploratory analyses of serotype 15C OPA responses in this study are not considered interpretable. The proportion of subjects achieving OPA titers ≥ LLOQ was 21.8% (95% CI 17, 28) in Cohort A (N=223); 31.3% (95% CI 25, 38) in Cohort B (N=210); and 28.6% (95% CI 20, 38) in Cohort C (N=103). In addition, the OPA GMTs in each study cohort were consistently lower than the serotype 15C LLOQ (note: the serotype 15C LLOQ is (b) (4). The OPA GMTs achieved by subjects in each of the cohorts were as follows: 58.9 (95% CI 52, 66) in Cohort A (N=234); 69.5 (95% CI 60, 80) in Cohort B (N=214); and 67.0 (95% CI 55, 81) in Cohort C (N=105).

6.3.12 Safety Analyses

6.3.12.1 Methods

Safety analyses were descriptive. Please see Section 6.3.7 for details regarding safety surveillance/monitoring, Section 6.3.1 for a listing of safety endpoints, and Section 6.3.9 for details regarding safety analysis populations.

6.3.12.2 Overview of Adverse Events

Solicited Local Injection Site Adverse Reactions

The proportions of participants who reported solicited local reactions within 10 days after PCV20 were generally similar across cohorts regardless of prior pneumococcal vaccination and also were generally similar to the corresponding control groups within Cohorts A (prior PPSV23 only) and B (prior PCV13 only) (Table 36). Across the 3 cohorts and after both PCV20 and control vaccines, most of these local reactions were of mild or moderate severity, and the most frequently reported local reaction was pain at the injection site (ranging from 43.0% after PCV13 in Cohort A to 61.2% after PCV20 in Cohort B).

Within each study cohort, the day of onset and duration of solicited local adverse reactions were similar (Data not shown, CSR Tables 14.10 and 14.11). Local reactions among PCV20 recipients had a mean onset of Day 1.4 (SD 0.6) or Day 3.1 (SD 2.2) (Day 1 was the day of vaccination) and generally resolved with mean durations of 2.0 (SD 1.3) to 3.9 days (SD 3.8) days across all vaccine groups and cohorts.

Table 36. Local Reactions, by Maximum Severity, Within 10 Days After Vaccination, Safety Population, Study B7471006

Local Reaction	Cohort A[a] PCV20 N[b]=253 n[c] (%)	Cohort A[a] PCV13 N[b]=121 n[c] (%)	Cohort B[a] PCV20 N[b]=245 n[c] (%)	Cohort B[a] PPSV23 N[b]=126 n[c] (%)	Cohort C[a] PCV20 N[b]=125 n[c] (%)
Any local reaction[d]	134 (53.0)	53 (43.8)	157 (64.1)	73 (57.9)	68 (54.4)
Pain at Injection Site[e]					
Any	127 (50.2)	52 (43.0)	150 (61.2)	71 (56.3)	66 (52.8)
Mild	116 (45.8)	47 (38.8)	134 (54.7)	51 (40.5)	59 (47.2)
Moderate	11 (4.3)	4 (3.3)	15 (6.1)	18 (14.3)	7 (5.6)
Severe	0 (0.0)	1 (0.8)	1 (0.4)	2 (1.6)	0 (0.0)
Swelling[f]					
Any (>2.0 cm)	25 (9.9)	8 (6.6)	23 (9.4)	18 (14.3)	5 (4.0)
Mild	13 (5.1)	8 (6.6)	14 (5.7)	8 (6.3)	2 (1.6)
Moderate	9 (3.6)	0 (0.0)	9 (3.7)	9 (7.1)	3 (2.4)
Severe	3 (1.2)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Redness[f]					
Any (> 2.0 cm)	20 (7.9)	3 (2.5)	21 (8.6)	16 (12.7)	6 (4.8)
Mild	9 (3.6)	2 (1.7)	7 (2.9)	6 (4.8)	2 (1.6)
Moderate	8 (3.2)	1 (0.8)	13 (5.3)	9 (7.1)	4 (3.2)
Severe	3 (1.2)	0 (0.0)	1 (0.4)	1 (0.8)	0 (0.0)

[a] Cohort A: vaccination with PPSV23 ≥1 year and ≤5 years prior to enrollment, and no prior PCV13 vaccination; Cohort B: vaccination with PCV13 ≥6 months prior to enrollment, and no prior PPSV23 vaccination; Cohort C: vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to enrollment)
[b] N = number of subjects with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
[c] n = Number of subjects with the specified characteristic.
[d] Any local reaction = any pain at injection site, any swelling >2.0 cm, or any redness >2.0 cm during Day 1 to Day 10 after vaccination.
[e] Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity. Any = mild, moderate or severe.
[f] Mild is >2.0 to 5.0 cm, moderate is >5.0 to 10.0 cm, severe is >10.0 cm. Any = mild, moderate or severe.
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471006. Clinical Study Report, Table 13, p46-47.

Solicited Systemic Adverse Reactions

The proportions of participants who reported prompted systemic events within 7 days after PCV20 were generally similar across cohorts regardless of prior pneumococcal vaccination and also were generally similar to the corresponding control groups within Cohorts A (prior PPSV23 only) and B (prior PCV13 only) (Table 37). The rate of fever was low; fever was reported after PCV20 in 2 participants (0.8%) with prior PPSV23 only, and after PPSV23 in 2 participants (1.6%) with prior PCV13 only.

Across the 3 cohorts and after both PCV20 and control vaccines, most systemic events were mild or moderate in severity, and the most frequently reported systemic event was muscle pain (ranging from 31.4% after PCV13 in Cohort A to 46.0% after PPSV23 in Cohort B).

Within each study cohort, the day of onset and duration of solicited systemic adverse reactions were similar (Data not shown, CSR Tables 14.15 and 14.16). Systemic adverse reactions had a mean onset day between Day 1.7 (SD 1.1) to Day 3.5 (SD 2.1) (Day 1 was the day of vaccination) and generally resolved with mean durations between 2.0 days (SD 1.7) to 4.2 (SD 5.4) days for all vaccine groups and cohorts.

Table 37. Systemic Events, by Maximum Severity, Within 7 Days After Vaccination, Safety Population, Study B7471006

Local Reaction	Cohort A[a] PCV20 N[b]=253 n[c] (%)	Cohort A[a] PCV13 N[b]=121 n[c] (%)	Cohort B[a] PCV20 N[b]=245 n[c] (%)	Cohort B[a] PPSV23 N[b]=126 n[c] (%)	Cohort C[a] PCV20 N[b]=125 n[c] (%)
Any Systemic Adverse Reaction[d]	131 (51.8)	53 (43.8)	123 (50.2)	75 (59.5)	66 (52.8)
Muscle pain[e]					
Any	81 (32.0)	38 (31.4)	83 (33.9)	58 (46.0)	47 (37.6)
Mild	66 (26.1)	29 (24.0)	62 (25.3)	40 (31.7)	35 (28.0)
Moderate	14 (5.5)	6 (5.0)	21 (8.6)	15 (11.9)	11 (8.8)
Severe	1 (0.4)	3 (2.5)	0 (0.0)	3 (2.4)	1 (0.8)
Fatigue[e]					
Any	73 (28.9)	27 (22.3)	76 (31.0)	42 (33.3)	41 (32.8)
Mild	45 (17.8)	12 (9.9)	48 (19.6)	25 (19.8)	24 (19.2)
Moderate	28 (11.1)	12 (9.9)	25 (10.2)	17 (13.5)	15 (12.0)
Severe	0 (0.0)	3 (2.5)	3 (1.2)	0 (0.0)	2 (1.6)
Headache[e]					
Any	45 (17.8)	22 (18.2)	33 (13.5)	27 (21.4)	24 (19.2)
Mild	32 (12.6)	15 (12.4)	24 (9.8)	26 (20.6)	16 (12.8)
Moderate	12 (4.7)	7 (5.8)	9 (3.7)	1 (0.8)	7 (5.6)
Severe	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Joint pain[e]					
Any	17 (6.7)	13 (10.7)	29 (11.8)	20 (15.9)	21 (16.8)
Mild	12 (4.7)	6 (5.0)	19 (7.8)	13 (10.3)	16 (12.8)
Moderate	5 (2.0)	6 (5.0)	10 (4.1)	7 (5.6)	5 (4.0)
Severe	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Fever					
≥38.0°C	2 (0.8)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)
≥38.0°C to 38.4°C	2 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
>38.4°C to 38.9°C	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
>38.9°C to 40.0°C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>40.0°C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Use of antipyretic or pain medication[f]	40 (15.8)	18 (14.9)	42 (17.1)	25 (19.8)	22 (17.6)

[a] Cohort A: vaccination with PPSV23 ≥1 year and ≤5 years prior to enrollment, and no prior PCV13 vaccination; Cohort B: vaccination with PCV13 ≥6 months prior to enrollment, and no prior PPSV23 vaccination; Cohort C: vaccination with PCV13 followed by PPSV23 (PPSV23 vaccination ≥1 year prior to enrollment)
[b] N = number of subjects with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
[c] n = Number of subjects with the specified characteristic.
[d] Any systemic adverse reaction = any fever ≥38.0°C, any fatigue, any headache, any muscle pain, or any joint pain during Day 1 to Day 7 after vaccination.
[e] Mild = does not interfere with activity, moderate = some interference with activity, severe = prevents daily activity. Any = mild, moderate or severe.
[f] Severity was not collected for use of antipyretic or pain medication. The numbers in the table reflect yes responses (i.e., number of events reported).
Source: STN 1259731/0.1, module 5.3.5.1, Study B7471006. Clinical Study Report, Table 14, p49-51.

Unsolicited Adverse Events (AEs) Reported Through 30-Days Post-Vaccination

In the PCV20 groups, the proportions of subjects reporting AEs were low and generally similar across the 3 cohorts (7.5% in Cohort A (prior PPSV23 only), 4.9% in Cohort B (prior PCV13 only), and 10.4%, in Cohort C (prior PCV13 and PPSV23)) and were similar to the proportions after PCV13 (9.0%) and after PPSV23 (11.0%) (Data not shown, CSR Table 15).The most frequently reported AEs were in the SOC *Infections and infestations* (1.2%-3.2% across study groups).

Newly Diagnosed Chronic Medical Conditions

The proportions of participants who reported any NDCMC within 6 months after vaccination were low (≤4.0%) in all vaccine groups and generally similar with no clear or consistent differences between groups (Data not shown, Supplemental Table 14.29). There were no NDCMCs (Data not shown, CSR Appendix 16.2.7.10) considered related to the study vaccine in the study.

Immediate Adverse Reactions

Across all study groups, immediate AEs after vaccination were reported by ≤0.8% of subjects (Data not shown, CSR Supplemental Table 14.22). Dizziness and paresthesia were reported 30 minutes after vaccination by one participant in Cohort A (prior PPSV23 only) who received PCV20. The investigator attributed these symptoms to dehydration, anxiety and hypotension and were not considered related to the vaccine (STN 125731/0.22). Dizziness was reported as an immediate AE by one participant in Cohort B (prior PCV13 only) who received PPSV23 (Data not shown, Supplemental Table 14.22); this immediate AE was considered related to PPSV23 by the investigator (CSR Appendix 16.2.7.7).

Other Significant Adverse Events

No participants reported other significant adverse events during the study.

Solicited Adverse Reactions by Subgroups

Subgroup analyses were performed by sex for the proportions of participants reporting prompted local reactions and systemic events by maximum severity as well as for unsolicited AEs within 1 month post-vaccination. However, the number of participants by sex reporting AEs within 1 month after vaccination were too low to allow meaningful comparisons; therefore, this review focuses on subgroup analyses of solicited adverse reactions by sex. Because ≥90.2% of subjects were White and ≥90.4% of subjects were Non-Hispanic/non-Latino, subgroup analyses by race and by ethnicity were not provided.

Subgroup Analyses by Sex

- Local Reactions: The proportions of participants who reported injection site erythema and swelling within 10 days after vaccination were generally similar for males and females with no consistent trends (Data not shown, CSR Supplemental Tables 14.12, 14.13, and 14.14, for Cohorts A (prior PPSV23 only), B (prior PCV13 only), and C (prior PCV13 and PPSV23), respectively). There appeared to be a trend across all study cohorts of a higher proportion of females reporting any injection site pain and mild injection site pain compared to males; the difference was greatest in Cohort C, with 61.5% and 56.9% of females and 43.3% and 36.7% of males reporting any and mild injection site pain, respectively.

- Systemic reactions: In general, a higher proportion of females reported systemic reactions than males. The greatest differences were among Cohort C (prior PCV13 and PPSV23) followed by Cohort A (prior PPSV23 only) subjects (Data not shown, CSR Supplemental Tables 14.17, 14.18, and 14.19, for Cohorts A, B, and C, respectively).

6.3.12.3 Deaths

No deaths were reported during the study.

6.3.12.4 Nonfatal Serious Adverse Events

A total of 14 SAEs were reported in this study following vaccination through the 6-month safety follow-up. The proportions of participants who reported any SAEs within 6 months after vaccination were low (≤2.4%) in all vaccine groups (Data not shown, CSR Table 17). Less than 1% of participants reported any SAE within 1 month after vaccination in each vaccine group (Data not shown, CSR Supplemental Table 14.27). None of the SAEs reported were considered by the investigator to be related to study vaccine (Data not shown, CSR Appendix 16.2.7.9); therefore, no narratives were provided for SAEs in this study.

6.3.12.7 Dropouts and/or Discontinuations

No participants were withdrawn from the study for safety-related reasons. Therefore, there were no narratives for safety-related withdrawals.

6.3.13 Study Summary and Conclusions

Study B7471006 was a descriptive safety and immunogenicity study of PCV20 in adults ≥65 years of age previously vaccinated with PPSV23, PCV13, or PCV13 followed by PPSV23. At 1 month after PCV20 vaccination, OPA GMTs for most of the PCV13 serotypes were generally higher in participants with prior PCV13 only or prior PCV13 and PPSV23 (Table 34). At 1 month post-PCV20, OPA GMTs for the PCV13 serotypes were lowest in participants with prior PPSV23 only. At 1 month after PCV20 vaccination, OPA GMTs for the 7 new serotypes were generally highest in participants with prior PCV13 only. The OPA GMTs for the 7 new serotypes were the lowest in participants with prior PPSV23 only. OPA GMTs in participants with prior PCV13 and PPSV23 fell in between the OPA GMTs achieved by the other two study cohorts. The safety and tolerability profile of PCV20 was generally similar in participants with different prior pneumococcal vaccine history and was generally similar to PCV13 and PPSV23 control groups.

In the descriptive immunogenicity analyses, OPA GMTs in participants who received PPSV23 1 to 5 years prior to Prevnar 20 were diminished compared to OPA GMTs in participants who received Prevnar 13 at least 6 months previously and compared to OPA GMTs in participants who received Prevnar 13 followed by PPSV23, with the last PPSV23 dose given at least 1 year prior to Prevnar 20. These immunogenicity results from this study are reflected in the drug interactions section of the Prevnar 20 prescribing information.

6.4 Study B7471002

Study B7471002 was a descriptive Phase 2, multicenter, randomized (1:1), active controlled, double-blind trial to describe the safety and immunogenicity (serotype-specific OPA antibody titers) of PCV20 in approximately 400 adults 60-64 years of age in the U.S. with no prior pneumococcal vaccination history planned for enrollment. The treatment group received a single dose of PCV20 followed 1 month later by saline (placebo); the control group received a single dose of PCV13 followed 1 month later by a dose of PPSV23. PCV13 served as a control for safety and immunogenicity of the 13 original vaccine serotypes. PPSV23 served as a control for immunogenicity of the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F). No formal statistical hypotheses were planned. Safety monitoring were as described for study B7471007. MedDRA version 21.1 coding dictionary was applied in study B7471002.

Summary of Study Results

Immunogenicity

Of the 222 subjects enrolled and randomized to the treatment group, 221 received PCV20 on study day 1 and 213 received placebo on study days 28-35. Of the 222 subjects enrolled and randomized to the control group, 222 received PCV13 on study day 1 and 214 received PPSV23 on study days 28-35. For the 13-original vaccine-type serotypes, OPA GMTs were generally similar to or lower following PCV20 compared to PCV13. Based on data submitted to CBER on July 12, 2018, in support of Breakthrough Therapy Designation, the lower limit of the 95% CI for the OPA GMT ratios (PCV20/PCV13) was >0.5 for 10 serotypes. Based on CBER review of the preliminary data submitted to support Breakthrough Therapy Designation (received July 12, 2018), the lower limit of the 95% CI for the OPA GMT ratio was 0.47, 0.48, and 0.43 for serotypes 1, 5 and 19F, respectively. For the 7 new serotypes, OPA GMTs were generally higher following PCV20 compared to PPSV23, except for serotype 8.

Safety

No deaths, SAEs or newly diagnosed chronic medical conditions considered related to study vaccination were reported. Fourteen non-related SAEs were reported overall (5 in the PCV20/saline group and 9 in the PCV13/PPSV23 group). Within 1 month after vaccination 1, SAEs were reported by 0 (0%) and 1 (0.5%) of PCV20 and PCV13 recipients. Within 1 month after vaccination 2, 0 (0.0) and 4 (1.9%) of saline and PPSV23 recipients reported SAEs. From 1 month after vaccination 2 through 6 months post-vaccination 1, SAEs were reported by 5 (2.3%) and 4 (1.9%) of PCV20/saline and PCV13/PPSV23 recipients. One subject randomized to the PCV13/PPSV23 group reported a SAE of pneumococcal meningitis, with sequelae of hearing loss in the right ear. Serotyping identified the pneumococcal isolate as 7C, a non-vaccine serotype. The remaining non-related SAEs reported included neoplasms (4), transient ischemic attack (2), lacunar infarction, cerebrovascular accident, nephrolithiasis, respiratory distress, cardiomyopathy, and osteoarthritis. The proportion of subjects reporting any prompted local reaction within 10 days after vaccination was generally higher in the PCV20 group (60.9%) compared to PCV13 group (56.8%). Pain at the injection site was the most frequently reported local reaction in both study groups. In the PCV20 group, 57.7% reported injection site pain, 13.2% reported injection site swelling and 11.4% reported injection site redness. Severe injection site reactions were uncommon and reported by 1 subject following PCV20 (redness) and 1 subject following PCV13 (pain). Rates of prompted systemic reactions reported within 7 days after vaccination appeared to be similar between the two study groups, with the exception of higher rates of muscle pain reported in the PCV20 group (43.2%) compared to the PCV13 group (36.5%). A similar proportion of PCV20 and PCV13 recipients reported unsolicited AEs at 1 month post-Vaccination 1 (12-13%). Upper respiratory tract infection was the most frequently reported MedDRA Preferred Term after both PCV20 (3.2%) and PCV13 (2.3%).

Conclusions

The results from study B7471002 provided safety and immunogenicity data supporting Phase 3 clinical development of PCV20. The data from this study also supported Wyeth's request at the time for Breakthrough Therapy Designation.

6.5 Study B7471005

B7471005 was a randomized (1:1:1), controlled, double-blind, 3-arm multicenter study that evaluated the safety and immunogenicity of PCV20 in adults. A total of 104 healthy pneumococcal vaccine naïve Japanese adults 18-49 years of age residing in the U.S. were enrolled and randomized equally to receive PCV20, investigational complementary 7-valent

pneumococcal conjugate vaccine (c7vPnC) or PCV13 vaccine. Eligible subjects were Japanese adults born in Japan, whose parents and 4 grandparents were born in Japan (family tree by history), and who had not lived outside of Japan for >5 years total (confirmed by passport or interview). This trial provided the data to help support clinical development of PCV20 in Japan. MedDRA version 21.1 coding dictionary was applied in study B7471005.

Study Results

Immunogenicity

Before vaccination, OPA GMTs for all 20 serotypes were similar among the 3 vaccine groups. At 1 month after vaccination, increases in OPA GMTs were observed for all 20 serotypes in the PCV20 group. Most subjects in the PCV20 group achieved a ≥4-fold rise in OPA titers for all 20 serotypes from before to 1 month after vaccination, ranging from 54.8% of subjects (serotype 7F) to 97.0% of subjects (serotype 23F).

Safety

There were no deaths, SAEs or newly diagnosed chronic medical conditions reported during this study. The proportions of subjects reporting solicited local reactions within 14 days after vaccination were generally similar across the three study groups. Overall, 77%-79% of subjects reported any local reaction (77%-79% reported pain, 6% reported swelling, and 0%[14]-6% reported redness). The proportions of subjects reporting solicited systemic events within 14 days after vaccination were generally higher following PCV20 compared to the study controls and lowest among c7vPnC recipients. The one exception was joint pain, which was reported by a similar proportion of subjects (11% of PCV20 recipients, 12% of c7vPnC recipients, and 9% of PCV13 recipients). Fever was reported by 1 subject (PCV20 recipient); the temperature was >28.4°C and ≤38.9°C. Overall, at least 1 systemic adverse reaction was reported by 77%, 64.7% and 41.2% of PCV20, PCV13, and c7VpnC recipients respectively.

Unsolicited AEs were reported by 6% of subjects in the PCV20 and c7vPnC groups and 9% of subjects in the PCV13 group within 1 month after vaccination. Related unsolicited AEs included injection site erythema (PCV20), injection site swelling (PCV20), fatigue (c7vPnC), vomiting (c7vPnC) and headache (c7vPnC).

Conclusions

The results of this study supported continued development of PCV20 for use in adults.

6.6 Study B7471001

B7471001 was a first-in-human, randomized (1:1), active-controlled, observer-blinded[15] trial that evaluated the safety and immunogenicity of PCV20 in a total of 66 healthy pneumococcal vaccine naïve adults 18-49 years of age. The trial was conducted at the Pfizer Clinical Research Unit (PCRU) in New Haven, Connecticut. Subjects meeting eligibility criteria were admitted to the PCRU and randomized (1:1) to receive PCV20 or a U.S.-licensed tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Tdap manufactured by Sanofi Pasteur (Adacel)) as the active control.

[14] No 13vPnC recipients reported injection site redness within 14 days after vaccination.
[15] The assigned treatment was given by an unblinded dispenser and administrator (a member of the study site staff or clinic pharmacy) who was not involved in subject assessments. All other study personnel and the subject were blinded.

> ***Reviewer Comment:*** *This first-in-human trial included cardiac monitoring and risk mitigation proposed by CBER as a result of unexpected cardiac findings (diffuse, patchy areas of inflammation and/or irreversible necrosis) identified on histopathology in a small number of otherwise healthy-appearing rabbits in the initial repeat-dose toxicity study (<5%-10%). Study B7471007 was designed to monitor subjects for possible cardiac abnormalities following vaccination with PCV20 in order to investigate the clinical relevance of the preclinical cardiac toxicity findings.*

All subjects had a baseline 12-lead triplicate electrocardiogram (ECG), echocardiogram and cardiac troponin I (cTnI) performed at a screening visit (the echocardiogram could have been done on Day 0 as well). Subjects meeting eligibility criteria were then admitted to the PCRU on day 0 for a 7-day hospital stay (through Day 6). The 12-lead triplicate ECG and cTnI were repeated to confirm eligibility on study Day 0. cTnI testing was repeated on Days 2, 3, and 6 (1, 2 and 5 days after vaccination). An elevated cTnI concentration was defined as greater than the upper limit of normal of the lab reference range (≥0.3 ng/mL). Safety labs (complete blood count, liver function tests, creatinine and urinalysis) were performed on Day 0 and Day 6.

Safety monitoring were as described for study B7471007. The duration of subject participation was approximately 8 months, from screening through a 6-month telephone safety follow-up visit. Safety oversight was provided by an external Data Monitoring Committee (DMC). The classification of adverse events was based on MedDRA version 20.0 coding dictionary in this study.

Select Eligibility Criteria

Eligible subjects had to have an echocardiogram and 12-lead triplicate ECG without clinically significant findings and normal cTnI concentration at baseline. In addition to standard Phase 1 study exclusion criteria, subjects were not eligible if they had baseline laboratory test results outside of the normal reference range considered clinically significant, smoked >5 cigarettes per day, had a history of regular alcohol consumption in the past 6 months, high blood pressure, a history of or suspected cardiac disease (congenital or valvular disease, congestive heart failure, myocardial ischemia or infarction, myocarditis, pericarditis, cardiomyopathy, arrhythmia or other benign sinus arrhythmia, etc.) or elevated cTnI concentration at baseline or family history of sudden cardiac death or arrhythmia. Subjects were also not eligible if they had any history prior pneumococcal vaccination, any history of culture-proven IPD, any history of severe adverse reaction associated with a vaccine and/or a severe allergic reaction to any component of the investigational product or any Tdap-containing vaccine, or any known or suspected immunodeficiency.

Study Results

Subject Disposition

A total of 66 subjects were vaccinated; 33 (50%) received PCV20 and 33 (50%) received Tdap. All subjects participated through the 2-week follow up phone call. A total of 63 subjects (95.5%) completed the study through 6-months post-vaccination. Three PCV20 recipients were withdrawn after the 2-week follow-up. One subject was lost to follow up prior to the 1-month post-vaccination visit. Another subject was lost to follow up prior to the 6-month follow-up telephone call. A third subject was withdrawn after the 1-month follow-up due to an unrelated death due to a motor vehicle accident.

Demographics

Overall, 42.4% of subjects were male, 42.4% were White, 53% were Black, 3% were American Indian and 2% were other. By ethnicity, 24% of subjects were Hispanic (the remaining were not Hispanic). Subject ages ranged from 18 to 48 years, with a mean of 32 years. There were fewer males (30% vs. 55%), White subjects (33% vs. 52%), and Latino subjects (15% vs. 33%) randomized to the PCV20 group relative to the Tdap group.

Immunogenicity

The immunogenicity results from this Phase 1 descriptive study demonstrated that PCV20 is immunogenic in healthy adults 18-49 years of age. Pre-vaccination titers were generally low, although baseline titers to serotypes 10A, 11A, 22F, and 33F were generally higher. A numerical increase in OPA GMTs from before to 1 month after vaccination was observed for each of the 20 vaccine serotypes. The OPA GMTs were essentially unchanged after vaccination in the Tdap recipients.

Safety Laboratory Results

The cTnI testing results for all subjects at all time points (days 1 (day of vaccination), 2, 3, and 6) were below the upper limit of normal of the test (<0.3 ng/mL). One subject who had additional cardiac troponin T tested by another lab as part of a precautionary workup also had non-elevated results. There were no other clinically significant laboratory abnormalities or changes in any study subjects.

There were no clinically significant ECG results and no clinically significant ECG findings in subjects who had ECGs conducted after vaccination for three events of interest.

Solicited Local and Systemic Adverse Reactions

The most common solicited local reaction within 14 days after vaccination was pain at the injection site (69.7% and 63.6% in the PCV20 and Tdap recipients respectively) followed by limitation of arm movement (36.4% and 18.2% in the PCV20 and Tdap recipient respectively). Grade 3 pain and limitation of arm movement were reported by 1 subject (the same subject reported both) on day 2 after PCV20. No other grade 3 reactions were reported. Redness and swelling were reported by 1 (3.0%) subject each in the PCV20 group and by no subjects in the Tdap group. Injection site redness was reported on Day 6 and Day 8 and resolved 2 days after onset. The median duration of any injection site reaction was 2 days.

The most common solicited systemic event was new muscle pain (45.5% and 42.4% in the PCV20 and Tdap recipients, respectively), followed by fatigue and headache (39.4% and 30.3% in the PCV20 and Tdap groups, respectively). Most systemic events were mild or moderate in severity. The median duration ranged from 1 to 5 days in both groups. Approximately 21% and 18% of subjects used medication to treat pain/fever in the PCV20 and Tdap groups, respectively.

Unsolicited Adverse Events

Overall, 45.5% and 33.3% of subjects reported any AE in the PCV20 and Tdap groups respectively. The most frequently reported AEs were in the SOC *Gastrointestinal disorders* (15.2% vs. 9.1% among PCV20 and Tdap recipients, respectively). No AEs were categorized as cardiac events. Related AEs reported by PCV20 recipients included decreased appetite and limb discomfort those reported by Tdap recipients included limb discomfort, photophobia, nausea, and dizziness.

Serious Adverse Events, Withdrawals and New Onset Chronic Medical Conditions

There were no related SAEs, safety-related withdrawals or new onset chronic medical conditions reported in this study. Four subjects (3 PCV20 recipients and 1 Tdap recipient) reported non-related SAEs in this study. One subject in the Tdap group was hospitalized due to joint dislocation, ligament rupture, muscle rupture after a motor vehicle accident 20 days after vaccination. One subject, in the PCV20 group reported loss of consciousness secondary to carbon monoxide exposure and was hospitalized; a second PCV20 recipient reported back pain as an SAE 83 days after vaccination; a third subject in the PCV20 group was killed in a motor vehicle accident 75 days after vaccination. None of these events were considered related to vaccination.

Adverse Events of Interest

Three subjects experienced events of interest as described below.

1. A 20-year old Black female who met study eligibility criteria reported chest pain 61 days after vaccination with onset 3 days earlier. The subject described sharp, intermittent (5 times/day), left midsternal, chest pain associated with respiration, lasting approximately 5 minutes before resolving. She denied chest pain radiating into her arm or swelling in her arms and legs, shortness of breath, syncope, palpitations, nausea, or sweating. A physical examination was performed approximately one week later and showed mild tenderness to palpation in the intercostal musculature in the upper left chest, which improved with self-massage of the area. An ECG performed at the visit was normal. Costochondritis was suspected and follow-up over 3 weeks confirmed no change in the event. Contact with the subject at approximately 3 months later revealed the event had resolved ~3 months after onset. The subject contacted the site 175 days after vaccination to report that she was told she had a heart murmur during a routine physical examination. Two and half months later, she followed up to report that an echocardiogram had been performed, which was found to be normal. The subject did not comply with a request to provide the medical records and was considered lost to follow-up at approximately 9 months post-vaccination. The principal investigator felt that there was an anxiety component to the event and that the event was not related to study vaccination or procedures.
2. One 40-year-old American Indian/Alaskan native female subject with a history of gastroesophageal reflux disease and anxiety who met study eligibility criteria reported epigastric pain/discomfort in the early morning on the day after vaccination. An ECG, a cardiac troponin T (cTnT) level, and serial cTnI levels were obtained (3 times over the 12 hours after onset of symptoms). The subject was also placed on telemetry monitoring overnight. The cTnT result was not elevated (<0.01 ng/mL) at the time of the acute episode nor were any of the serial cTnI levels (<0.3 ng/mL) collected through the following morning. ECGs performed the evening of symptom onset were normal and the overnight telemetry showed no concerning changes. On day 2 after vaccination, the subject was still symptomatic and was assessed as having mild epigastric pain/discomfort consistent with gastrointestinal esophageal reflux disease (GERD) and with an element of anxiety. The symptoms resolved later that same day. The investigator discussed the event in detail with the consulting cardiologist for the study, and based on the brevity of the symptoms, normal cardiac troponin levels, and normal ECGs and telemetry monitoring, no further evaluation was warranted. The investigator considered the event to be an acute episode of GERD. The event was considered not related to the investigational product or to study protocol procedures.

3. A 39-year-old White male with anxiety and muscle spasm and who met eligibility criteria contacted the site 7 days post-vaccination to report on an unusual feeling in his chest at the level of the diaphragm, which awoke him from sleep. He described the sensation as a tension (a feeling of wanting to cry or "be very angry") lasting 30 minutes and then disappearing completely. He has experienced similar sensations prior to study participation. The subject denied chest pain or difficulty breathing. He contacted the site 3 times after that to describe the feeling and rated the intensity as a 4 or 5 out of 10 (twice) or a 1 out of 10 (last episode). All 3 episodes occurred over a 9-hour period and resolved spontaneously. The subject continued to experience "unusual sensations" of brief duration (reportedly lasting a few seconds) in the chest and abdominal areas. He was seen by the study site on February 24, 2017, at which time he had no pain or unusual sensations; the physical examination was normal; and an ECG performed at the visit was read as abnormal but not clinically significant, and the investigator considered that the ECG was normal. The subject returned to the site on March 8, 2017, for a planned study follow-up visit. Although there were no ongoing symptoms or complaints, an ECG was again performed. The ECG on that date was read as abnormal but not clinically significant. The episodes were determined by the investigators to be due to muscle twitches and anxiety and not related to the investigational product or procedures.

   Reviewer Comment: *On May 17, 2017, Wyeth submitted unblinded safety and immunogenicity results from study B7471001 through 1 month post-vaccination to support initiation of Phase 2 adult study B7471002. CBER's review of these data revealed no concerning safety findings. Although the study was not large enough to identify with >95% probability events that occur at a rate of <10%, CBER agreed in a letter dated June 19, 2017 that the lack of any abnormalities in cTnI (a sensitive marker of cardiac tissue damage) and the lack of cardiac-related adverse events within 1 month after vaccination supported Wyeth's proposal to proceed cautiously into a Phase 2 study in adults 60-64 years of age (Study B7471002) using traditional safety monitoring. CBER considered that there was no clear need or benefit to continue cardiac screening and monitoring in the proposed Phase 2 study in adults 60 through 64 years of age. This Phase 2 study would include an external DMC and limited daily enrollment until the DMC completed a safety review on the first 30 enrolled subjects.*

Conclusions

The safety and immunogenicity results from study B7471001 supported initiation of Phase 2 study B7471002 in adults 60-64 years of age. This Phase 2 study included a program level external DMC that would remain in place throughout the PCV20 clinical development program to conduct routine, periodic safety reviews of the Phase 2 and Phase 3 studies in the clinical program.

7. INTEGRATED OVERVIEW OF EFFICACY

As previously agreed to, Wyeth performed no formal meta-analysis of immunogenicity data pooled across trials, because each Phase 3 study had distinct study objectives and/or a distinct study design, including different study population with regard to age and prior pneumococcal vaccination status. Please see Sections 6.1, 6.2, and 6.3 for the results of each individual Phase 3 study.

Of note, in post hoc analyses presented in the summary of clinical efficacy, Wyeth submitted tables showing OPA GMT results from subjects ≥65 years of age in study B7471007 compared to subjects ≥65 years of age previously immunized with a pneumococcal vaccine in study

B7471006. In general, for all 20 vaccine serotypes, OPA GMTs tended to be lowest among subjects previously immunized with PPSV23 and highest among vaccine-naïve subjects or subjects previously immunized with PCV13 (Data not shown, Summary of Clinical Efficacy, Tables 12 and 13).

For the 13 original serotypes, OPA GMTs achieved by subjects who previously received PCV13 and PPSV23 were similar to the group with prior PCV13 alone. For the 7 new serotypes, OPA GMTs achieved by subjects with prior PCV13 and PPCV23 were generally lower than the prior PCV13 alone group but higher than the prior PPSV23 only group (Data not shown, Summary of Clinical Efficacy, Tables 12 and 13).

> ***Reviewer Comment:*** *The Prevnar 13 prescribing information includes a statement within Section 7 Drug Interactions indicating that prior receipt of PPSV23 within 1 year results in diminished immune responses to PCV13 compared to the responses of PPSV23 naïve individuals. This statement was based on data from pre-licensure clinical trials showing that OPA GMTs in subjects who received PCV13 one year after PPSV23 were diminished compared to those who received PCV13 alone. The cross-study comparisons described above from study B7471006 and from vaccine-naïve subjects ≥65 years of age in study B7471007 suggest a similar phenomenon with PCV20 (i.e., prior receipt of PPSV23 alone within 1-5 years of PCV20 results in diminished OPA GMTs to PCV20 compared to those of PPSV23 naïve individuals).*

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The integrated summary of safety includes safety results from the three Phase 3 clinical trials (B7471007, B7471008 and B7471006) submitted to this BLA. As agreed with CBER previously, Wyeth did not include safety data from Phase 1 and 2 studies, because the clinical trial material for Phase 1 and 2 studies were manufactured at a different scale from those used for Phase 3 studies and the final batches used for commercialization.

Each Phase 3 trial has a distinct design and/or different subject populations with regard to age and prior pneumococcal vaccination status. Therefore, each Phase 3 study is presented in the integrated overview of safety in side-by-side displays, except that data are pooled for subjects 18-49 years of age. Only data from pneumococcal-vaccine-naïve adults 18-49 years of age from study B7471007 Cohort 3 and from study B7471008 were pooled in the integrated summary of safety, because this was the only overlapping subject population across studies.

Since age and prior pneumococcal vaccination status are important factors when interpreting safety and tolerability results, results are summarized separately for studies with subjects of any age who were naïve to pneumococcal vaccine at trial enrollment, and for studies with subjects ≥65 years of age by prior pneumococcal vaccination status (naïve or previously vaccinated with PCV13, PPSV23, or both).

The methods for safety data collection and analysis were the same in all three Phase 3 trials, as described in Section 6.1.7. In each study, the analysis population for safety endpoints was the safety population, which included all subjects who received a study vaccination and had safety follow-up after vaccination. Subjects were included in the vaccine group corresponding to the vaccine actually administered.

8.2 Safety Database

A total of 7,048 immunocompetent adults ≥18 years of age were evaluated in six PCV20 pre-licensure trials. A total of 3,928 subjects and 2,247 subjects received PCV20 or active control, respectively and provided post-vaccination safety data from 5 randomized, double-blinded, active controlled clinical trials conducted in immunocompetent pneumococcal vaccine naïve adults ≥18 years of age in the U.S. and Sweden (172 subjects ≥65 years of age were randomized/enrolled in Sweden). Additional descriptive data were available from a sixth open-label study in adults ≥65 years of age in the U.S. and Sweden previously immunized with a pneumococcal vaccine prior to enrollment (624 PCV20 recipients and 245 active control recipients in B7471006).

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Table 1 in Section 5.3 includes a brief description of the three Phase 3 studies included in the integrated overview of safety.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Across the Phase 3 trials, 6470 subjects were vaccinated; 4263 subjects received PCV20 and 2207 received control vaccine. See Table 1 for a breakdown by study and age group.

Pneumococcal vaccine naïve subjects (N=5597) were enrolled and vaccinated in B7471007 (≥18 years of age) and B7471008 (18-49 years of age): 3639 received PCV20 and 1958 received control vaccine (PCV13 or PCV13/PPSV23). Across vaccine groups, 2997 (53.5%) were ≥60 years, 445 (8.0%) were 50-59 years, and 2155 (38.5%) were 18-49 years of age (Table 1 and Module 2.7.4 Summary of Clinical Safety Table 2).

Individuals ≥65 years of age (N=1885) were enrolled and vaccinated in B7471007 (pneumococcal vaccine naïve) and B7471006 (previously vaccinated); 1138 received PCV20 and 747 received control vaccine (PCV13/PPSV23, PCV13, or PPSV23). This total sample size includes 72 subjects ≥80 years of age (35 subjects ≥80 years of age in study B7471007 and 37 subjects ≥80 years of age in study B7471006). Across vaccine groups, 1012 (53.7%) were pneumococcal vaccine naïve, 375 (19.9%) had prior PPSV23 only, 373 (19.8%) had prior PCV13 only, and 125 (6.6%) had prior PCV13 followed by PPSV23 (Table 1 and Module 2.7.4 Summary of Clinical Safety Table 3).

All subjects <65 years of age were enrolled in the U.S. Among subjects ≥65 years of age in Phase 3 studies, 305 subjects were enrolled in Sweden and 1,145 were enrolled in the U.S. (840 pneumococcal vaccine naïve subjects ≥65 years of age in B7471007 Cohort 1 and 305 pneumococcal vaccine experienced subjects ≥65 years of age in study B7471006 Cohort A (subjects with prior PPSV23 only). Due to the small number of Swedish subjects, by-country subgroup safety analysis was not performed in B7471006.

Demographics of each study were previously described in Sections 6.1.10.1.1, 6.2.10.1.1, and 6.3.10.1.1. Demographic characteristics and smoking history for the pooled 18-49-year age group (B7471007 Cohort 3 and B7471008) were similar to those described for study B7471007 (Data not shown, Module 5.3.5.3 ISS Table 3).

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

The pooling of data from 447 subjects 18-49 years of age (Cohort 3) in study B7471007 and 1708 subjects 18-49 years of age in study B7471008 were supported by the identical age of

study subjects, identical active control (PCV13), identical safety endpoints (including use of the same MedDRA version for safety reporting), identical methods for safety data collection and analysis, and overlap in the time frame when the studies were conducted as well as overlap in the study sites within the U.S. where the studies were conducted. A total of 15 out of the 21 sites where study B7471008 was conducted were the same sites used in study B747100716, representing 1310 out of the total 1718 subjects enrolled in study B7471008.

8.4 Safety Results

8.4.1 Deaths

Two unrelated deaths were reported in PCV20 pre-licensure studies. One was reported in a 60-year old male in Cohort 1 of study B7471007. This subject died due to a self-inflicted gunshot wound 48 days after receiving Vaccination 2. In addition, one death was reported in a 37-year-old female PCV20 recipient in study B7471001.The cause of death was due to a motor vehicle accident 75 days after vaccination.

8.4.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events were summarized separately for each Phase 3 study in Sections 6.1.12.4, 6.2.12.4, and 6.3.12.4. Rates of SAEs within 6 months after vaccination among the pooled 18-49-year-old subjects in studies B7471007 (Cohort 3) and B7471008 were 0.7% among the 1,798 PCV20 recipients and 0.3% among the 357 PCV13 recipients.

8.4.3 Study Dropouts/Discontinuations

Subject disposition for each of the Phase 3 studies was summarized in Sections 6.1.10.1.3, 6.2.10.1.3, and 6.3.10.1.3. Withdrawal due to AEs were reported for 20 subjects in Cohort 1 of Study B7471007 (see Section 6.1.12.7). No withdrawals due to AEs were reported in other cohorts of study B7471007 nor studies B7471008 or B7471006.

8.4.4 Common Adverse Events

Common unsolicited AEs from each of the Phase 3 studies were summarized in Sections 6.1.12.2, 6.2.12.2, and 6.3.12.2. Common unsolicited AEs among pooled 18-49-year-old subjects in studies B7471007 (Cohort 3) and B7471008 were similar to those described in Sections 6.1.12.2 and 6.2.12.2 (Data not shown, ISS Table 5).

Other Significant Adverse Events

Seven subjects who received PCV20 (2 subjects in Cohort 3 of study B7471007 and 5 subjects in study B7471008) and 1 subject who received PCV13 in study B7471008 became pregnant while participating in B7471007 and B7471008. These pregnancies were not associated with AEs and were summarized previously in Sections 6.1.12.2 and 6.2.12.2.

8.4.6 Systemic Adverse Events

Solicited systemic adverse events (AEs) were previously summarized in Sections 6.1.12.2, 6.2.12.2, and 6.3.12.2. Solicited systemic AEs among pooled 18-49-year-old subjects in studies B7471007 (Cohort 3) and B7471008 were similar to those described in Section 6.2.12.2 (study B7471008 results) since a large proportion of subjects come from study B7471008 (Data not shown, Summary Clinical Safety Table 6).

[16] Study B7471007 was a much larger study overall involving a total of 63 sites in the U.S. and Sweden. Subjects 18-49 years of age in study B7471007 were only enrolled in U.S. sites.

Rates of solicited systemic adverse reactions in pneumococcal-vaccine-naïve participants ≥65 years of age in study B7471007 were presented side by side with those of B7471006 subjects previously immunized with a pneumococcal vaccine in the Summary of Clinical Safety (i.e., Integrated Summary of Safety). Rates of headache, muscle pain, joint pain and use of antipyretic pain medication were generally higher among subjects previously immunized with PCV13 and PPSV23 compared to all other subjects (i.e., subjects previously immunized with PCV13 only or PPSV23 only and pneumococcal vaccine-naïve subjects). Rates of fatigue were lowest among pneumococcal vaccine-naïve adults and highest among subjects previously immunized with PCV13 and PPSV23.

> ***Reviewer Comment:*** *These across study comparisons are acceptable for the purpose of the integrated summary of safety, because studies B7471007 and B7471006 were very similar. Both studies had identical safety methods for safety data collection and analysis, identical safety endpoints, overlap in the age of subjects enrolled (both enrolled subjects ≥65 years of age), overlap in the time frame when the studies were conducted as well as overlap in 31 out of the 44 study sites used in study B7471006 (representing 624 (71.3%) out of 875 subjects enrolled in the study).*

8.4.7 Local Reactogenicity

Solicited local reactions were previously summarized in Sections 6.1.12.2, 6.2.12.2, and 6.3.12.2. Solicited local reactions among pooled 18-49-year-old subjects in studies B7471007 (Cohort 3) and B7471008 were similar to those described in Section 6.3.12.2 (study B7471008 results) since a large proportion of subjects come from study B7471008 (Data not shown, Summary Clinical Safety Table 4).

Rates of solicited local injection site reactions in pneumococcal vaccine-naïve participants ≥65 years of age in study B7471007 were presented side by side with those of B7471006 subjects ≥65 years of age previously immunized with a pneumococcal vaccine. Rates of injection site pain were generally higher in PCV20 recipients previously immunized with PPSV23, PCV13 or both PCV13 and PPSV23 compared to pneumococcal vaccine-naïve subjects. The rate of injection site pain was numerically highest in PCV20 recipients previously immunized with PCV13, followed by PCV20 recipients previously immunized with PCV13 and PPSV22 or PPSV23 alone. Rates of injection site swelling were generally higher among PCV20 recipients previously immunized with PPSV23 or PCV13 (but not PCV13 and PPSV23). Rates of injection site redness were similar across pneumococcal vaccine-naïve and pneumococcal vaccine-experienced subjects.

8.6 Safety Conclusions

Post-vaccination safety data were collected from 6 randomized studies in which 7,048 immunocompetent adults ≥18 years of age were immunized with either PCV20 (N=4,552) or an active control (N=2,496). This included an open-label safety assessment among 869 (624 PCV20 recipients and 249 control recipients) adults ≥65 years of age previously immunized with at least one dose of a pneumococcal vaccine prior to enrollment. No safety concerns were identified when a single dose of PCV20 was administered to pneumococcal-vaccine-naïve or pneumococcal-vaccine-experienced adults ≥18 years of age.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Risk Summary

All pregnancies have a risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Prevnar 20 administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy (see Clinical Data).

A developmental toxicity study was performed in female rabbits administered PCV20 prior to mating and during gestation. The dose was 0.5 mL at each occasion (a single human dose is 0.5 mL). This study revealed no evidence of harm to the fetus due to PCV20 (see Animal Data).

Animal Data

In a fertility and developmental toxicity study, female rabbits were administered PCV20 by intramuscular injection twice prior to mating (17 days and 4 days prior to mating) and twice during gestation (Gestation Days 10 and 24), 0.5 mL/rabbit/occasion (a single human dose). No adverse effects on pre-weaning development were observed. There were no vaccine-related fetal malformations or variations.

Clinical Data

Pre-licensure studies excluded females who were pregnant or breastfeeding. Under screening criteria, a urine pregnancy test was collected on day 1 prior to vaccination of subjects 18 through 59 years of age (cohorts 2 and 3) in study B7471007 and on day 1 prior to vaccination of subjects 18-49 in study B7471008. A total of 8 pregnancies were reported among participants in prelicensure PCV20 studies (studies B7471007 and B7471008); this includes 7 subjects who received PCV20 and 1 subject who received PCV13. Six of the eight total pregnancies were conceived after vaccination.

Two pregnancies (both PCV20 recipients) had estimated conception dates that were prior to vaccination (Day-4 and Day-19) were reported at the 1-month post-vaccination visit. The subject with the estimated conception date 4 days prior to vaccination gave live birth to a full-term male infant at an estimated 39 weeks gestation. The pregnancy outcome of the subject with an estimated conception date 19 days prior to vaccination could not be determined, as the site informed Wyeth that the subject's telephone number was disconnected (subject (b) (6) .

Of the 5 pregnancies among PCV20 recipients with estimated conception dates after vaccination, all resulted in full-term live births. The one PCV13 recipient who became pregnant reported being in a motor vehicle accident 187 days after vaccination and reported a spontaneous abortion 9 days after the accident. This PCV13 recipient's pregnancy had an estimated conception date of approximately 4 months after vaccination. Although the investigator considered there was a reasonable possibility that this event was related to the study vaccine, Wyeth considered the event was more likely triggered by the motor vehicle accident and an associated fetal genetic anomaly post-fetal demise showed "likely trisomy 21").

Because of the small sample size of pregnancies reported during pre-licensure PCV20 studies (N=8) and the fact that six of the eight pregnancies were conceived after vaccination, the clinical data on pregnancy outcomes is not adequate to make meaningful conclusions about safety of the vaccine when used during pregnancy.

9.1.2 Use During Lactation

It is not known whether PCV20 is excreted in human milk. Data are not available to assess the effects of PCV20 on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PCV20 and any potential adverse effects on the breastfed child from PCV20 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of Prevnar 20 in persons less than 18 years of age have not been established.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the submission of this original BLA required a Pediatric Study Plan for the claimed indications. Wyeth requested a full waiver of the pediatric study requirement in persons from birth through 16 years of age for the pneumonia indication, because the necessary studies are impossible or highly impracticable (505B(a)(4)(A)(i) of the Act). Because Prevnar 13 efficacy has not been demonstrated against pneumonia in pediatric age groups, the approval of Prevnar 20 for the prevention of pneumonia in pediatric patients would require the demonstration of efficacy in a clinical endpoint study. Such a study would not be logistically feasible given the large number of subjects that would be needed in order to demonstrate efficacy. In addition, there are currently no reliable methods for detecting vaccine-type nonbacteremic pneumonia in children (the most common type of pneumonia). A urine antigen detection assay to detect pneumonia due to the serotypes in PCV13 was developed for adults and used in the study which supported the adult Prevnar 13 pneumonia indication. However, this assay has not been validated for use in children to date due to high rates of pneumococcal carriage.

Wyeth requested a partial waiver of the pediatric study requirement in infants from birth to <6 weeks of age for the invasive pneumococcal disease indication, because Prevnar 20 does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group, and Prevnar 20 is not likely to be used by a substantial number of pediatric patients in this age group (section 505B(a)(4)(B)(iii) of the Act). Due to limitations of the neonatal immune response, initiating vaccination at 0 to <6 weeks of age with Prevnar 20 would not provide a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age. In addition, with the exception of Hepatitis B vaccine, for which a birth dose is routinely recommended to prevent perinatal transmission of hepatitis B virus, infant immunizations in the U.S. are generally not administered before 6 weeks of age.

Wyeth is requesting a deferral of pediatric studies in persons 6 weeks through 16 years of age to support the invasive pneumococcal disease indication on the basis that Prevnar 20 is ready for approval for use in adults and the pediatric studies have not been completed (505B(a)(3)(A)(i) of the Act). Wyeth is conducting four studies in persons 6 weeks through 16 years of age as part of their global clinical development plan. The review team concurred with Wyeth's proposal that of these four studies, the three studies listed below in Section 11.6 (B7471011, B7471013, and B7471014) are sufficient to support a pediatric assessment in the

U.S. for this age group. During the review cycle, Wyeth revised the timelines that were submitted in the agreed Pediatric Study Plan for these deferred studies along with a justification for the changes. CBER and PeRC agreed to these revisions. Please see Section 11.6 of the clinical review for timelines for conducting each of these three required pediatric postmarketing studies under PREA.

9.1.4 Immunocompromised Patients

The safety and effectiveness of Prevnar 20 have not been established in immunocompromised individuals.

9.1.5 Geriatric Use

The safety and effectiveness of Prevnar 20 have been established in adults ≥65 years of age. Of the total number of Prevnar 20 recipients ≥18 years of age in Phase 3 clinical trials (N=4263), 26.7% (n=1138) were ≥65 years of age and 1.7% (n=72) were ≥80 years of age. Please refer to Sections 6.1 and 6.3 for the data in these age groups.

10. CONCLUSIONS

The data submitted to this BLA provide evidence to support the safety and effectiveness of a single dose of Prevnar 20 in adults ≥18 years of age for the prevention of invasive pneumococcal disease caused by the 20 pneumococcal vaccine serotypes and pneumococcal pneumonia caused by PCV13 serotypes contained in the vaccine.

Under the accelerated approval regulations, the available safety and immunogenicity data submitted to this BLA support the approval of Prevnar 20 for the prevention of pneumococcal pneumonia caused by the 7 new serotypes contained in the vaccine (8, 10A, 11A, 12F, 15B, 22F, 33F) in adults 18 years of age and older. As a condition of accelerated approval, Wyeth is required to further study Prevnar 20 to verify and describe its clinical benefit in postmarketing study B7471015.

This application includes data obtained from 6 clinical trials performed in 7048 immunocompetent adults ≥18 years of age in the United States and Sweden; 4552 have received PCV20, and 2496 have received control. Overall, the safety profile of a single dose of PCV20 was comparable to that observed following a dose of Prevnar 13.

In study B7471007, immunologic noninferiority of PCV20 compared to PCV13 (for the 13 original serotypes) and PPSV23 (for the 7 new serotypes) following a single vaccination was demonstrated for 19 of 20 vaccine serotypes (except serotype 8) in pneumococcal vaccine naïve adults ≥60 years of age. Serotype 8 narrowly missed the pre-specified 2-fold non-inferiority margin (95% LL = 0.49). In supportive secondary analyses, 77.8% of subjects ≥60 years of age achieved a ≥4-fold increase in anti-serotype 8 OPA titers.

The effectiveness of Prevnar 20 in younger adults 18-49 years of age and 50-59 years of age was demonstrated in study B7471007 by immunobridging to the established effectiveness in the 60-64-year-old adult age group (Cohort 1 Subset).

In study B7471008, clinical lot consistency was demonstrated based on demonstration of immunologic equivalence of 3 separately manufactured lots of 20PnC in pneumococcal vaccine naïve adults 18-49 years of age.

Study B7471006 demonstrated an acceptable safety and tolerability profile of PCV20 when administered to adults previously immunized with PCV13 or PPSV23. In the descriptive immunogenicity analyses, OPA GMTs in participants who received PPSV23 (one) 1 to five (5) years prior to Prevnar 20 were diminished compared to OPA GMTs in participants who received Prevnar 13 at least 6 months previously and compared to OPA GMTs in participants who received Prevnar 13 followed by PPSV23, with the last PPSV23 dose given at least 1 year prior to Prevnar 20. These immunogenicity results from this study are reflected in the drug interactions section of the Prevnar 20 prescribing information.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 38 summarizes PCV20 risk-benefit considerations in adults ≥18 years of age.

Table 38. Risk Benefit Considerations of Vaccination with Prevnar 20 in Adults ≥18 Years of Age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *S. pneumoniae* can cause meningitis, bacteremia and pneumonia in adults, resulting in substantial morbidity and mortality. Complications of pneumococcal pneumonia include empyema and pericarditis. Pneumococcal meningitis commonly results in neurologic sequelae, including hearing loss and brain damage. • Conditions that increase the risk of serious pneumococcal disease include immunosuppressive conditions, functional or anatomic asplenia, chronic heart, pulmonary, liver or renal disease, cigarette smoking, alcoholism, cerebrospinal fluid leak, and cochlear implant (Gierke et al 2021b). Adults 65 years or older are also at increased risk for pneumococcal disease.	• Invasive pneumococcal disease (IPD) and pneumococcal pneumonia are serious and life-threatening conditions that can result in significant morbidity and mortality in adults ≥18 years of age. • The risk of serious pneumococcal disease is greatest in immunocompromised adults and immunocompetent adults with certain risk factors.
Unmet Medical Need	• Prevnar 13 (PCV13) and Pneumovax 23 (PPSV23) are two pneumococcal vaccines approved for use in persons ≥18 years of age in the U.S. PCV13 includes 13 shared serotypes with PCV20, and it is thought to elicit a T-cell dependent immune response. PPSV23 includes the 7 new serotypes in PCV20, however PPSV23 is thought to elicit a T-cell independent immune response which is characterized by an antibody response that is of short duration, an absent or blunted memory response, and no affinity maturation. • IPD caused by the 7 new serotypes represents one-quarter of the non-PCV13 IPD burden in adults ≥65 years of age, despite routine administration of PPSV23 to adults ≥65 years of age. • Data suggest that PPSV23 protects adults and the elderly against IPD, however no consistent vaccine effect has been observed for prevention of pneumonia • Effective antibiotic therapy is available for the treatment of IPD in adults; however, antibiotic resistance is increasingly common making treatment more difficult. • Several studies note no reduction in the incidence of serotype 3 IPD in US children < 5 years of age between 2011 and 2019, no reduction in the incidence of serotype 3 IPD in US adults ≥ 65 years of age, and the relatively lower immunogenic response induced by PCV13 to this serotype compared to the other vaccine serotypes,	• In adults ≥18 years of age, there is an unmet medical need for effective prevention of invasive pneumococcal disease and pneumococcal pneumonia caused by the 7 new serotypes included in Prevnar 20 (8, 10A, 11A, 12F, 15B, 22F, 33F). • Serotype 3 continues to be a common cause of IPD in adults and children in the US and globally.
Clinical Benefit	• The effectiveness of Prevnar 20 in pneumococcal vaccine naïve adults ≥60 years of age was inferred by demonstrating noninferiority of OPA antibody responses after Prevnar 20 to the corresponding OPA antibody responses after PCV13 for each of the 13 original serotypes and to the corresponding OPA antibody responses after PPSV23 for each of the 7 new serotypes. • Prevnar 20 effectiveness against IPD in pneumococcal vaccine naïve adults 18-49 years of age and 50-59 years of age were inferred by separate comparisons of OPA antibody responses in each age group to the OPA antibody responses in adults 60-64 years of age (immunobridging), in which Prevnar 20 effectiveness was established, as described above. For the pneumonia indication, the same comparisons, using OPA antibody responses as a surrogate endpoint as defined in the accelerated approval regulations, were used to support the reasonable likelihood of vaccine effectiveness against pneumonia caused by the 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F). A post-approval clinical endpoint study will be required to verify and describe clinical benefit for the pneumonia indication for the 7 new serotypes. • Based on post-hoc analyses from study 6115A1-3006 (“CAPiTA” study) (not adjusted for multiplicity), serotype 3 specific PCV13 vaccine efficacy (VE) for the primary (CAP) endpoint approached statistical significance in the per protocol population (PPP) and reached statistical	• The submitted immunogenicity data are adequate to establish the effectiveness of a single dose of Prevnar 20 in adults ≥18 years of age for the prevention of vaccine-type IPD. • Serotype 3-specific OPA GMTs induced by PCV20 were non-inferior to those induced by PCV13. Thus, PCV20 vaccine effectiveness against serotype 3 type disease is anticipated to be similar to Prevnar 13 effectiveness, which reached statistical significance based on the mITT population in study 6115A1-3006 (“CAPiTA” study). • Based on the use of a surrogate endpoint under the Accelerated Approval Regulations, the submitted immunogenicity data provide evidence for the effectiveness of a single dose of Prevnar 20 in adults ≥18 years of age for the prevention of vaccine-type pneumonia.

	significance in the modified intent-to-treat population (mITT). Serotype 3 was one of the four most frequently isolated serotypes from primary endpoint (CAP) cases in study 6115A1-3005. • VE against serotype 3 CAP was 56.3% (95% CI -12.4, 84.8%) in the per-protocol population (PPP). In the modified intent-to-treat population (mITT), VE for serotype 3 reached statistical significance (60.0% (95% CI 5.2, 84.8). For the secondary endpoints listed below, VE estimates did not reach statistical significance. Fewer cases were observed for these two secondary endpoints. • For non-bacteremic CAP, VE was 58.3% (95% CI -27.1, 88.5) in the PPP. Results were similar in the mITT. • For IPD, VE was 75.0% (95% CI -152.6, 99.5) in the PPP. Results were similar in the mITT. • In descriptive immunogenicity analyses in study B7471006, OPA GMTs are diminished when PCV20 is administered 1-5 years after PPSV23 compared to when it is given ≥ 6-months after PCV13 or after PCV13 followed by PPSV23 with the last PPSV23 dose at least 1 year prior.	
Risk	• The most common risks of vaccination with Prevnar 20 include injection site pain, muscle pain, fatigue and headache. The vast majority of reactions are mild or moderate in severity and resolve quickly. Severe reactions were infrequent (≤3.0%) • No other safety signals were apparent in adults ≥18 years of age who are either pneumococcal vaccine naïve or adults who previously received PPSV23 1 through 5 years prior, PCV13 ≥6 months prior, or PCV13 followed by PPSV23 (PPSV23 given ≥1 year prior).	• All the evidence indicates that the safety profile of Prevnar 20 is acceptable in pneumococcal-vaccine-naïve adults, in adults previously immunized with PPSV23 at least 1 year prior and in adults previously immunized with PCV13 ≥6 months prior.
Risk Management	• Wyeth's pharmacovigilance plan consists of routine postmarketing safety surveillance (monitoring for any unanticipated risks in surveillance systems and postmarketing adverse reaction reports).	• If Prevnar 20 were approved for adults ≥18 years of age, routine pharmacovigilance measures would be adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

Data submitted to this BLA establish the benefit of vaccination with Prevnar 20 with respect to the prevention of disease caused by twenty *S. pneumoniae* serotypes contained in the vaccine in adults ≥18 years of age. The risks of vaccination with Prevnar 20 in this population have been found to be minimal. Therefore, the overall risk-benefit profile of this product for adults ≥18 years of age is determined to be favorable.

The greatest benefit is expected among a subpopulation of adults who are at increased risk of invasive pneumococcal disease or pneumococcal pneumonia due to age, underlying medical conditions or other risk factors.

11.4 Recommendations on Regulatory Actions

According to my review of the clinical data, the safety and effectiveness of a single dose of PCV20 in pneumococcal vaccine naïve adults ≥18 years of age are supported for the prevention of vaccine-type IPD and vaccine-type pneumococcal pneumonia.

The approval of Prevnar 20 for the prevention of pneumonia caused by the 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) is based on an immunologic surrogate endpoint (OPA antibody titer), as defined in the Accelerated Approval regulations, that is reasonably likely to predict prevention of pneumococcal pneumonia caused by the 7 new vaccine serotypes in PCV20. As a condition of accelerated approval for the pneumonia indication for the 7 new serotypes, Wyeth commits to conduct a post-approval confirmatory study to verify and describe clinical benefit (Study B7471015).

11.5 Labeling Review and Recommendations

CBER communicated with Wyeth to achieve consistency with CBER's current guidance on the intent and format of prescribing information. Specific comments on the prescribing information were provided by CBER to Wyeth who made the requested revisions. All issues were satisfactorily resolved. The final prescribing information was reviewed by the clinical team and found to be acceptable.

11.6 Recommendations on Postmarketing Actions

The clinical review of the data submitted to this BLA did not identify safety concerns that would prompt the need for a postmarketing safety study. Wyeth's proposal to monitor for any unanticipated risks in surveillance systems and postmarketing adverse reaction reports (i.e., routine pharmacovigilance) is acceptable.

As a condition of the accelerated approval of PCV20 for the prevention of pneumonia caused by the 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) in adults, Wyeth is required to further evaluate PCV20 in an adequate and well-controlled confirmatory clinical study to verify and describe clinical benefit (21 CFR 601.41). Wyeth has made a commitment to conduct study B7471015, a Phase 4 real-world study using a test-negative design to evaluate the effectiveness of Prevnar 20 against CAP caused by the 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) in adults ≥65 years of age. Study B7471015 is a postmarketing requirement under the accelerated approval regulations. A draft protocol for study B7471015 was submitted to STN 125731/0.8 on January 15. 2021. A final protocol will be submitted by August 31, 2020. Study completion is estimated to occur on May 31, 2027. The final clinical study report will be submitted by November 30, 2027. Given that the uptake of Prevnar 20 will largely depend on

the ACIP recommendation expected in October 2021, enrollment may need to be conducted over 5 respiratory seasons beginning in October 2022.

Postmarketing studies that Wyeth is required to conduct under PREA after licensure are listed below. The protocols for each of these studies were submitted and reviewed by CBER in 2020.

Pediatric Research Equity Act Postmarketing Requirements

1. Deferred pediatric study, B7471011, under PREA to evaluate the safety and effectiveness (immunogenicity) of the 2, 4, 6, and 12-month schedule of Prevnar 20 in U.S. infants 6 weeks through 12 months of age.

   Final Protocol Submission: May 8, 2020

   Study Completion: August 31, 2022

   Final Report Submission: December 31, 2022

2. Deferred pediatric study, B7471013, under PREA to evaluate the safety of the 2, 4, 6, and 12-month schedule of Prevnar 20 in U.S., European, and Canadian infants.

   Final Protocol Submission: March 23, 2020

   Study Completion: August 31, 2022

   Final Report Submission: December 31, 2022

3. Deferred pediatric study, B7471014, under PREA to evaluate the safety and effectiveness (immunogenicity) of Prevnar 20 in children and adolescents 15 months through 17 years of age.

   Final Protocol Submission: September 11, 2020

   Study Completion: December 31, 2021

   Final Report Submission: December 31, 2022

In addition, Wyeth has an ongoing trial evaluating the safety and immunogenicity of PCV20 co-administered with seasonal inactivated influenza vaccine in adults ≥65 years of age. (b) (4)