BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125731/189
CBER Received Date	October 26, 2022
PDUFA Goal Date	April 27, 2023
Division / Office	DVRPA/OVRR
Priority Review	Yes
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Review Completion Date / Stamped Date	April 27, 2023
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Applicant	Wyeth Pharmaceuticals, LLC, a subsidiary of Pfizer, Inc.
Established Name	Pneumococcal 20-valent Conjugate Vaccine
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 saccharide • ~51 µg diphtheria cross reactive material carrier protein* • 125 µg aluminum as aluminum phosphate adjuvant * CRM protein content is dependent on the saccharide-to-protein ratio of the saccharides used in the formulation
Dosage Form and Route of Administration	Suspension for intramuscular (IM) injection
Dosing Regimen	Four-dose immunization series consisting of a 0.5 mL IM injection administered at 2, 4, 6 and 12-15 months of age
Indications and Intended Populations	In individuals 6 weeks through 17 years: active immunization for the prevention of 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 individuals 6 weeks through 5 years of age: active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.
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
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CFR	Code of Federal Regulations
CRM197	cross-reacting material 197 (carrier protein)
CSF	cerebrospinal fluid
CSR	clinical study report
FDA	Food and Drug Administration
GMT	geometric mean titer
Hib	*Haemophilus influenzae* type b
IPD	invasive pneumococcal disease
IR	Information Request
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
PCV7	Prevnar (7-valent pneumococcal conjugate vaccine)
PCV13	Prevnar 13 (13-valent pneumococcal conjugate vaccine)
PCV15	Vaxneuvance (15-valent pneumococcal conjugate vaccine)
PCV20	Prevnar 20 (20-valent pneumococcal conjugate vaccine)
PeRC	Pediatric Review Committee
PPSV23	Pneumovax 23 (23-valent pneumococcal polysaccharide vaccine)
PREA	Pediatric Research Equity Act
PRP	polyribosyl-ribitol-phosphate
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
US	United States
USPI	United States Prescribing Information

1. Executive Summary

Wyeth Pharmaceuticals, LLC submitted a Biologics License Application supplement (sBLA) to support use of Pneumococcal 20-valent Conjugate Vaccine (Prevnar 20; PCV20) in individuals 6 weeks through 17 years of age. The proposed indications include 1) active immunization for the prevention of 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 individuals 6 weeks through 17 years of age, and 2) active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in individuals 6 weeks through 5 years of age. The infant primary series consists of four doses, with a single intramuscular injection at 2, 4, 6, and 12-15 months of age.

Wyeth submitted data from four clinical studies. The submitted studies include three deferred Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) for the invasive pneumococcal disease (IPD) indication (studies B7471011, B7471013, and B7471014) included in the June 10, 2021 approval letter for the original BLA. Phase 3 study B7471011 was designed to evaluate the safety and immunogenicity (effectiveness) of a 4-dose series of PCV20 for the prevention of vaccine-type IPD in pneumococcal vaccine-naïve infants in the United States (US). Phase 3 study B7471013 was designed to describe the safety of a 4-dose series of PCV20 in pneumococcal vaccine-naïve infants in the US, Canada, South America and Europe. Phase 2 study B7471003 was designed to describe the safety and immunogenicity of a 4-dose series of PCV20 in pneumococcal vaccine-naive infants. Phase 3 study B7471014 was a single-arm study designed to describe the safety and immunogenicity of PCV20 when given as a single catch-up vaccination to healthy children 15 months through 4 years of age previously vaccinated with at least 3 doses of PCV13, or healthy individuals 5 through 17 years of age regardless of prior pneumococcal vaccination status. For studies B7471014 and B7471003, this clinical review focuses on safety data; CBER did not consider these studies designed to demonstrate vaccine effectiveness.

The effectiveness of PCV20 when administered according to the proposed catch-up vaccination schedules in individuals initiating vaccination at 7 months through 17 years of age and in individuals 15 months through 17 years of age previously vaccinated or incompletely vaccinated with a pneumococcal conjugate vaccine is supported by evidence from clinical study B747101 in younger children who received a 4-dose series of Prevnar 20 and by evidence from clinical studies of catch-up vaccination with Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM`197 Protein]; PCV13) and Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]; PCV7).

Wyeth also submitted a letter cross-referencing data from two previously conducted well-controlled, clinical endpoint efficacy studies with PCV7: the Finnish Otitis Media trial and the Northern California Kaiser Permanente trial. CBER agreed that these PCV7 efficacy data support the effectiveness of PCV20 for the prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, because PCV20 and PCV7 vaccines are manufactured and formulated similarly and contain 7 of the same polysaccharide conjugates.

Study B7471011 Immunogenicity Analyses Supporting PCV20 IPD Indication
The effectiveness of a 4-dose series of PCV20 for the prevention of vaccine-type IPD in individuals 6 weeks through 15 months of age was demonstrated based on immunologic noninferiority comparisons of PCV20 to U.S.-licensed PCV13 in Phase 3 study B7471011.

Antibody responses elicited by PCV20 and PCV13 in these age groups were measured using a serotype-specific multiplex direct-binding Luminex® immunoassay (dLIA), designed to determine the concentration of serotype-specific polysaccharide-binding IgG antibodies, and opsonophagocytic activity (OPA) assays to measure serotype-specific functional OPA titers for the 20 pneumococcal serotypes of PCV20. A serotype-specific IgG antibody concentration corresponding to ≥0.35 µg/mL using the World Health Organization (WHO) enzyme linked immunosorbent assay (ELISA) has been used as the threshold value for the clinical evaluation of pneumococcal conjugate vaccines when measured one month after Dose 3 of the 4-dose immunization series. The dLIA, used to measure the IgG antibody concentration in study B7471011, was bridged to the WHO ELISA to establish dLIA specific threshold values for each vaccine serotype that correspond to the established ≥0.35 µg/mL WHO ELISA threshold value.

For each vaccine serotype, the primary endpoints were defined as 1) the proportion of participants achieving a pre-defined serum immunoglobulin G (IgG) antibody concentration (≥0.35 µg/mL for all serotypes except for serotypes 5, 6B, 12F, and 19A which were ≥0.23 µg/mL, ≥0.10 µg/mL, ≥0.69 µg/mL and ≥0.12 µg/mL respectively) measured 4 weeks after the third dose, and 2) the IgG geometric mean antibody concentration (GMC) measured 4 weeks after the fourth dose. For each of the 13 matched serotypes, IgG responses in the PCV20 group were to be compared with the corresponding response in the PCV13 group. For the 7 additional serotypes (serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F), IgG responses in the PCV20 group were to be compared with the lowest response among the 13 matched vaccine serotypes excluding serotype 3 in the PCV13 group. Serotype 3 was not included, because postmarketing data suggest there has been no indirect (population-level) impact of PCV13 vaccination on the incidence of serotype 3 IPD in the US (or in other countries using PCV13) following US-licensure of PCV13 in 2010 (Pilishvili 2019).

For the 13 matched serotypes in PCV20 and PCV13, noninferiority was determined if the lower limit of the 2-sided 95% CI for the difference between the proportion of participants (PCV20 – PCV13) achieving the pre-defined IgG antibody concentration was >-10% for each serotype at 4-weeks post-dose 3 and if the lower limit of the 2-sided 95% CI of the IgG GMC ratio (PCV20/PCV13) was >0.5 for each serotype at 4-weeks post-dose 4.

Study B7471011 Post-Dose 3 Noninferiority Comparison Results
IgG antibody responses measured one month after dose 3 of PCV20 were noninferior to those following PCV13 for 8 of the 13 matched serotypes and 6 of the 7 additional serotypes, as assessed by the percentage of participants meeting the predefined serotype-specific IgG concentration one month after Dose 3, using a 10% noninferiority criterion (the lower bound of the 2-sided 95% CI for the difference in percentages [PCV20 minus PCV13] greater than -10%). Five of the 13 matched serotypes (serotypes 1, 3, 4, 9V and 23F) did not meet the pre-specified noninferiority criterion, as the lower bounds of the 2-sided 95% CIs for the difference in percentages (PCV20 minus PCV13) were -12.1%, -20.1%, -12.0%, -11.3%, and -11.4% respectively. One additional serotype (serotype 12F) also did not meet the NI criterion when compared to serotype 23F (the PCV13 serotype with the lowest percentage excluding serotype 3) in the PCV13 group, the lower bound of the 2-sided 95% CI for the difference in percentage (PCV20 minus lowest PCV13) was -41.6%.

In the absence of an established correlate of protection, CBER acknowledged that the clinical relevance of the 6 missed primary endpoints could be further assessed taking into consideration the totality of immunogenicity data was taken into consideration in the assessment the post-dose 3 noninferiority analyses. Additional IgG GMC data at one month after Dose 3 (a key secondary endpoint) and OPA data at one month after Dose 3 (an exploratory endpoint in a

randomly selected subset of participants) support the effectiveness of PCV20 for each of the 6 serotypes that failed to meet the post-dose 3 pre-specified non-inferiority criterion.

At one month after Dose 3, IgG GMCs in the PCV20 group were noninferior to the corresponding IgG GMCs in the PCV13 group for all 20 vaccine serotypes, including the 6 serotypes that missed the noninferiority criterion based on the percentage of participants meeting pre-defined IgG concentrations at one month after Dose 3. For serotypes 1, 3, 4, 9V, 23F and 12F, for which non-inferiority was not met 1 month after Dose 3 (for the percentage of participants meeting the pre-defined serotype-specific IgG concentration), OPA GMTs at 1 month after Dose 3 were numerically similar across groups for the 5 matched serotypes and an OPA antibody response was generated to additional serotype 12F.

Study B7471011 Post-Dose 4 Noninferiority Comparison Results
For each of the 13 matched serotypes, IgG GMCs in the PCV20 group were noninferior to the corresponding IgG GMCs in the PCV13 group. For each of the 7 additional serotypes, IgG GMCs in the PCV20 group were noninferior to the IgG GMC for serotype 1 (the lowest result among the 13 matched vaccine serotypes excluding serotype 3) in the PCV13 group.

Safety Analyses Supporting IPD and OM Indications
The safety of PCV20 in individuals from 6 weeks through 17 years of age was evaluated in 3 randomized, double-blind, active-controlled, clinical trials and one single-arm clinical trial. Across the 4 studies, a total of 3063 participants received at least one dose of PCV20, and a total of 1720 participants received at least one dose of PCV13 (PCV13). Globally, 2232 participants who received at least one dose of a 4-dose series of PCV20 and 1717 participants who received at least one dose of a 4-dose series of PCV13 were included in the safety analysis. In the US (including the US territory of Puerto Rico), 1567 participants received at least one dose of a 4-dose series of PCV20 and 1376 participants received at least one dose of a 4-dose series of PCV13. In study B4741014, a total of 831 participants 15 months through 17 years of age received a single dose of PCV20 when given as a single catch-up or supplemental (i.e., 5th) pneumococcal conjugate vaccine.

Globally, across the 3 infant trials, the proportion of participants reporting 1 or more SAEs within 6 months after the fourth dose of PCV20 was 4.5% (101 of 2232 participants). This was similar to the proportion of participants with SAEs after vaccination with PCV13 [3.7% (64 of 1717 participants)]. The proportions of SAEs observed from the first dose to 1 month after the third dose were 1.1% and 1.2% for PCV20 and PCV13, and from the fourth dose to 1 month after the fourth dose were 0.7% and 0.5% respectively. In the PCV20 group, two febrile seizures considered possibly related to vaccination with PCV20 were reported. One case occurred 14 days after the fourth dose given with MMR and varicella vaccine. One case occurred 7 days after the fourth dose of PCV20 in an individual with diagnosis of COVID-19 infection. One participant experienced isolated injection site hypersensitivity (redness) within approximately 30 minutes of PCV20 after each of the first 3 doses resolving on the same day, this was not observed after the fourth dose.

In Study B7471014, five participants (5.2%) reported SAEs within 6 months after vaccination (2 participants [1.0%] ≥15 to <24 months of age and 3 participants [1.5%] ≥10 to <18 years of age). One participant (0.5%) ≥15 to <24 months of age reported an SAE within 1 month after vaccination. No SAEs were considered related to the vaccination in this study.

In individuals 2, 4, 6, and 12 through 15 months of age vaccinated with a 4-dose schedule, the most commonly reported solicited adverse reactions >10% were irritability (>60%), pain at the

injection site (>30%), drowsiness (>30%), decreased appetite and injection site redness (>20%), injection site swelling (>10%), and fever (>10%).

In individuals 15 months through 17 years of age vaccinated with a single dose, the most commonly reported solicited adverse reactions >10% were irritability (>60% in individuals less than 2 years of age), pain at the injection site (>50%), drowsiness (>40% in individuals less than 2 years of age), fatigue and muscle pain (>20% in individuals 2 years of age and older), decreased appetite (>20% in individuals less than 2 years of age), injection site swelling and injection site redness (>10%), headache (>10% in individuals 5 years of age and older), and fever (>10% in individuals less than 2 years of age).

Overall, in studies B7471011, B741013 and B7471003, the available safety data on the use of a 4-dose series of PCV20 when administered at 2, 4, 6 and 12-15 months of age was generally consistent with the available safety data on the use of US-licensed PCV13 (the active control for safety). In the single-arm study, B7471014, the safety data support the use PCV20 when given as a single catch-up or supplemental (i.e., 5th) pneumococcal conjugate vaccine in individuals 15 months through 17 years of age. No new safety concerns were identified in any of the studies.

Concomitant Vaccination
In study B7471011, the concomitant administration of Pediarix and Hiberix with each of the 3 infant doses of either PCV20 or PCV13 were evaluated 1 month after the third dose. Concomitant administration of single doses of M-M-R II and VARIVAX with the fourth dose of either PCV20 or PCV13 were evaluated 1 month following vaccination. There was no evidence that PCV20, as compared to PCV13, interfered with the antibody responses to these concomitantly administered vaccines.

Pediatric Assessment and Pediatric Research Equity Act
This submission fulfills the Wyeth's PMRs 2, 3, and 4 for the invasive pneumococcal indication identified in the June 10, 2021 approval letter for the original PCV20 BLA (STN 125731). The Pediatric Review Committee (PeRC) at FDA agreed that these PMRs are fulfilled.

This submission also triggered PREA for the new indication of otitis media. Wyeth requested a partial waiver of the pediatric study requirement in individuals from birth through <6 weeks of age for the otitis media indication, because the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. Wyeth also requested a partial waiver of the pediatric study requirement for the otitis media indication in individuals 6 years through 17 years of age, because the necessary studies are impossible or highly impracticable due to the low incidence of acute otitis media in this age group.

The pediatric assessment for the otitis media indication in individuals 6 weeks through 5 years of age consists of data from two previously conducted well-controlled clinical endpoint efficacy studies with PCV7: the Finnish Otitis Media trial and the Northern California Kaiser Permanente trial. These studies supported the effectiveness of PCV13 in children 6 weeks through 5 years of age for the prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, are described in detail in the PCV13 prescribing information, and are included in the PCV20 prescribing information. The pediatric assessment for the otitis media indication also consists of safety data in infants and children 6 weeks through 5 years of age from the three IPD PMR studies noted above.

The PeRC at FDA agreed with Wyeth's Pediatric Study Plan for the otitis media indication, including both partial waiver requests.

Postmarketing Plans
Wyeth's pharmacovigilance plan (PVP) is considered acceptable. A review of the PCV20 postmarketing Vaccine Adverse Event Reporting System (VAERS) data concerning vaccinees of all ages did not identify new safety concerns. As such, the available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy or a safety-related PMR study. Wyeth's pharmacovigilance plan (PVP) addresses Important Identified Risks by performing enhanced pharmacovigilance activities in its Periodic Adverse Experience Report, based on interval and cumulative data. Important Identified Risks include the following: hypersensitivity reaction (including face edema, dyspnea and bronchospasm) in all ages and seizures (including febrile seizures) in young children (i.e., <2 years of age).

Clinical Reviewer Conclusion and Recommendation
The totality of clinical safety and effectiveness data presented in this application support approval of the PCV20 candidate vaccine for 1) active immunization for the prevention of 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 individuals 6 weeks through 17 years of age, and 2) active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in individuals 6 weeks through 5 years of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Subgroup analyses for immunogenicity endpoints are described for study B7471011. 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). Subgroup analyses for immunogenicity endpoints are described for study B7471011. Subgroup analyses for safety endpoints are described the largest infant study (B7471011) and for study B7471014.

Study B7471011 Immunogenicity Subgroup Analyses
Descriptive subgroup analyses by sex and race were conducted for the primary and key secondary immunogenicity endpoints of study B7471011. The observed serotype-specific IgG responses among PCV20 recipients and among PCV13 recipients were generally higher among females compared to males, particularly for the post-dose 4 primary endpoint. The observed serotype-specific IgG responses were generally higher among Black or African American participants compared to White participants for each primary and key secondary endpoint. The numbers of participants in the other race subgroups were too small for meaningful analysis.

Study B7471011 Safety Subgroup Analyses
Descriptive subgroup analyses by sex, race and receipt of concomitant influenza vaccine were conducted for the primary safety endpoints in study B7471011. Rates of solicited local and systemic reactions among PCV20 recipients and among PCV13 recipients were generally similar between females and males. Rates of solicited systemic reaction were generally similar between White and Black or African American participants. Rates of solicited local injection site redness and injection pain were lower among Black or African American participants compared to White participants; whereas rates of injection site swelling were generally higher among Black or African American participants compared to White participants. These trends were not observed in the overall safety population. The numbers of participants in the other race subgroups were too small for meaningful analysis.

Within 7 days after dose 3 and dose 4 of PCV20 and PCV13, rates of solicited local reactions were similar in those who did and did not receive a concomitant influenza vaccine. Within 7 days after dose 4 of PCV20 and PCV13, rates of solicited systemic reactions were similar in those who did and did not receive a concomitant influenza vaccine. Within 7 days after study dose 3 of PCV20 and PCV13, rates of solicited systemic reactions, including fever, were generally higher among participants who received concomitant influenza vaccine compared to participants who did not receive concomitant influenza vaccine. In the subgroup that received influenza vaccine with dose 3, 24.3% and 17.9% of PCV20 and PCV13 recipients reported any fever; in the subgroup that did not receive influenza vaccine with dose 3, 11.0% and 13.1% reported any fever. A similar trend was observed with rates of decreased appetite and irritability after dose 3.

The percentages of participants with unsolicited AEs from Dose 1 to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4 were generally similar across each of the sex, race, and co-administered influenza vaccine subgroups and in the PCV20 and PCV13 study groups within each subgroup.

Study B7471014 Safety Subgroup Analyses
In study B7471014, safety results were generally comparable across sex and race subgroups within each age-based cohort, with no clear or consistent trends.

1.2 Patient Experience Data

Patient experience data were 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 common bacterial cause of IPD, including meningitis and bacteremia, as well as otitis media in children (Gierke 2021). IPD can result in significant morbidity, permanent sequelae, and death. Among children 2 years of age or younger, bacteremia without a known site of infection is the most common invasive clinical presentation of pneumococcal infection, accounting for 40% of invasive disease in this age group (Gierke 2021). With the decline of invasive *Haemophilus influenzae* type b (Hib) disease, *S. pneumoniae* has become the leading cause of bacterial meningitis among children younger than age 5 years in the US (Gierke 2021).

As of 2020, there are 100 identified serotypes of *S. pneumoniae.* Although most *S. pneumoniae* serotypes can cause IPD, only a few serotypes cause most pneumococcal infections (Gierke 2021). The ranking and serotype prevalence differ by patient age group and geographic area (Gierke 2021). According to US multistate surveillance, the incidence of IPD during 2018-2019 was 7.2 per 100,000 children aged <5 years and 1.5 per 100,000 individuals 5-18 years, respectively (Kobayashi 2022). PCV13 serotypes (including serotype 6C[1]) accounted for 21% and 34% of IPD cases in individuals <5 years and 5-18 years, respectively (Kobayashi 2022). Additional serotypes unique to PCV15 caused 15% and 23% of IPD cases in individuals <5 years and 5-18 years, respectively (Kobayashi 2022). Additional serotypes unique to PCV20 accounted for 15% and 13% of IPD cases in individual <5 years and 5-18 years, respectively (Gierke 2023).

1 The CDC includes serotype6C with PCV13 serotypes when presenting pneumococcal epidemiology due to cross protection from 6A antigen.

Among PCV13 serotypes, serotypes 3, 19A and 19F were the most frequently isolated at 46%, 32%, 14%, respectively (Gierke 2023). Following licensure of PCV13, there has been no evidence of an indirect (population-level) impact of PCV13 vaccination on the incidence of serotype 3 IPD in the US or in other countries using PCV13 (Pilishvili 2019).

S. pneumoniae is also a common cause of acute otitis media. It is the second most common cause of acute otitis media (following non-b *Haemophilus influenzae)*, accounting for 15-20% of cases (Wald, 2018). AOM occurs primarily in children <5 years of age. The peak age for AOM in the US is between 6 and 12 months of age.

Children with functional or anatomic asplenia, particularly those with sickle cell disease, and children with immunocompromising conditions are at very high risk for invasive disease (Gierke 2021). Other conditions that increase the risk of IPD in children include chronic heart disease, lung disease (including asthma if treated with high-dose oral corticosteroid therapy), liver disease, CSF leak, and having a cochlear implant (Gierke 2021). Rates are also increased among children of certain racial and ethnic groups, including Alaska Natives, African Americans, and certain American Indian groups (Navajo and White Mountain Apache). The reason for this increased risk by race and ethnicity is not known with certainty but has also been noted for invasive *Haemophilus influenzae* infection (*H. influenzae* types a through f are also encapsulated bacterium) (Gierke 2021). Attendance at a childcare center has also been shown to increase the risk of IPD and acute otitis media 2- or 3-fold among children younger than age 5 years (Gierke 2021).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Available therapy for IPD in individuals 6 weeks through 17 years of age and for otitis media caused by *S. pneumoniae* in individuals 6 weeks through 5 years of age includes antibiotic therapy. However, treatment has been complicated by increased frequency of antibiotic-resistant strains.

2.3 Safety and Efficacy of Pharmacologically Related Products

Three pneumococcal vaccines are licensed and available for use in children in the US. Vaxneuvance™ (Pneumococcal 15-valent Conjugate Vaccine: Merck Sharp & Dohme Corp.; PCV15) is indicated for the prevention of invasive disease caused by serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F in children 6 weeks through 17 years of age. PCV13 (PCV13) is indicated for the prevention of invasive disease caused by serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in children 6 weeks through 17 years of age and for the prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in children 6 weeks through 5 years of age. Pneumovax® 23 (Pneumococcal Vaccine, Polyvalent: Merck Sharp & Dohme Corp.; PPSV23), a vaccine comprised of unconjugated purified polysaccharides from 23 pneumococcal serotypes, is approved for the prevention of pneumococcal disease in persons ≥2 years of age who are at increased risk for pneumococcal disease. The safety and effectiveness of each vaccine are described in the corresponding prescribing information.

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

PCV20 was licensed for use in adults ≥18 years of age in the US in June of 2021. The safety and immunogenicity of PCV20 in adults are described in the prescribing information

(PCV20 Prescribing Information) and the BLA clinical review memorandum. At the time of this submission, PCV20 (known as APEXXNAR in the European Union) has not been approved for use in individuals <18 years of age outside of the US.

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

Regulatory Pathway to Licensure

IPD Indication in Individuals 6 weeks through 15 Months of Age
PCV20 effectiveness against IPD in individuals 6 weeks through 15 months of age was demonstrated in a single study (B7471011) based on comparisons of serotype-specific antibody responses at 1 month after Dose 3 and 1 month after Dose 4 of PCV20 to the antibody responses after vaccination with PCV13. Antibody responses elicited by PCV20 and PCV13 in this age group were measured using a serotype-specific multiplex direct-binding Luminex® immunoassay (dLIA), designed to determine the concentration of serotype-specific polysaccharide-binding IgG antibodies, and OPA assays to measure serotype-specific functional OPA titers for the 20 pneumococcal serotypes of PCV20. A serotype-specific IgG antibody concentration corresponding to ≥0.35 µg/mL using the World Health Organization (WHO) enzyme linked immunosorbent assay (ELISA) has been used as the threshold value for the clinical evaluation of pneumococcal conjugate vaccines when measured one month after Dose 3 of the 4-dose immunization series. The dLIA, used to measure the IgG antibody concentration, was bridged to the WHO ELISA to establish dLIA specific threshold values for each vaccine serotype that correspond to the established ≥0.35 µg/mL WHO ELISA threshold value.

During an end-of-Phase 2 meeting, Wyeth and CBER reached agreement on study endpoints and criteria for demonstrating immunologic noninferiority. The agreed upon co-primary pneumococcal immunogenicity endpoints in study B7471011 included the following:

- The proportion of participants achieving the predefined serum serotype-specific IgG antibody concentration at one month after the third dose.
    - The predefined IgG concentration was ≥0.35 µg/mL for all serotypes except for serotypes 5, 6B, 12F, and 19A which were ≥0.23 µg/mL, ≥0.10 µg/mL, ≥0.69 µg/mL and ≥0.12 µg/mL respectively.
- Pneumococcal serotype-specific IgG antibody GMC at one month after the fourth dose

Other agreed upon pneumococcal immunogenicity endpoints included the following:

- IgG antibody GMCs at one month after the dose as a key secondary endpoint.
- OPA GMTs as an exploratory endpoint; there is no standardized OPA assay for use in pediatric populations.

For each of the 13 matched serotypes, IgG responses in the PCV20 group were to be compared with the corresponding response in the PCV13 group. For the 7 additional serotypes (serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F), IgG responses in the PCV20 group were to be compared with the lowest response among the 13 matched vaccine serotypes excluding serotype 3 in the PCV13 group.

Agreement was also reached regarding the primary and secondary concomitant vaccine antigen study endpoints and pre-specified criteria for demonstrating lack of immunologic interference.

IPD Indication in Individuals 15 Months through 17 Years of Age
During the end-of-Phase 2 meeting, CBER agreed to Wyeth's proposal that the effectiveness of PCV20 catch-up vaccination(s) in previously unvaccinated individuals 7 months of age and older and in previously vaccinated or incompletely vaccinated individuals 15 months of age through 17 years of age can be extrapolated based on the demonstration of vaccine effectiveness in individuals 6 weeks through 15 months of age. Based on historical data with PCV13 and PCV7, it was anticipated that the IgG antibody responses to vaccination in healthy individuals 15 months through 17 years of age would generally meet or exceed the corresponding responses in healthy infants and toddlers; in addition, there were no clear differences in disease pathogenesis and course in these two pediatric sub-populations. The proposed PCV20 catch-up vaccination schedules were also supported by evidence from clinical studies of catch-up vaccination with PCV13 and PCV7.

Otitis Media Indication
CBER did not consider immunogenicity data from study B7471011 to support the proposed otitis media indication. There is no consensus regarding serologic criteria for assessing effectiveness against otitis media, as the anticapsular antibody concentrations that prevent otitis media are likely to be higher than antibody concentrations needed to prevent IPD, and an antibody concentration that confers protection against pneumococcal otitis media has not been determined (Siber 2007).

CBER agreed that the assessment of PCV20 effectiveness against otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in individuals 6 weeks through 5 years of age would consist of data from two previously conducted well-controlled clinical endpoint efficacy studies with PCV7: the Finnish Otitis Media trial and the Northern California Kaiser Permanente trial. These studies supported the effectiveness of PCV13 in children 6 weeks through 5 years of age for the prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, are described in detail in the PCV13 prescribing information, and are included in the PCV20 prescribing information.

The Finnish Otitis Media (FinOM) trial was a randomized, double-blind trial in which 1,622 infants were equally randomized to receive either PCV7 or a control vaccine Recombivax HB (Hepatitis B vaccine (Recombinant) [HepB]) at 2, 4, 6, and 12-15 months of age. Tympanocentesis was performed on children diagnosed with acute otitis media (AOM) and the middle-ear fluid was cultured. If *S. pneumoniae* was isolated, serotyping was performed. The vaccine efficacy against AOM episodes due to vaccine serotypes in the per-protocol population (the primary endpoint) was 57% (95% CI: 44%, 67%).

In the Northern California Kaiser Permanente trial, the efficacy of PCV7 against otitis media was assessed from the beginning of the trial in October 1995 through April 1998. The otitis media analysis included 34,146 infants randomized to receive either PCV7 (N=17,070), or the control vaccine (N=17,076), at 2, 4, 6, and 12-15 months of age. In this trial, no routine tympanocentesis was performed, and no standard definition of otitis media was used by study physicians. The primary otitis media endpoint was efficacy against all otitis media episodes in the per-protocol population. Vaccine efficacy for this primary endpoint was 7% (95% CI: 4%, 10%).

Pediatric Safety Database
During the end-of-Phase 2 meeting, CBER agreed with Wyeth's proposed pediatric safety database supporting licensure of PCV20 in individuals 6 weeks of age through 17 years of age. CBER also agreed with the following:

- safety data from studies B7471011 and B7471013 would support the safety of the proposed catch-up vaccination schedules in individuals 7 months of age and older with no prior pneumococcal vaccination history.
- Safety data from study B7471014 would support the safety of proposed catch-up/supplemental vaccination with a single dose of PCV20 in individuals 15 months of age and older regardless of prior pneumococcal vaccination history (i.e., including individuals previously immunized with ≥3 doses of PCV13).

Major Regulatory Activity
The timeline below includes a list of major regulatory activity associated with the submission of this sBLA. Wyeth did not submit a request for a pre-sBLA meeting.

- Ma, 24, 2017: Fast Track Designation granted
- February 6, 2020: End-of-Phase 2 meeting
- August 14, 2020: Breakthrough Therapy Designation granted for IPD indication
- January 5, 2023: Priority Review Classification

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission of this sBLA 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 four clinical studies included in this sBLA 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).

Bioresearch Monitoring (BIMO) inspections were issued for four clinical study sites that participated in the conduct of B7471011. The inspections did not reveal substantive issues that impact the data submitted in this application. Please refer to Kanaeko R. Ravenell's review memo for more details.

3.3 Financial Disclosures

Covered clinical studies (B7471003, B7471011, B7471013, and B7471014):
Was a list of clinical investigators provided? ☒ Yes ☐ No
Total number of investigators identified: 1,548
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): 9

Covered clinical studies (B7471003, B7471011, B7471013, and B7471014):
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: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 3 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 (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 9 Is an attachment provided with the reason? ☒ Yes ☐ No (Request explanation from applicant)

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Manufacturing process development, in-process testing, release and stability testing were reviewed with the initial BLA submission and were found to be adequate to support licensure.

4.2 Assay Validation

The CBER clinical serologic assay reviewers confirmed that the validation data support the adequacy of the following assays used in the evaluation of primary, secondary and exploratory study endpoints in study B7471011:

- (b) (4) plex direct-binding Luminex immunoassays (dLIAs)
- Microcolony opsonophagocytic activity (OPA) assay
- Hib ELISA
- (b) (4) assay provided by (b) (4)
- (b) (4) measles, mumps, rubella II and VZV (MMRV) IgG assays
- Poliovirus neutralization assay for serotypes 1, 2, and 3
- Diphtheria, Tetanus, Pertussis (b) (4) Assay (DTP(b) (4) IgG assay)

Please refer to the review memos by Dr. Mustafa Akkoyunlu (Hib, (b) (4) -plex dLIAs, pneumococcal mcOPA), Dr. Marion Major (Hepatitis B), Dr. Shuang Tang (MMR and VZV), and Dr. Diana Kouiavskaia (poliovirus) for more details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Protection against pneumococcal disease is conferred mainly by antibodies (immunoglobulin G [IgG] directed against capsular polysaccharides) and OPA killing of *S. pneumoniae*. PCV20 induces IgG antibodies and OPA against the 20 vaccine serotypes.

4.5 Statistical

The CBER statistical reviewer concluded that the datasets and the analyses provided in this application were adequate to assess the safety and effectiveness of PCV20 for use in individuals 6 weeks through 17 years of age. Please refer to Dr. Ruoxuan Xiang's review memos (one covering serologic assay data and one covering clinical data) for more details.

4.6 Pharmacovigilance

The pharmacovigilance reviewer considers Wyeth's PVP acceptable. Based on a review of PCV20 clinical trial data and postmarketing VAERS data concerning vaccinees of all ages, the CBER Epidemiology/Pharmacovigilance reviewer did not identify any safety concerns or potential risk for PCV20 use in individuals 6 weeks through 17 years of age that would require a post-marketing study or a Risk Evaluation and Mitigation Strategy. Wyeth's PVP plan addresses Important Identified Risks by performing enhanced pharmacovigilance activities in its Periodic Adverse Experience Report, based on interval and cumulative data. Important Identified Risks include the following: hypersensitivity reaction (including face edema, dyspnea and bronchospasm) in all ages and seizures (including febrile seizures) in young children (i.e., <2 years of age). Please refer to Dr. Phillip Blanc's review memo for more details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This review covers data submitted from 4 clinical trials evaluating PCV20 in pediatric populations aged 6 weeks through 17 years of age (Table 1).

1) Study B7471011 was a randomized, double-blind study conducted in the US evaluating the safety and immunogenicity (effectiveness) of a 4-dose series of PCV20 when administered at 2, 4, 6 and 12-15 months of age compared to PCV13. Participants also received Pediarix (DTaP-HBV-IPV) and Hiberix concomitantly at 2, 4, and 6 months of age and M-M-R_{II} and Varivax concomitantly at 12-15 months of age as study vaccination.
2) Study B7471013 was a randomized, double-blind study conducted in the US, Canada, South America and Europe evaluating the safety of a 4-dose series of PCV20 when administered at 2, 4, 6 and 12-15 months of age compared to PCV13.
3) B7471014 was an open-label, single-arm study conducted in the US evaluating a single dose of PCV20 in individuals ≥15 months through <5 years of age with at least 3 prior doses of PCV13 and individuals ≥5 through <18 years of age regardless of prior pneumococcal conjugate vaccine vaccination history. For purposes of US-licensure, this study supported the safety of a single catch-up or supplemental dose of PCV20 in this age group. CBER agreed that effectiveness of PCV20 in this age group would be supported by the demonstration of effectiveness of PCV20 in study B7471011.
4) Study B7471003 was a randomized, double-blind study conducted in the US to describe the safety and immunogenicity of a 4-dose series of PCV20 when given at 2, 4, 6, and 12-15 months of age compared to PCV13.

An integrated summary of safety, consisting of safety data from each of the four clinical studies submitted to this BLA, was also evaluated.

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

The following modules of the sBLA 125731/189.0 were reviewed:

- m1.3 Administrative Information
- m1.6 Correspondence Regarding Meetings
- 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 sBLA are listed below by amendment number:

- Am 2: Response to Nov 28, 2022 PVP Information request (IR) pertaining to the reason for which PCV13 important identified risks were not included in the PVP submitted for PCV20.
- Am 3: Response to Dec 2, 2022 clinical IR for cross reference to PCV7 otitis media efficacy data, summary of SAEs (including narratives) from non-US studies B7471012 and B7471016, and the total number of pediatric participants globally vaccinated with PCV20 in studies B7471011, B7471012, B747103 and B7471014.
- Am 5: Response to Dec 15, 2022 safety dataset IRs
- Am 6: Response to Dec 15, 2022 clinical IR regarding missing Pediatric Administrative Information (submitted to Module 1.9)
- Am 9: Follow-up correspondence for the updated AE datasets, tables and listings that have been updated to remove any investigator-assessed events that represent solicited reactions during the 7 day active monitoring period.
- Am 11: Additional narratives in response to Dec 2, 2022 clinical IR and revised draft US Prescribing Information (USPI) in response to Dec 15, 2022 safety dataset IRs
- Am 18: Additional narratives from studies B7471012 and B7471016 in response to Dec 2, 2022 clinical IR and updated USPIs in response to Dec 15, 2022 safety dataset IRs
- Am 20: Follow-up response to Feb 17, 2023 IR regarding the validation study for the WHO ELISA used in the bridging of [(b) (4)] plex dLIA
- Am 22: Response to Mar 13, 2023 IR to revise pre-specified immunogenicity analyses for serotype 12F using a dLIA cutoff of 0.69 µg/mL.
- Am 23: Response to Mar 16, 2023 IR to update the CSR for studies B7471011 and B747104 as applicable as well as draft labeling to reflect the revised dLIA specific cut-off of 0.69 µg/mL for serotype 12F calculations when evaluating the % of participants with pre-defined IgG concentrations.
- Am 24: Cross reference to PCV7 IPD efficacy data described in PCV20 USPI
- Am 27: Response to first round of labeling comments dated Mar 22, 2023
- Am 33: Response to clinical IR regarding solicited safety data in study B7471013
- Am 34: Revised Serotype 12F data

5.3 Table of Studies/Clinical Trials

Table 1. Clinical Studies Submitted in Support of Effectiveness and Safety Determinations for Prevnar 20 (PCV20) in Pediatric Populations 6 Weeks Through 17 Years of Age, Total N=4304 (PCV20: N=2804; Prevnar 13 (PCV13): N=1500)

Study NCT # Country	**Study Description**	**Study Population at Enrollment**	**Study Vaccines and Schedule**	**Number Completing Vaccine Schedule**
B7471011 NCT04382326 US, PR	Phase 3, randomized, double-blind, active controlled study evaluating the safety and immunogenicity of a 4-dose series of PCV20. Participants followed for safety through 6 months after the last study vaccination	Infants 6 through 14 weeks of age	• PCV20 and PCV13 at 2, 4, 6, and 12-15 months of age • Pediarix and Hiberix at 2, 4, and 6 months of age • M-M-R-II and Varivax at 12-15 months of age	• PCV20: 853 • PCV13: 844
B7471013 NCT04379713 North & South America, Europe	Phase 3, randomized, double-blind, active controlled study evaluating the safety of a 4-dose series of PCV20	Infants 6 through 14 weeks of age	PCV20 and PCV13 at 2, 4, 6, and 12-15 months of age Concomitant vaccinations permitted per national/ local recommendations	• PCV20: 923 (includes 486 US participants) • PCV13: 462
B7471014 NCT04642079 US	Phase 3, open-label, single-arm descriptive safety and immunogenicity[a] study in individuals ≥15 months through 17 years of age with or without prior pneumococcal vaccination history	• Individuals ≥15 months to <5 years of age with ≥3 prior PCV13 doses (last dose >2 months prior) • Individuals ≥5 years to <17 years regardless of prior pneumococcal vaccination history	Single dose of PCV20	PCV20: 831
B7471003 NCT03512288 US	Phase 2, randomized, double-blind, active controlled, study describing the safety and immunogenicity of a 4-dose series of PCV20	Infants 6 through 14 weeks of age	• PCV20 and PCV13 at 2, 4, 6, and 12-15 months of age • Pediarix at 2, 4, and 6 months	• PCV20: 197 • PCV13: 194

Source: STN 125731/189, Module 5.2, Tabular Listing of al Clinical Studies
Abbreviations: US: United States; PR: Puerto Rico; NCT: National Clinical Trial number from ClinicalTrials.gov. PCV20: Prevnar 20; PCV13: Prevnar 13.
a. Study B7471014 included immunogenicity assessments to meet European regulatory requirements and are therefore not included in this review.

5.5 Literature Reviewed

Choi EH, F Zhang, YJ Lu, R Malley, 2016, Capsular Polysaccharide (CPS) Release by Serotype 3 Pneumococcal Strains Reduces the Protective Effect of Anti-Type 3 CPS Antibodies, ClinVaccine Immunol, 23(2):162-167.

Gierke, R, AP Wodi, and M Kobayashi, 2021, The Pink Book Pneumococcal Disease. Available at: https://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html#pneumoniae.

Gierke R, 2023. Current Epidemiology of Pediatric Pneumococcal Disease, United States (ACIP Presentation). https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-22/Pneumococcal-02-Gierke-508.pdf

Kobayashi, M, JL Farrar, R Gierke, AJ Leidner, D Campos-Outcalt, RL Morgan, SS Long, KA Poehling, AL Cohen, 2022, Use of 15-Valent Pneumococcal Conjugate Vaccine Among US Children: Updated Recommendations of the Advisory Committee on Immunization Practices – United States, Morbidity and Mortality Weekly Report, 71(37):1174-1181.

Pilishvili, T, 2019, 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Effects on Disease Caused by Serotype 3 (ACIP Presentation). Available at: https://stacks.cdc.gov/view/cdc/78091

Prevnar 13 Prescribing Information, Wyeth Pharmaceuticals, accessed on April 22, 2023, https://www.fda.gov/media/107657/download

Prevnar 20 prescribing information, Wyeth Pharmaceuticals, Inc, accessed April 21, 2023, PREVNAR 20 | FDA

Siber GR, I Chang, S Baker, P Fernsten, KL O'Brien, M Santosham, KP Klugman, SA Madhi, P Paradiso, R Kohberger, 2007, Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies, Vaccine,25(19):3816-3826.

Vaxneuvance Prescribing Information, Merck & Co., Inc., accessed April 22, 2023, https://www.fda.gov/media/150819/download

Wald et al. Antibiotic Recommendations for Acute Otitis Media and Acute Bacterial Sinusitis: Conundrum No More. Pediatr Infect Dis J. 2018;37(12):1255-1257. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6151174/pdf/nihms950710.pdf.

WHO Weekly Epidemiological Record No.8, February 22, 2019, 85-104. Available at: https://www.who.int/publications/i/item/10665-310968

6. Discussion of Individual Studies/Clinical Trials

6.1 Study B7471011 (NCT04382326)

Study Title: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine in Healthy Infants

This study was initiated on May 20, 2020 and was completed (last patient last visit) on September 2, 2022.

Study B7471011 was the main study to support the safety and immunogenicity of PCV20 for the prevention of vaccine-type IPD in individuals 6 weeks through 15 months of age. Concomitant administration of PCV20 with Pediarix (DTaP-HBV-IPV) and Hiberix at 2, 4, and 6 months of age and with M-M-R-II and Varivax at 12-15 months of age was also evaluated in study B7471011.

6.1.1 Objectives, Endpoints, and Statistical Criteria

Primary Safety Objective

To describe the safety profile of PCV20 in study participants receiving at least 1 dose of investigational product and having safety data reported after any vaccination.

- Endpoints:
    1. Percentage of participants reporting prompted local reactions within 7 days after each vaccination (injection site redness, swelling, and pain)
    2. Percentage of participants reporting prompted systemic events within 7 days after each vaccination (fever, decreased appetite, irritability, drowsiness/increased sleep, and use of antipyretic/pain medication)
    3. Percentage of participants reporting unsolicited AEs from dose 1 to 1-month post-dose 3 (PD3) and from dose 4 to 1-month post-dose 4 (PD4)
    4. Percentage of participants reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) from dose 1 through 6 months post-dose 4

Primary Pneumococcal Immunogenicity Objectives

1. To demonstrate that the IgG antibody response to each of the 13 matched pneumococcal serotypes at one month after the third dose of PCV20 is noninferior to the corresponding antibody response one month after the third dose of PCV13.
    a. Primary endpoint: percentage of participants achieving the predefined pneumococcal serotype-specific IgG concentrations one month after the third dose. The pre-defined IgG concentration was ≥0.35 µg/mL for 10 of the 13 matched serotypes (1, 3, 4, 6A, 7F, 9V, 14, 18C, 19F and 23F); the predefined level was ≥0.23 µg/mL, ≥0.10 µg/mL, and ≥0.12 µg/mL for serotypes 5, 6B and 19A, respectively.
    b. -10% noninferiority criterion: Lower limit of the 2-sided 95% CI for the difference in proportions (*p*PCV20 – *p*PCV13) > -0.1, where *p* is the percentage of participants with antibody levels ≥ the predefined serotype-specific IgG concentration.

2. To demonstrate that the IgG antibody response to each of the 7 additional pneumococcal serotypes one month after the third dose of PCV20 is noninferior to the lowest response among the 13 matched serotypes at 1 month after the third dose of PCV13. If the lowest response was to serotype 3, the next lowest response in the PCV13 group was used in the comparison.
    a. Primary endpoint: percentage of participants achieving the predefined pneumococcal serotype-specific IgG concentrations at one month after the third dose; the predefined level was ≥0.35 µg/mL for 6 of the 7 additional serotypes (8, 10A, 11A, 15B, 22F, and 33F); the predefined level was ≥0.69 µg/mL for serotype 12F.
    b. -10% non-inferiority criterion: Lower limit of the 2-sided 95% CI for the difference in proportions (*p*PCV20 – *p*PCV13) > -0.1, where *p* is the percentage of participants with antibody levels ≥ the predefined serotype-specific IgG concentration.

3. To demonstrate that the antibody response to each of the 13 matched pneumococcal serotypes one month after the fourth dose of PCV20 is non-inferior to the corresponding antibody response after the fourth dose of PCV13
    a. Primary endpoint: pneumococcal serotype-specific IgG antibody GMC at one month after the fourth dose
    b. 2-fold noninferiority criterion: Lower limit of the 2-sided 95% CI for the IgG GMC ratio (PCV20-PCV13) > 0.5.

4. To demonstrate that the antibody response to each of the 7 additional pneumococcal serotypes one month after the fourth dose of PCV20 is non-inferior to the lowest response among the 13 matched serotypes at 1 month after the third dose of PCV13. If the lowest IgG GMC in the PCV13 group was to serotype 3, the next lowest IgG GMC in the PCV13 group was used in the comparison.
    a. Primary endpoint: pneumococcal serotype-specific IgG antibody GMC at one month after the fourth dose
    b. 2-fold noninferiority criterion: Lower limit of the 2-sided 95% CI for the IgG GMC ratio (PCV20-PCV13) > 0.5.

    Reviewer Comment: *IPD surveillance data suggest that there is little to no population-level impact of PCV13 on serotype 3 IPD in all age groups in the US and in countries using PCV13. Serotype 3 is known to have unique genetic, phenotypic, physiologic characteristics and various mechanisms that may explain reduced PCV13 effectiveness against this serotype (Choi 2016; WHO 2019; Pilishvili 2019). Since this serotype behaves differently from other PCV13 vaccine serotypes, IgG results to vaccine serotype 3 were not used as the comparator in the noninferiority assessments for the 7 additional vaccine serotypes.*

Key Secondary Pneumococcal Immunogenicity Objectives

1. To demonstrate that the antibody response to each of the 13 matched pneumococcal serotypes one month after the third dose of PCV20 is noninferior to the corresponding antibody response after the third dose of PCV13
    a. Secondary endpoint: pneumococcal serotype-specific IgG antibody GMC at one month after the fourth dose
    b. 2-fold noninferiority criterion: Lower limit of the 2-sided 95% CI for the IgG GMC ratio (PCV20-PCV13) > 0.5.

2. To demonstrate that the antibody response to each of the 7 additional pneumococcal serotypes one month after the 3rd dose of PCV20 is non-inferior to the lowest response among the 13 serotypes contained in PCV13. If the lowest GMC in the PCV13 group is from serotype 3, the next lowest GMC in the PCV13 group was used in the comparison.
    a. Secondary endpoint: pneumococcal serotype-specific IgG antibody GMC at one month after the fourth dose
    b. 2-fold noninferiority criterion (1 month after the 4th vaccination): Lower limit of the 2-sided 95% CI for the IgG GMC ratio (PCV20 group/PCV13 group) > 0.5.

Primary Concomitant Immunogenicity Objective

1. To demonstrate that, at one-month after the third dose, the antibody responses to concomitant vaccine antigens [i.e., diphtheria, tetanus, pertussis, Hepatitis B, and Poliomyelitis (types 1, 2 and 3) antigens contained in DTaP-HBV-IPV vaccine and to polyribosyl-ribitol-phosphate (PRP) antigen contained in Hib vaccine] when co-administered

with PCV20 are noninferior to corresponding antibody responses when DTaP-HBV-IPV and Hib vaccines are administered concomitantly with PCV13.

a. Primary endpoints:
   i. Percentage of participants achieving an anti-diphtheria toxoid antibody concentration ≥0.1 IU/mL at 1 month after the third dose as measured by a multiplexed Luminex immunoassay
   ii. Percentage of participants achieving an anti-tetanus toxoid antibody concentration ≥0.1 IU/mL at 1 month after the third dose as measured by a multiplexed Luminex immunoassay
   iii. Percentage of participants achieving an anti-acellular pertussis (PT, FHA and PRN antigens) antibody concentration ≥ the observed anti-pertussis antibody concentration achieved by 95% of PCV13 recipients at 1 month after the third dose as measured by a multiplex Luminex immunoassay
   iv. Percentage of participants achieving an anti-Hepatitis B antibody concentration ≥10 mIU/mL at 1 month after the third dose as measured by a (b) (4)
   v. Percentage of participants achieving an anti-poliomyelitis neutralizing antibody titer ≥1:8 to poliovirus types 1, 2, and 3 at one month after the third dose as measured by an antibody (b) (4) test
   vi. Percentage of participants achieving an anti-PRP antibody response ≥0.15 µg/mL at one month after the third dose as measured by an IgG ELISA

b. -10% noninferiority criterion: the lower limit of the 2-sided 95% CI for the difference in proportions (*p*PCV20 group – *p*PCV13 group) > -0.1, where *p* is the percentage of participants with antibody levels ≥ the pre-specified level for each concomitant antigen.

Secondary Concomitant Immunogenicity Objective

1. To demonstrate, at one-month after the fourth dose, the antibody responses to MMR and Varicella vaccine antigens, when co-administered with PCV20 are noninferior to the corresponding antibody responses when MMR and Varicella vaccines are administered concomitantly with PCV13. Responses to the following antigens in MMR and Varicella vaccine were assessed: measles, mumps, rubella, and varicella.
   a. Secondary endpoint: Antibody GMCs to measles, mumps, rubella and varicella virus antigens at one month after the fourth dose as measured by a multiplex Luminex immunoassay
   b. 2-fold noninferiority criterion: the lower limit of the 2-sided 95% CI for the antibody GMC ratio (PCV20-PCV13) is > 0.5 for each concomitant vaccine antigen.

2. To further describe the immune responses induced to the PRP antigen at one month after the third dose of Hib vaccine when given with PCV20 versus PCV13.
   a. Secondary endpoint: Percentage of participants achieving an alternative pre-specified anti-PRP antibody response ≥1.0 µg/mL at one month after the third dose as measured by an IgG ELISA
   b. Difference in percentages of participants achieving the alternative prespecified antibody levels to Hib between the PCV20 and PCV13 groups at one month after dose 3.

   Reviewer Comment: Because the dLIA is biased relative to the WHO ELISA at the low end of the assays, the dLIA is not considered reliable for evaluating fold increases in IgG concentrations in clinical studies. Please refer to Dr. Akkoyunlu's review memo for more information.

6.1.2 Design Overview

This is a Phase 3, multicenter, randomized, double-blind, active-controlled study conducted in the US. Approximately 2,000 infants ≥42 days to ≤98 days of age were to be randomized (1:1) to receive either PCV20 or PCV13 at 2, 4, and 6 months of age (Doses 1-3) and 12-15 months of age (Dose 4). Other routine pediatric vaccines administered as part of this study include DTaP-HBV-IPV (Pediarix), *Haemophilus influenzae* type b, MMR, and Varicella vaccines. Immunogenicity assessments were made at 1 month after dose 3, prior to dose 4 and 1 month after dose 4. Standard safety monitoring was performed through 6 months after the last study vaccination. This study included an external data monitoring committee.

6.1.3 Population

Participants were eligible for inclusion in the study if all of the following inclusion criteria were met:

1. Male or female born at >36 weeks of gestation and ≥42 days to ≤98 days of age at the time of consent
2. Healthy as determined by clinical assessment, including medical history
3. Parent(s)/legal guardian(s) is capable of giving signed informed consent, is willing and able to comply with all scheduled visits, treatment plan and other study procedures, and can be contacted by telephone during study participation
4. Available for duration of the study

Participants were excluded from enrollment if any of the following exclusion criteria were met:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of investigational product or any diphtheria toxoid-containing vaccine
2. Significant neurological disorder or history of seizure including febrile seizure or significant stable or evolving disorders
3. Major known congenital malformation or serious chronic disorder.
4. History of microbiologically proven invasive disease caused by *S pneumoniae*.
5. Known or suspected immunodeficiency (congenital or acquired).
6. Any contraindication to intramuscular injection.
7. Congenital, functional, or surgical asplenia.
8. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results
9. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.
10. Prior receipt of diphtheria, tetanus, pertussis, poliomyelitis, and/or Hib vaccine.
11. Previous receipt of >1 dose of hepatitis B vaccine; or receipt of a single hepatitis B vaccine dose administered at >30 days old.
12. Currently immunosuppressive therapy or planned receipt through the last blood draw. If systemic corticosteroids have been administered <14 days for treatment of an acute illness, participants should not be enrolled until corticosteroid therapy has been discontinued for at least 28 days.
13. Receipt of blood/plasma products or immunoglobulins since birth or planned receipt through the last planned blood draw
14. Participation in other studies involving investigational drugs, vaccines, or devices within 28 days prior to study entry and/or during study participation or intrauterine exposure to investigational vaccines
15. Recent febrile (temperature ≥38.0°C) or other acute illness within 48 hours of vaccination.

16. Receipt of any inactivated or otherwise non-live vaccine within 14 days or any live vaccine within 28 days before study vaccination (except influenza vaccine which may be given at any time during influenza season and permitted concomitant vaccines on the same day as study vaccinations).

6.1.4 Study Treatments or Agents Mandated by the Protocol

PCV20: 20-valent pneumococcal conjugate vaccine manufactured by Wyeth Pharmaceuticals

- Dose: 0.5 mL administered IM
- Schedule: study visits at 2, 4, 6 and 12 through 15 months of age
- Composition: saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F 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 0.5mL dose. The vaccine contains (b) (4) succinate buffer, (b) (4) sodium chloride, (b) (4) polysorbate 80, 0.125 mg aluminum as aluminum phosphate, and ~ 51 µg CRM_{197} per 0.5mL dose.
- Presentation: white suspension supplied as pre-filled syringe
- Vendor/manufacturer lot numbers: CL3157 and DW1636.

PCV13: 13-valent pneumococcal conjugate vaccine manufactured by Wyeth Pharmaceuticals

- Dose: 0.5 mL administered IM
- Schedule: study visits at 2, 4, 6, and 12 through 15 months of age
- Composition: 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 0.5mL dose. The vaccine contains (b) (4) succinate buffer, (b) (4) sodium chloride, (b) (4) polysorbate 80, 0.125 mg aluminum as aluminum phosphate and (b) (4) CRM_{197}, per 0.5mL dose.
- Presentation: white suspension supplied in pre-filled syringe
- Vendor/manufacturer lot numbers: CL3161 and DN4736.

Pediarix: Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (Recombinant) and inactivated poliovirus vaccine manufactured by GlaxoSmithKline Biologicals

- Dose: 0.5 mL administered IM
- Schedule: study visits at 2, 4, and 6 months of age
- Composition: 25 Lf of diphtheria (b) (4) toxoid, 10 Lf of tetanus toxoid, 25 µg of inactivated pertussis toxin (PT), 25 µg of (b) (4) filamentous hemagglutinin (FHA), 8 µg of pertactin (69 kiloDalton outer membrane protein), (b) (4) 10 µg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 (b) (4) poliovirus (MEF-1), 32 DU of Type 3 poliovirus (Saukett), and not more than (b) (4) aluminum.
- Presentation: turbid, white suspension supplied in pre-filled syringe
- Vendor manufacturer lot numbers: F4H92

Hiberix: Haemophilus b conjugate vaccine (Tetanus Toxoid Conjugate) manufactured by GlaxoSmithKline Biologicals

- Dose: 0.5 mL administered IM
- Schedule: study visits at 2, 4, and 6 months of age
- Composition: 10 µg of purified Haemophilus b capsular PRP conjugated to approximately 25 µg of tetanus toxoid
- Presentation: solution supplied as a vial of lyophilized vaccine to be reconstituted with the accompanying vial of saline diluent.

- Vendor manufacturer lot numbers: G4XX7

M-M-R_{II}: Measles, mumps and rubella virus vaccine live manufactured by Merck Sharp & Dohme Corp.

- Dose: 0.5 mL administered IM
- Schedule: single dose at 12 through 15 months of age
- Composition: not less than 3.0 $\log_{10}$ $TCID_{50}$ (tissue culture infectious doses) of measles virus; 4.1 $\log_{10}$ $TCID_{50}$ of mumps virus; and 3.0 $\log_{10}$ $TCID_{50}$ of rubella virus.
- Presentation: suspension supplied as a lyophilized vaccine to be reconstituted using accompanying sterile diluent
- Vendor manufacturer lot numbers: T028935

Varivax: Varicella virus vaccine live manufactured by Merck Sharp & Dohme Corp.

- Dose: 0.5 mL administered IM
- Schedule: single dose at 12 through 15 months of age
- Composition: minimum of 1350 plaque-forming units (PFU) of Oka/Merck varicella virus when reconstituted and stored at room temperature for a maximum of 30 minutes.
- Presentation: suspension supplied as a lyophilized vaccine to be reconstituted using the accompanying sterile diluent
- Vendor manufacturer lot numbers: T025945

6.1.6 Sites and Centers

Study B7471011 was conducted at a total of 107 sites in the US and Puerto Rico.

6.1.7 Surveillance/Monitoring

Safety Monitoring

Safety monitoring in study B7471011 include the following:

1. Immediate adverse reactions within 30 minutes after each study vaccination
2. Solicited[2] local reactions through 7 days[3] after each study vaccination (injection site erythema, edema and pain),
3. Solicited systemic adverse reactions and use of antipyretic/pain medication through 7 days after each study vaccination (decreased appetite, drowsiness, irritability, and fever),
4. Unsolicited adverse events through 1 month after each study vaccination, and
5. SAEs and newly diagnosed chronic medical conditions through 6 months after the last study vaccination.

Solicited local reactions and solicited systemic adverse reactions were recorded daily by parents/guardians using an electronic diary, and these reactions were graded according to a pre-specified toxicity grading scale (see Table 12 and Table 13 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 adverse events in the case report form. The need for an unscheduled visit was considered for participants with a ≥ grade 3 injection site reaction or any grade 4 systemic reaction within 7 days post-vaccination.

[2] Parents/legal guardians were given a digital thermometer, a measuring device and an electronic diary (e-diary) to record prompted local reactions and systemic adverse events daily. 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.

[3] Study days 1 through 7 (day 1 = day of vaccination)

The intensity of AEs and SAEs were assigned to one of three categories:

- Mild: event is easily tolerated, causing minimal discomfort and not interfering with everyday activities
- Moderate: event causes sufficient discomfort and interferes with normal everyday activities
- Severe: event prevents normal everyday activities.

A SAE is one that led to death or serious deterioration in the health of the participant that either resulted in:

- A life-threatening illness or injury,
- Permanent impairment of a body structure or function,
- Inpatient or prolonged hospitalization,
- Medial or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or function.

Immunogenicity Monitoring

Blood samples were collected from all participants 1 month after dose 3 (visit 4), prior to dose 4 on the day of dose 4 administration (visit 5), and 1 month after dose 4 (visit 6) for measurement of serotype-specific IgG antibody concentrations and OPA antibody titers to each of the 20 serotypes contained in PCV20. IgG concentrations for cross-reactive serotypes 15C and 6C and OPA titers for 15C were also measured in random subsets of participants.

Antibody responses to concomitant vaccine antigens were assayed in subset of participants randomly selected by an independent unblinded statistician to ensure equal representation of both vaccine groups. For diphtheria, tetanus, pertussis, hepatitis B, and polio antigen response testing, the subset was limited to the participants who received the same lot for all 3 doses of PEDIARIX. For Hib testing, the subset was limited to participants who received the same lot for all 3 doses of HIBERIX.

6.1.8 Endpoints and Criteria for Study Success

Please see Section 6.1.1 of this clinical review.

6.1.9 Statistical Considerations & Statistical Analysis Plan

For the primary pneumococcal immunogenicity assessments, noninferiority was assessed with an alpha level of 0.05 (2-sided). No adjustments were made for multiplicity, because noninferiority was to be demonstrated only if criteria were met for each of the 20 pneumococcal antigens at each timepoint (1 month after dose 3 and 1 month after dose 4).

For the primary concomitant immunogenicity assessments, noninferiority was assessed with an alpha level of 0.05 (2-sided). No adjustments were made for multiplicity, because noninferiority was to be demonstrated only if criteria were achieved for all concomitant antigens [diphtheria toxoid, tetanus toxoid, pertussis antigen (PT, FHA, PRN), HBsAg, poliovirus strains, and Hib]. Since noninferiority assessments of concomitant antigens are meaningful only if pneumococcal noninferiority criteria are met, there were no type I error adjustments.

For the key secondary pneumococcal assessment and the secondary concomitant immunogenicity assessments (i.e., for the pneumococcal IgG GMCs at 1 month after dose 3 and the measles, mumps, rubella, and varicella vaccine antigens at 1 month after dose 4),

noninferiority was assessed similarly to that for the pneumococcal serotype-specific IgG GMCs; however, the analyses were not powered.

If ≥1 pneumococcal serotypes or concomitant antigens miss the co-primary noninferiority criteria, additional assessments were to be used to supplement antibody response characterization:

- Pneumococcal assessments: e.g., IgG GMCs post-dose 3, pre-dose 4 IgG GMCs, post-dose 3 and post-dose 4 OPA GMTs
- Concomitant antigen assessments: e.g., GMCs of antibody levels

IgG antibody concentrations below the serotype-specific assay LLOQ were set to 0.5xLLOQ in the analysis of IgG GMCs.

- The IgG assay LLOQs (in µg/mL) were as follows: (b) (4) (serotype 1), (b) (4) (serotype 3), (b) (4) (serotype 4), (b) (4) (serotype 5), (b) (4) (serotype 6A), (b) (4) (serotype 6B), (b) (4) (serotype 7F), (b) (4) (serotype 8), (b) (4) (serotype 9V), (b) (4) (serotype 10A), (b) (4) (serotype 11A), (b) (4) (serotype 12F), (b) (4) (serotype 14), (b) (4) (serotype 15B), (b) (4) (serotype 18C), (b) (4) (serotype 19A), (b) (4) (serotype 19F), (b) (4) (serotype 22F), (b) (4) (serotype 23F), and (b) (4) (serotype 33F).
- The OPA assay LLOQs (in titers) were as follows: (b) (4) (serotype 1), (b) (4) (serotype 3), (b) (4) (serotype 4), (b) (4) (serotype 5), (b) (4) (serotype 6A), (b) (4) (serotype 6B), (b) (4) (serotype 7F), (b) (4) (serotype 8), (b) (4) (serotype 9V), (b) (4) (serotype 10A), (b) (4) (serotype 11A), (b) (4) (serotype 12F), (b) (4) (serotype 14), (b) (4) (serotype 15B), (b) (4) (serotype 18C), (b) (4) (serotype 19A), (b) (4) (serotype 19F), (b) (4) (serotype 22F), (b) (4) (serotype 23F), and (b) (4) (serotype 33F).

Sample size calculation:

- For the primary pneumococcal objective, the study targeted enrollment of a total of approximately 2,000 participants in order to yield approximately 1,600 evaluable participants, assuming a 20% non-evaluable rate. Based on data from the Phase 2 infant study B7471003, 1,600 evaluable subjects would provide 93% power to demonstrate noninferiority for at least 37 (out of 40 total) noninferiority assessments (Table 4 in study protocol).
- For the primary concomitant antigen objective, the evaluable sample sizes needed to achieve 99% power to detect noninferiority for each antigen range from ~36 (HBV antigen) to ~367 per vaccine group (PRN antigen) (see Table 5 of study protocol).
- For the secondary concomitant antigen objective, the evaluable sample sizes needed to achieve 99% power to detect noninferiority to each post-dose 4 antigen ranged from ~20 (varicella) to ~240 (rubella).

Analysis populations:
The criteria for inclusion in the analysis populations used for the statistical analysis of safety and pneumococcal immunogenicity results are listed below. The primary pneumococcal immunogenicity analyses at 1 month post-dose 3 and 1 month post-dose 4 were based on the dose 3 evaluable population and dose 4 evaluable population, respectively. For immunogenicity analyses, subjects were analyzed according to their randomized vaccine assignment. For safety analyses, participants were analyzed according to the vaccine actually received.

- Dose 3 evaluable immunogenicity population:
  - were eligible and randomized
  - were 42 to 98 days of age, inclusive, on the day of Dose 1,
  - received the first 3 vaccinations to which they are randomized,

- have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 3, and
- have no other major protocol deviations as determined by the clinician.

Note: The statistical analysis of concomitant immunogenicity results 1 month after Dose 3 were primarily based on the Dose 3 evaluable immunogenicity population restricted to those who also received the appropriate concomitant vaccines with the first 3 doses.

- Dose 4 evaluable immunogenicity population:
  - were eligible and randomized,
  - were 42 to 98 days of age, inclusive, on the day of Dose 1,
  - received all 4 vaccinations as randomized, and are 365 to 455 days of age, inclusive, on the day of Dose 4,
  - have at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 4, and
  - have no other major protocol deviations as determined by the clinician.

  Note: The statistical analysis of concomitant immunogenicity results 1 month after Dose 4 were primarily based on the Dose 4 evaluable immunogenicity population restricted to those who also received the corresponding concomitant vaccines.

- All-available immunogenicity population: This analysis population includes all randomized participants who received at least 1 dose of the investigational product and have at least 1 valid immunogenicity result.

- Safety population: The safety population includes all randomized participants who received at least 1 dose of the investigational product and who had safety follow-up after any dose.

  Note: Safety data after Dose 4 were summarized on the subset of the safety population who also received Dose 4 with safety follow-up after Dose 4. Statistical analyses of e-diary results were based on the safety population among those with any e-diary data collected after the specified vaccination.

Analysis timing and unblinding:
The primary analysis was performed when safety and immunogenicity data were collected through 1 month after dose 4,and included available safety data from participants who completed the 6-month safety follow-up visits. During the five weeks following unblinding of Wyeth's study team at the time of the primary analysis through the database lock after the final participant's final visit in the study, designated staff outside of the study team performed blinded review of new reports of SAEs and NDCMCs. Investigators and their site staff remained blinded through completion of the study. Laboratory personnel performing the immunologic assays remained blinded until all assays were completed and assay results finalized.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Disposition of Enrolled Participants

A total of 1997 participants were randomized to PCV20 (N=1004) and PCV13 (N=993). Study visit completion rates were similar across study groups (Table 2).

Table 2. Disposition of All Randomized Participants, Study B7471011

Disposition	PCV20 n (%)	PCV13 n (%)
Randomized[a]	1004 (100.0)	993 (100.0)
Not vaccinated	3 (0.3)	3 (0.3)
Vaccinated	--	--
Dose 1	1001 (99.7)	990 (99.7)
Dose 2	966 (96.2)	949 (95.6)
Dose 3	934 (93.0)	926 (93.3)
Dose 4	853 (85.0)	844 (85.0)
Completed 1 month follow-up after Dose 3	930 (92.6)	924 (93.1)
Completed 1 month follow-up after Dose 4	851 (84.8)	839 (84.5)
Completed 6-month follow-up telephone contact[b]	885 (88.1)	842 (84.8)
Completed all visits per protocol	821 (81.8))	802 (80.8)
Total withdrawn	183 (18.2)	191 (19.2)

Source: Adapted from STN 125731/189.0, module 5.3.5.1, Study B7471011 Clinical Study Report, Table 3, p33-34.
a. This value is the denominator for the percentage calculations.
b. The number of participants in the 6-month follow-up telephone contact includes participants who had previously withdrawn from vaccination but whose parent(s)/legal guardian(s) consent to the safety follow-up.

Overall, a total of 374 (18.7%) randomized participants were withdrawn during the study. The rates of withdrawal were similar by time of withdrawal and withdrawal reason across study groups (data not shown; ref. Table 3 in clinical study report (CSR)). The most common reason for withdrawal among the 1997 randomized participants included lost to follow-up (5.6%), withdrawal by parent/guardian (5.3%), no longer meets eligibility criteria (4.8%) and protocol deviations (2.6%). Six participants (2 in the PCV20 group and 4 in the PCV13 group) were withdrawn due to an adverse event. Other reasons included physician decision (0.1%) and other (0.2%).

Populations Analyzed

Section 6.1.9 defines the analysis populations used for statistical analysis of safety and immunogenicity results. The proportions of participants included in the each of the analysis populations (i.e., the safety population, all-available immunogenicity population, Dose 3 evaluable immunogenicity population, and Dose 4 evaluable immunogenicity populations) were similar between the two study groups (Table 3). The most common reason for exclusion from the Dose 3 evaluable immunogenicity population and Dose 4 evaluable immunogenicity population included no blood drawn within the protocol-defined time window or not receiving the study vaccination as randomized. The most common reason for exclusion from the all-available immunogenicity population was not having at least 1 valid immunogenicity result. No analyses were performed for the all-available immunogenicity population, because the difference between the number of participants in the Dose 3 evaluable immunogenicity population and the all-available immunogenicity population was <10%.

Table 3. Study B7471011 Analysis Populations

Population	PCV20 n (%)	PCV13 n (%)
Randomized[a]	1004 (100.0)	993 (100.0)
Vaccinated	1001 (99.7)	990 (99.7)
Safety population[b]	1001 (99.7)	990 (99.7)
Excluded from Safety Population	3 (0.3)	3 (0.3)
Reason for exclusion[c]	--	--
Did not receive any vaccination	3 (0.3)	3 (0.3)
All-available immunogenicity population	908 (90.4)	889 (89.5)
Excluded from all-available immunogenicity population	96 (9.6)	104 (10.5)
Reason for exclusion[c]	--	--
Did not receive any vaccination	3 (0.3)	3 (0.3)
Did not have at least 1 valid immunogenicity result	93 (9.3)	101 (10.2)
Dose 3 evaluable immunogenicity population	833 (83.0)	803 (80.9)
Excluded from Dose 3 evaluable immunogenicity population	171 (17.0)	190 (19.1)
Reason for exclusion[c]	--	--
Not eligible at randomization/dose[d]	6 (0.6)	5 (0.5)
Not 42 to 98 days of age at Dose 1	2 (0.2)	3 (0.3)
Did not receive first 3 vaccinations as randomized	64 (6.4)	64 (6.4)
No blood drawn within 27 to 56 days after Dose 3	93 (9.3)	112 (11.3)
Did not have at least 1 valid immunogenicity result within 27 to 56 days after Dose 3	5 (0.5)	8 (0.8)
Other major protocol deviation	3 (0.3)	1 (0.1)
Dose 4 evaluable immunogenicity population	755 (75.2)	745 (75.0)
Excluded from Dose 4 evaluable immunogenicity population	249 (24.8)	248 (25.0)
Reason for exclusion[c]	--	--
Not eligible at randomization/dose[d]	6 (0.6)	5 (0.5)
Not 42 to 98 days of age at Dose 1	2 (0.2)	3 (0.3)
Did not receive all 4 vaccinations as randomized	145 (14.4)	147 (14.8)
Not 365 to 455 days of age at Dose 4	1 (0.0)	0 (0.0)
No blood drawn within 27 to 56 days after Dose 4	91 (9.1)	91 (9.2)
Did not have at least 1 valid immunogenicity result within 27 to 56 days after Dose 4	4 (0.4)	4 (0.4)
Other major protocol deviation	2 (0.2)	1 (0.1)

Source: Adapted from STN 125731/189.0, module 5.3.5.1, Study B7471011 Clinical Study Report, Table 4, p36-38.
a. These values are the denominators for the percentage calculations by subpopulation.
b. Two participants were randomized to PCV13 but received PCV20 at Dose 2 and 1 participant was randomized to PCV13 but received PCV20 at Dose 4. Data collected after the incorrect study vaccine administration are excluded from local reaction and systemic event summary tables and figures. Adverse events from participants who received any incorrect study vaccination in a specified reporting time period are excluded from the summary tables and figures for that and all subsequent reporting periods. All data are included in the listings.
c. Reasons are listed in hierarchical order. Each excluded participant is counted only once under the first applicable reason.
d. Violation of any protocol defined inclusion or exclusion criteria.

Reviewer Comment: *Participants in study B7471011 were permitted to receive influenza and rotavirus vaccines concomitantly with PCV20 or PCV13 according to local or national recommendations. The proportion of participants receiving a concomitant influenza vaccine and the proportion of participants receiving a concomitant rotavirus vaccine were similar across the two study groups in Study B7471011. Among PCV20 recipients, 11.7% and 10.1% received an influenza vaccine with Dose 3 and Dose 4 of PCV20, respectively; 65.8% to 87.3% received rotavirus vaccine with each of the first 3 doses of PCV20. No immunogenicity subgroup analyses based on concomitantly administered influenza or rotavirus vaccines were provided in this sBLA.*

6.1.10.1.1 Demographics

Table 4 summarizes baseline demographic characteristics for the safety population. The two study groups were similar with regard to all baseline demographics. Overall, the safety population included 48.5% females, 65.3% White, 11.0% Black, 7.1% multiracial, 1.5% Asian, 0.4% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander and 4.5 not reported; 30.4% were Hispanic/Latino; 89.2% were from the US and 10.8% were from Puerto Rico. Overall, the median age at Dose 1 was 64.0 days (range 42, 97) and the median age at Dose 4 was 372 days (range 365-460). Demographic characteristics for the Dose 3 and Dose 4 evaluable immunogenicity populations were similar to those for the safety population.

Table 4. Demographic Characteristics, Safety Population, Study B7471011

Characteristic	PCV20 n (%)	PCV13 n (%)	Total n (%)
Sex	--	--	--
Male	518 (51.7)	505 (51.2)	1023 (51.5)
Female	483 (48.3)	482 (48.8)	965 (48.5)
Race	--	--	--
White	754 (75.3)	742 (75.2)	1496 (75.3)
Black or African American	110 (11.0)	108 (10.9)	218 (11.0)
Asian	16 (1.6)	16 (1.6)	32 (1.6)
American Indian or Alaska Native	4 (0.4)	3 (0.3)	7 (0.4)
Native Hawaiian or other Pacific Islander	2 (0.2)	2 (0.2)	4 (0.2)
Multiracial	68 (6.8)	73 (7.4)	141 (7.1)
Not Reported	47 (4.7)	43 (4.4)	90 (4.5)
Ethnicity	--	--	--
Hispanic/Latino	312 (31.2)	293 (29.7)	605 (30.4)
Non-Hispanic/non-Latino	661 (66.0)	659 (66.8)	1320 (66.4)
Not reported	28 (2.8)	35 (3.5)	63 (3.2)
Geographic region	--	--	--
USA	893 (89.2)	881 (89.3)	1774 (89.2)
Puerto Rico	108 (10.8)	106 (10.7)	214 (10.8)
Age at Dose 1 (days)	--	--	--
Mean (SD)	65.9 (7.98)	65.6 (7.13)	65.8 (7.57)
Median	64.0	64.0	64.0
Min, max	(42, 97)	(43, 96)	(42, 97)
Age at Dose 4 (days)	--	--	--
Mean (SD)	378.4 (15.75)	378.7 (15.47)	378.5 (15.61)
Median	372.0	373.0	372.0
Min, max	(365, 460)	(366, 455)	(365, 460)

Source: STN 125731/189.0, module 5.3.5.1, Study B7471011 Clinical Study Report, Table 5, p39.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. Participants who received any incorrect study vaccination during the study are excluded.
b. n = Number of participants with the specified characteristic

6.1.11 Efficacy Analyses

The study design did not include clinical efficacy endpoints. Rather, the study evaluated serologic antibody endpoints to assess the antibody response to study vaccines as discussed in Section 6.1.1.

6.1.11.1 Analyses of Primary Endpoint(s)

Primary Pneumococcal Analyses

IgG antibody responses following PCV20 were noninferior to those following PCV13 for 8 of the 13 matched serotypes, as assessed by the percentage of participants meeting the predefined serotype-specific IgG concentration one month after Dose 3, using a 10% noninferiority criterion (the lower bound of the 2-sided 95% CI for the difference in percentages [PCV20-PCV13] greater than -10%) (Table 5). Five of the 13 matched serotypes (serotypes 1, 3, 4, 9V and 23F) did not meet the pre-specified noninferiority criterion, as the lower bounds of the 2-sided 95% CIs for the difference in percentages (PCV20-PCV13) were -12.1%, -20.1%, -12.0%, -11.3%, and -11.4% respectively.

IgG antibody responses following PCV20 were noninferior to those following PCV13 for 6 of the 7 additional serotypes, except for serotype 12F. Serotype 12F did not meet the pre-specified noninferiority criterion as the lower bound of the 2-sided 95% CI for the difference in percentages (PCV20-PCV13) was less than -10% (-41.6%).

Additional IgG GMC data at one month after Dose 3 and OPA data at one month after Dose 3, presented in Table 8 and Table 10 respectively, support the effectiveness of PCV20 for each of the 6 serotypes that failed to meet the pre-specified noninferiority criterion.

Table 5. Comparison of the Percentage of Infant Participants with Pre-Defined Pneumococcal Immunoglobulin G (IgG) Concentrations for Vaccine Serotypes at 1 Month Post-Dose 3[a], Dose 3 Evaluable Immunogenicity Population, Study B7471011

Vaccine Serotypes	Pre-Defined Level (µg/mL)	PCV20 N[b]	PCV20 n[c]	PCV20 % (95% CI)[d]	PCV13 N[b]	PCV13 n[c]	PCV13 % (95% CI)[d]	PCV20-PCV13 Difference[a] % (95% CI)[e]
PCV13 serotype	--	--	--	--	--	--	--	--
1	≥0.35	833	665	79.8 (76.9, 82.5)	802	709	88.4 (86.0, 90.5)	-8.6 (**-12.1**, -5.1)
3	≥0.35	833	434	52.1 (48.6, 55.5)	802	542	67.6 (64.2, 70.8)	-15.5 (**-20.1**, -10.8)
4	≥0.35	833	664	79.7 (76.8, 82.4)	802	707	88.2 (85.7, 90.3)	-8.4 (**-12.0**, -4.9)
5	≥0.23	833	687	82.5 (79.7, 85.0)	802	696	86.8 (84.2, 89.1)	-4.3 (-7.8, -0.8)
6A	≥0.35	833	779	93.5 (91.6, 95.1)	802	769	95.9 (94.3, 97.2)	-2.4 (-4.6, -0.2)
6B	≥0.10	831	734	88.3 (85.9, 90.4)	801	740	92.4 (90.3, 94.1)	-4.1 (-7.0, -1.2)
7F	≥0.35	833	805	96.6 (95.2, 97.8)	802	783	97.6 (96.3, 98.6)	-1.0 (-2.7, 0.7)
9V	≥0.35	833	682	81.9 (79.1, 84.4)	802	720	89.8 (87.5, 91.8)	-7.9 (**-11.3**, -4.6)
14	≥0.35	832	777	93.4 (91.5, 95.0)	802	755	94.1 (92.3, 95.7)	-0.8 (-3.1, 1.6)
18C	≥0.35	833	771	92.6 (90.6, 94.2)	802	747	93.1 (91.2, 94.8)	-0.6 (-3.1, 1.9)
19A	≥0.12	833	809	97.1 (95.7, 98.1)	802	787	98.1 (96.9, 98.9)	-1.0 (-2.6, 0.5)

Vaccine Serotypes	Pre-Defined Level (µg/mL)	PCV20 N[b]	PCV20 n[c]	PCV20 % (95% CI)[d]	PCV13 N[b]	PCV13 n[c]	PCV13 % (95% CI)[d]	PCV20-PCV13 Difference[a] % (95% CI)[e]
19F	≥0.35	833	807	96.9 (95.5, 98.0)	802	775	96.6 (95.1, 97.8)	0.2 (-1.5, 2.0)
23F	≥0.35	833	649	77.9(74.9, 80.7)	802	686	85.5 (82.9, 87.9)	-7.6 (**-11.4**, -3.9)
Seven Additional Serotypes	--	--	--	--	--	--	--	--
8	≥0.35	833	806	96.8 (95.3, 97.9)	802	686	85.5 (82.9, 87.9)	11.2 (8.6, 14.0)
10A	≥0.35	833	685	82.2 (79.5, 84.8)	802	686	85.5 (82.9, 87.9)	-3.3 (-6.9, 0.3)
11A	≥0.35	833	772	92.7 (90.7, 94.4)	802	686	85.5 (82.9, 87.9)	7.1 (4.2, 10.2)
12F	≥0.69	833	400	48.0 (44.6, 51.5)	802	686	85.5 (82.9, 87.9)	-37.5 (**-41.6**, -33.3)
15B	≥0.35	833	818	98.2 (97.0, 99.0)	802	686	85.5 (82.9, 87.9)	12.7 (10.2, 15.4)
22F	≥0.35	833	819	98.3 (97.2, 99.1)	802	686	85.5 (82.9, 87.9)	12.8 (10.3, 15.5)
33F	≥0.35	833	722	86.7 (84.2, 88.9)	802	686	85.5 (82.9, 87.9)	1.1 (-2.2, 4.5)

Source: STN 125731/189.0 module 5.3.5.1, Study B74710011 Clinical Study Report. Table 9, p 50-51.
Note: Noninferiority for a serotype was met if the lower bound of the 2-sided CI for the percentage difference (Prevnar 20 minus Prevnar 13) >-10% (10% NI criterion) for that serotype.
a. For the PCV13 serotypes, the compared results are from the corresponding serotype in the PCV13 group. For the 7 additional serotypes, the compared results are from serotype 23F (PCV13 serotype with the lowest percentage, not including serotype 3) in the PCV13 group.
b. N = number of participants with valid assay results for the specified serotype. These values are the denominators for the percentage calculations.
c. n = Number of participants with an IgG concentration ≥ the predefined level for the given serotype.
d. Exact 2-sided CI, based on the Clopper and Pearson method.
e. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.

For each of the 13 matched serotypes, IgG GMCs in the PCV20 group were noninferior (lower bound of 2-sided 95% CI of the IgG GMC ratio (PCV20/PV13) was >0.5) to the corresponding IgG GMCs in the PCV13 group. For each of the 7 additional serotypes, IgG GMCs in the PCV20 group were noninferior to the IgG GMC for serotype 1 (the lowest result among the 13 matched vaccine serotypes excluding serotype 3) in the PCV13 group (Table 6).

Table 6. Comparison of the Pneumococcal Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) for Vaccine Serotypes at 1 Month Post-Dose 4[a], Dose 4 Evaluable Immunogenicity Population, Study B7471011

Vaccine Serotypes	PCV20 n[b]	PCV20 GMC[c]	PCV20 (95% CI)[c]	PCV13 n[b]	PCV13 GMC[c]	PCV13 (95% CI)[c]	GMC Ratio[a,d] (PCV20/PCV13) % (95% CI)[d]
PCV13 serotypes	--	--	--	--	--	--	--
1	755	1.47	(1.37, 1.57)	744	2.12	(1.97, 2.27)	0.69 (0.63, 0.76)
3	755	0.56	(0.53, 0.60)	745	0.85	(0.80, 0.90)	0.66 (0.61, 0.73)
4	754	3.77	(3.52, 4.04)	745	4.84	(4.50, 5.22)	0.78 (0.70, 0.86)
5	755	1.87	(1.74, 2.00)	745	2.51	(2.33, 2.70)	0.74 (0.67, 0.82)
6A	755	9.01	(8.45, 9.61)	745	11.69	(10.91, 12.53)	0.77 (0.70, 0.85)
6B	753	4.01	(3.70, 4.35)	744	5.74	(5.27, 6.24)	0.70 (0.62, 0.79)
7F	755	3.91	(3.70, 4.14)	745	5.18	(4.88, 5.49)	0.76 (0.70, 0.82)

Vaccine Serotypes	PCV20 n[b]	PCV20 GMC[c]	PCV20 (95% CI)[c]	PCV13 n[b]	PCV13 GMC[c]	PCV13 (95% CI)[c]	GMC Ratio[a,d] (PCV20/PCV13) % (95% CI)[d]
9V	755	3.44	(3.23, 3.67)	744	4.30	(4.02, 4.59)	0.80 (0.73, 0.88)
14	755	5.68	(5.27, 6.12)	745	6.34	(5.88, 6.83)	0.90 (0.81, 1.00)
18C	755	3.46	(3.24, 3.70)	745	4.69	(4.34, 5.05)	0.74 (0.67, 0.82)
19A	754	3.53	(3.30, 3.77)	745	4.13	(3.84, 4.45)	0.85 (0.77, 0.94)
19F	755	5.01	(4.68, 5.36)	745	5.79	(5.36, 6.25)	0.86 (0.78, 0.96)
23F	755	3.95	(3.63, 4.31)	745	6.18	(5.66, 6.75)	0.64 (0.57, 0.72)
Seven Additional Serotypes	--	--	--	--	--	--	--
8	755	3.97	(3.73, 4.22)	744	2.12	(1.97, 2.27)	1.87 (1.71, 2.06)
10A	755	6.22	(5.75, 6.72)	744	2.12	(1.97, 2.27)	2.94 (2.64, 3.26)
11A	755	3.53	(3.31, 3.78)	744	2.12	(1.97, 2.27)	1.67 (1.51, 1.84)
12F	755	1.85	(1.73, 1.99)	744	2.12	(1.97, 2.27)	0.88 (0.79, 0.97)
15B	755	12.59	(11.78, 13.45)	744	2.12	(1.97, 2.27)	5.95 (5.39, 6.55)
22F	755	10.60	(9.92, 11.33)	744	2.12	(1.97, 2.27)	5.01 (4.54, 5.52)
33F	755	9.31	(8.71, 9.96)	744	2.12	(1.97, 2.27)	4.40 (3.99, 4.85)

Source: STN 125731/189.0 module 5.3.5.1, Study B74710011 Clinical Study Report. Table 8, p 46.
Abbreviations: LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: Noninferiority for a serotype was met if the lower bound of the 2-sided CI of IgG GMC ratio (Prevnar 20/Prevnar 13) >0.5 (2-fold NI criterion) for that serotype.
a. For the PCV13 serotypes, the GMCs are from the corresponding serotype in the PCV13 group. For the 7 additional serotypes, the GMCs are from serotype 1 (PCV13 serotype with the lowest GMC, not including serotype 3) in the PCV13 group.
b. n = Number of participants with valid IgG concentrations for the specified serotype.
c. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
d. 2-Sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations (PCV20 – PCV13) and the corresponding CIs (based on the Student t distr bution).

Primary Concomitant Antigen Analyses

At 1 month after Dose 3, antibody responses to the co-administered diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib vaccine antigens in the PCV20 group were noninferior compared to the corresponding responses in the PCV13 group; the lower bound of the 2-sided, 95% confidence interval for the difference in proportions of participants achieving pre-specified antibody levels (PCV20-PCV13) was greater than -10% (Table 7). In a secondary analysis at 1 month after Dose 3, the antibody responses to the co-administered Hib vaccine antigen (PRP) using an alternative pre-specified anti-PRP antibody response (≥1.0 µg/mL) in the PCV20 group were noninferior compared to the corresponding response in the PCV13 group (Table 7).

Table 7. Comparison of the Percentage of Infant Participants with Prespecified Antibody Concentrations to Concomitant Antigens at 1 Month After Dose 3 in a Randomly Selected Subset of Participants, Dose 3 Evaluable Immunogenicity Population, Study B7471011

Concomitant Vaccine Antigen	N[a]	n[b]	Predefined Antibody Level	PCV20 %	N[a]	n[b]	PCV13 %	Difference (95% CI[c]) (PCV20-PCV13)
Diphtheria	370	346	≥0.1 IU/mL	93.5	363	355	97.8	-4.3 (-7.5, -1.4)
Tetanus	370	369	≥0.1 IU/mL	99.7	363	361	99.4	0.3 (-1.0, 1.7)
Pertussis	--	--	--	--	--	--	--	--
PT	370	351	≥14.40 EU/mL[d]	94.9	363	345	95.0	-0.2 (-3.5, 3.1)
FHA	370	354	≥26.60 EU/mL[d]	95.7	363	345	95.0	0.6 (-2.5, 3.9)
PRN	370	347	≥13.00 EU/mL[d]	93.8	363	345	95.0	-1.3 (-4.7, 2.2)
HBsAg	118	118	≥10 mIU/mL	100.0	127	127	100.0	0.0 (-3.2, 2.9)

Concomitant Vaccine Antigen	N[a]	n[b]	Predefined Antibody Level	PCV20 %	N[a]	n[b]	PCV13 %	Difference (95% CI[c]) (PCV20-PCV13)
Poliovirus	--	--	--	--	--	--	--	--
Type 1	111	111	≥1:8	100.0	117	117	100.0	0.0 (-3.4, 3.2)
Type 2	115	115	≥1:8	100.0	120	119	99.2	0.8 (-2.4, 4.6)
Type 3	115	115	≥1:8	100.0	120	120	100.0	0.0 (-3.2, 3.1)
Hib (primary)	124	124	≥0.15 µg/mL	100.0	125	125	100.0	0.0 (-3.0, 3.0)
Hib (secondary)	124	93	≥1.0 µg/mL[e]	75.0	125	90	72.0	3.0 (-8.0, 14.0)

Source: STN 125731/189.0 module 5.3.5.1, Study B74710011 Clinical Study Report. Table 14.30, p 182-183.
Abbreviations: HBsAg = hepatitis B surface antigen; mIU/mL = milli-international units per milliliter; PT = pertussis toxoid. Hib = *Haemophilus influenzae* type b.
Note: For this table, the Dose 3 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with the first 3 doses.
Note: Antibody concentrations to the diphtheria, tetanus, pertussis, hepatitis B, poliovirus, and Hib vaccine antigens were determined on sera collected 1 month after Dose 3 from randomly selected subsets of participants with sufficient sera volumes.
Note: Noninferiority for a concomitant antigen was met if the lower bound of the 2-sided, 95% confidence interval for the difference in proportions of participants achieving pre-specified antibody levels (PCV20-PCV13) was greater than -10%.
a. N = number of participants with valid assay results for the specified antigen. These values are the denominators for the percentage calculations.
b. n = Number of participants with an antibody concentration ≥ the prespecified level for the specified concomitant vaccine antigen.
c. 2-Sided CI based on the Miettinen and Nurminen method for the difference in proportions, expressed as a percentage.
d. The observed antipertussis antibody concentration achieved by 95% of PCV13 recipients.
e. Alternative prespecified level for an exploratory concomitant immunogenicity endpoint.

6.1.11.2 Analyses of Secondary Endpoints

At 1 month after Dose 3, IgG GMCs in the PCV20 group were noninferior (lower bound of 2-sided 95% CI of the IgG GMC ratio (PCV20/PV13) was >0.5) to the corresponding IgG GMCs in the PCV13 group for all 20 vaccine serotypes, including the 6 serotypes that missed the noninferiority criterion based on the percentage of participants meeting pre-defined IgG concentrations at one month after Dose 3. For each of the 13 matched serotypes, IgG GMCs in the PCV20 group were noninferior to the corresponding IgG GMCs in the PCV13 group. For each of the 7 additional serotypes, IgG GMCs in the PCV20 group were noninferior to the IgG GMC for serotype 19A (the lowest result among the 13 matched vaccine serotypes excluding serotype 3) in the PCV13 group (Table 8).

Table 8. Comparison of the Pneumococcal Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) for Vaccine Serotypes at 1 Month Post-Dose 3[a], Dose 3 Evaluable Immunogenicity Population, Study B7471011

Vaccine Serotypes	PCV20 n[b]	PCV20 GMC[c]	PCV20 (95% CI)[c]	PCV13 n[b]	PCV13 GMC[c]	PCV13 (95% CI)[c]	GMC Ratio[a,d] (PCV20/PCV13) % (95% CI)[d]
PCV13 serotypes	--	--	--	--	--	--	--
1	833	0.74	(0.70, 0.79)	802	1.14	(1.06, 1.22)	0.65 (0.59, 0.72)
3	833	0.36	(0.33, 0.38)	802	0.51	(0.48, 0.55)	0.70 (0.64, 0.76)
4	833	0.75	(0.70, 0.81)	802	1.08	(1.00, 1.17)	0.70 (0.63, 0.78)
5	833	0.66	(0.61, 0.71)	802	0.96	(0.88, 1.04)	0.69 (0.61, 0.77)
6A	833	1.95	(1.81, 2.10)	802	2.69	(2.48, 2.92)	0.72 (0.65, 0.81)
6B	831	0.61	(0.55, 0.68)	801	1.02	(0.91, 1.14)	0.60 (0.51, 0.70)
7F	833	1.71	(1.62, 1.81)	802	2.29	(2.16, 2.43)	0.75 (0.69, 0.81)
9V	833	0.87	(0.81, 0.93)	802	1.21	(1.12, 1.30)	0.72 (0.65, 0.80)
14	832	2.16	(2.01, 2.33)	802	2.72	(2.51, 2.95)	0.79 (0.71, 0.89)
18C	833	1.31	(1.23, 1.39)	802	1.71	(1.59, 1.84)	0.77 (0.70, 0.84)
19A	833	0.72	(0.67, 0.76)	802	0.91	(0.85, 0.97)	0.79 (0.72, 0.86)

Vaccine Serotypes	PCV20 n[b]	PCV20 GMC[c]	PCV20 (95% CI)[c]	PCV13 n[b]	PCV13 GMC[c]	PCV13 (95% CI)[c]	GMC Ratio[a,d] (PCV20/PCV13) % (95% CI)[d]
19F	833	1.59	(1.50, 1.67)	802	2.00	(1.88, 2.12)	0.79 (0.73, 0.86)
23F	833	0.82	(0.75, 0.90)	802	1.25	(1.14, 1.37)	0.66 (0.58, 0.75)
Seven Additional Serotypes	--	--	--	--	--	--	--
8	833	1.80	(1.70, 1.91)	802	0.91	(0.85, 0.97)	1.98 (1.81, 2.16)
10A	833	1.21	(1.09, 1.33)	802	0.91	(0.85, 0.97)	1.32 (1.18, 1.49)
11A	833	1.39	(1.30, 1.48)	802	0.91	(0.85, 0.97)	1.52 (1.39, 1.67)
12F	833	0.55	(0.50, 0.60)	802	0.91	(0.85, 0.97)	0.60 (0.54, 0.67)
15B	833	4.40	(4.11, 4.71)	802	0.91	(0.85, 0.97)	4.82 (4.39, 5.30)
22F	833	3.71	(3.45, 3.99)	802	0.91	(0.85, 0.97)	4.06 (3.68, 4.48)
33F	833	1.49	(1.36, 1.64)	802	0.91	(0.85, 0.97)	1.64 (1.46, 1.83)

Source: STN 125731/189.0 module 5.3.5.1, Study B74710011 Clinical Study Report. Table 12, p 57-58.
Abbreviations: LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: Note: Noninferiority for a serotype was met if the lower bound of the 2-sided CI of IgG GMC ratio (Prevnar 20/Prevnar 13) >0.5 (2-fold NI criterion) for that serotype. a. For the PCV13 serotypes, the GMCs are from the corresponding serotype in the PCV13 group. For the 7 additional serotypes, the GMCs are from serotype 19A (PCV13 serotype with the lowest GMC, not including serotype 3) in the PCV13 group.
b. n = Number of participants with valid IgG concentrations for the specified serotype.
c. GMCs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
d. 2-Sided CIs were calculated by exponentiating the mean differences of the logarithms of the IgG concentrations (PCV20 – PCV13) and the corresponding CIs (based on the Student t distr bution).

Secondary Concomitant Antigen Analyses

At 1 month after Dose 4, antibody responses to the co-administered measles, mumps, rubella and varicella virus vaccine antigens in the PCV20 group were noninferior compared to the corresponding responses in the PCV13 group; the lower bound of the 2-sided, 95% confidence interval for the GMC ratios (PCV20/PCV13) was greater than 0.5 (Table 9).

Table 9. Concomitant Vaccine Antigen GMCs and GMC Ratios at 1 Month After Dose 4, Randomly Selected Subset of Participants, Dose 4 Evaluable Immunogenicity Population.

Concomitant Vaccine Antigen	n[a]	PCV20 GMC (95% CI[b])	n[a]	PCV13 GMC (95% CI[b])	GMC Ratio (95% CI[c]) (PCV20/PCV13)
Measles (AU/mL)	234	278 (244, 316)	232	215 (185, 251)	1.29 (1.05, 1.58)
Mumps (AU/mL)	234	37 (31, 44)	232	34 (29, 40)	1.08 (0.85, 1.38)
Rubella (IU/mL)	234	50 (44, 56)	232	40 (35, 47)	1.23 (1.02, 1.48)
Varicella (mIU/mL)	231	233 (207, 262)	229	235 (209, 264)	0.99 (0.84, 1.17)

Source: STN 125731/189.0 module 5.3.5.1, Study B74710011 Clinical Study Report. Table 144.32, p 185.
Abbreviations: AU/mL = arbitrary units per milliliter; GMC = geometric mean concentration; LLOQ = lower limit of quantitation; mIU/mL = milli-international units per milliliter.
Note: For this table, the Dose 4 evaluable immunogenicity population was restricted to only those participants who received the appropriate concomitant vaccines with Dose 4.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: Antibody concentrations to the measles, mumps, rubella, and varicella vaccine antigens were determined on sera collected 1 month after Dose 4 from a randomly selected subset of participants with sufficient sera volumes.
a. n = Number of participants with valid assay results for the specified antigen.
Note: Noninferiority for a concomitant antigen was met if the lower bound of the 2-sided CI of GMC ratio (Prevnar 20/Prevnar 13) >0.5 (2-fold NI criterion) for that serotype.
b. GMs and 2-sided CIs were calculated by exponentiating the mean logarithm of the concentrations and the corresponding CIs (based on the Student t distribution).
c. CIs for the ratio are exponentiations of a CI, based on the Student t distribution for the mean difference of the logarithms of the measures (PCV20 – PCV13).

6.1.11.3 Subpopulation Analyses

Descriptive subgroup analyses were conducted for the primary and key secondary endpoints by sex and race. The observed serotype-specific IgG responses among PCV20 recipients and among PCV13 recipients were generally higher among females compared to males, particularly for the post-dose 4 primary endpoint (data not shown; ref CSR Tables 14.24 to 14.26). The observed serotype-specific IgG responses were generally higher among Black or African American participants compared to White participants for each primary and key secondary endpoint (Data not shown; ref CSR Tables 14.27 to 14.29). The numbers of participants in the other race subgroups were too small for meaningful analysis.

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

Serotype-specific OPA GMTs at 1 month after Dose 3 and 1 month after Dose 4 were descriptively evaluated in a subset of participants in Study B7471011. For serotypes 1, 3, 4, 9V, 23F and 12F, for which noninferiority was not met 1 month after Dose 3 (for the percentage of participants meeting the pre-defined serotype-specific IgG concentration), OPA GMTs at 1 month after Dose 3 were numerically similar in the PCV20 and PCV13 study groups for the 5 matched serotypes (serotypes 1, 3, 4, 9V and 23F) and an OPA antibody response was generated to additional serotype 12F (Table 10). For the remaining 13 matched serotypes, OPA GMTs at 1 month after Dose 3 were numerically similar in the PCV20 and PCV13 study groups. At 1 month after Dose 4, OPA GMTs for the 13 matched vaccine serotypes were generally numerically lower in the PCV20 group compared to the PCV13 group (Table 11). At both timepoints, OPA GMTs were generally numerically higher in the PCV20 group compared to the PCV13 group for the 7 additional serotypes.

Table 10. Pneumococcal Opsonophagocytic Activity Antibody Geometric Mean Titers (GMTs) at 1 Month Post-Dose 3 for Vaccine Serotypes, Dose 3 Evaluable Immunogenicity Population Random Subset of Participants, Study B7471011

Vaccine Serotypes	PCV20 n[a]	PCV20 GMT[b]	PCV20 (95% CI)[b]	PCV13 n[a]	PCV13 GMT[b]	PCV13 (95% CI)[b]
PCV13 serotypes	--	--	--	--	--	--
1	103	26	(21, 33)	98	34	(27, 42)
3	105	51	(43, 61)	97	63	(53, 76)
4	97	339	(252, 455)	90	280	(207, 378)
5	103	32	(27, 39)	98	39	(32, 47)
6A	104	910	(763, 1084)	96	936	(757, 1156)
6B	99	318	(242, 419)	91	516	(409, 651)
7F	91	1222	(1020, 1465)	87	1149	(926, 1424)
9V	94	661	(482, 906)	87	594	(421, 838)
14	103	415	(323, 535)	97	420	(330, 535)
18C	95	1153	(910, 1460)	87	996	(754, 1317)
19A	93	108	(78, 149)	84	109	(79, 151)
19F	102	84	(67, 105)	97	116	(90, 149)
23F	96	255	(186, 350)	86	295	(215, 406)

Vaccine Serotypes	PCV20 n[a]	PCV20 GMT[b]	PCV20 (95% CI)[b]	PCV13 n[a]	PCV13 GMT[b]	PCV13 (95% CI)[b]
Seven Additional Serotypes	--	--	--	--	--	--
8	100	665	(503, 880)	112	18	(17, 20)
10A	101	2558	(1869, 3501)	109	37	(33, 42)
11A	100	289	(212, 395)	108	50	(46, 55)
12F	92	7677	(5952, 9901)	110	28	(24, 33)
15B	97	1560	(1090, 2233)	110	18	(16, 22)
22F	97	6797	(5170, 8936)	113	9	(9, 9)
33F	85	7388	(4803, 11365)	111	198	(177, 220)

Source: STN 125731/189.0 module 5.3.5.1, Study B74710011 Clinical Study Report. Table 14, p 64-65.
Abbreviations: LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: OPA titers were determined on serum from randomly selected subsets of participants assuring equal representation of both vaccine groups.
a. n = Number of participants with valid OPA titers for the specified serotype.
b. GMTs and 2-sided CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distr bution).

Table 11. Pneumococcal Opsonophagocytic Activity Antibody Geometric Mean Titers (GMTs) at 1 Month Post-Dose 4 for Vaccine Serotypes, Dose 4 Evaluable Immunogenicity Population Random Subset of Participants, Study B7471011

Vaccine Serotypes	PCV20 n[a]	PCV20 GMT[b]	PCV20 (95% CI)[b]	PCV13 n[a]	PCV13 GMT[b]	PCV13 (95% CI)[b]
PCV13 serotypes	--	--	--	--	--	--
1	94	36	(27, 48)	91	66	(50, 87)
3	92	62	(49, 78)	88	102	(86, 120)
4	85	621	(435, 887)	82	961	(714, 1294)
5	94	55	(45, 67)	91	69	(54, 87)
6A	93	1384	(1092, 1753)	91	1767	(1329, 2348)
6B	92	666	(489, 906)	88	1211	(861, 1703)
7F	84	2022	(1673, 2444)	81	2099	(1741, 2531)
9V	85	2609	(1913, 3558)	79	3210	(2500, 4123)
14	92	667	(523, 850)	91	593	(462, 761)
18C	84	1973	(1472, 2643)	83	2425	(1914, 3072)
19A	85	844	(622, 1145)	78	1357	(1007, 1829)
19F	93	246	(179, 337)	91	373	(272, 513)
23F	84	827	(554, 1235)	77	1532	(1118, 2100)
Seven Additional Serotypes	--	--	--	--	--	--
8	89	1228	(901, 1673)	97	26	(21, 31)
10A	99	3674	(2746, 4916)	102	57	(44, 74)
11A	90	2728	(1975, 3768)	89	69	(53, 89)
12F	86	9320	(7037, 12343)	103	31	(26, 37)
15B	92	3035	(2138, 4308)	100	23	(17, 30)
22F	86	11077	(7956, 15422)	101	15	(11, 20)
33F	80	19216	(13193, 27990)	97	363	(292, 451)

Source: STN 125731/189.0 module 5.3.5.1, Study B74710011 Clinical Study Report. Table 15, p 66.
Abbreviations: LLOQ = lower limit of quantitation.
Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.
Note: OPA titers were determined on serum from randomly selected subsets of participants assuring equal representation of both vaccine groups.
a. n = Number of participants with valid OPA titers for the specified serotype.

b. GMTs and 2-sided CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding Cis (based on the Student t distr bution).

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 and 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 7 days after vaccination, then the e-diary was considered transmitted. E-diary transmission rates were similar between study groups for each of the 7 days following each of the 4 study doses, ranging overall from 72.9% to 91.8% (data not shown; ref. CSR Table 7). Although transmission rates for all 7 days were low, ranging from 43.4% to 57.5% overall, the rates were similar across study groups. Transmission rates by day and across all 7 days generally decreased with each study dose.

6.1.12.2 Overview of Adverse Events

Solicited Local Reactions Through 7 Days After Each Study Vaccination (Doses 1-4)
The proportions of participants with solicited local injection site reactions within 7 days after doses 1 through 4 by maximum severity were similar between the two study groups (Table 12). Injection site pain was the most frequently reported injection site reaction followed by redness and swelling. Most reactions were mild or moderate in severity (≤0.4% locally were severe). The median day of onset for local reactions following doses 1 through 4 was Day 1 or Day 2 (Day 1 = day of vaccination), and local reactions resolved within a median duration of 1 or 2 days.

Table 12. Proportions of Participants with Solicited Local Reactions, by Maximum Severity, at the PCV20 or PCV13 Injection Site Within 7 Days After Each Vaccination, Safety Population By Dose, Study B7471011

Graded Local Reaction	Dose 1 PCV20 N[a]=993 (%)	Dose 1 PCV13 N[a]=974 (%)	Dose 2 PCV20 N[a]=940 (%)	Dose 2 PCV13 N[a]=924 (%)	Dose 3 PCV20 N[a]=914 (%)	Dose 3 PCV13 N[a]=901 (%)	Dose 4 PCV20 N[a]=826 (%)	Dose 4 PCV13 N[a]=815 (%)
Any local reaction[b]	59.8	56.5	53.1	52.7	50.8	49.1	44.8	45.9
Pain at injection site[c]	--	--	--	--	--	--	--	--
Any	49.1	45.3	44.0	41.7	38.6	39.0	35.7	35.8
Mild	30.6	30.4	29.3	27.7	25.7	25.5	24.1	27.1
Moderate	18.4	14.9	14.8	14.0	12.9	13.4	11.3	8.7
Severe	0.1	0	0	0	0	0	0.4	0
Redness[d]								
Any (>2.0 cm)	25.5	24.6	23.2	26.4	25.4	27.2	23.5	26.6
Mild	21.5	22.3	21.2	23.1	21.1	23.5	19.6	22.0
Moderate	4.0	2.4	2.0	3.4	4.3	3.7	3.9	4.7
Severe	0	0	0	0	0	0	0	0
Swelling[d]	--	--	--	--	--	--	--	--
Any (>2.0 cm)	16.4	18.8	15.5	17.3	17.1	17.6	14.9	17.3
Mild	11.5	14.7	11.5	13.5	12.5	13.8	10.7	13.6
Moderate	4.8	4.1	4.0	3.8	4.6	3.8	4.2	3.7
Severe	0.1	0	0	0	0	0.1	0	0

Source: STN 125731/189.0 module 5.3.5.1, B7471011 Clinical Study Report. Table 17, p 79-82.
Note: Local reactions were collected in the e-diary from Day 1 through Day 7 after each dose. No Grade 4 reactions were reported in study B7471011.

a. N = number of participants with any e-diary data reported after the specified dose. This value is the denominator for the percentage calculations.
b. Any local reaction: any redness >0.0 cm, any swelling >0.0 cm, or any pain at the injection site after the specified dose.
c. Mild: hurts if gently touched; moderate: hurts if gently touched with crying; severe: causes limitation of limb movement.
d. Mild: >0.0 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm.

Solicited Systemic Reactions Through 7 Days After Each Study Vaccination (Doses 1-4)
The proportions of participants with solicited irritability, drowsiness and decreased appetite within 7 days after doses 1 through 4 by maximum severity were similar across study groups (Table 13). Irritability was the most frequently reported systemic reaction followed by drowsiness and decreased appetite. Most reactions were mild or moderate in severity (≤4.5% systemically were severe). The median day of onset for systemic reactions following doses 1 through 4 was Day 1 or Day 2, and systemic reactions resolved within a median duration of 1 to 3 days.

The proportion of participants with fever overall and by severity was highest after dose 2 in both study groups. The proportion of participants who were given antipyretic or pain medication was also highest after dose 2.

After Dose 1, fever rates overall and by severity were numerically higher in the PCV20 group compared to the PCV13 group (10.3% vs 7.5% overall). After Dose 2, fever rates were numerically higher overall (17.3% vs 16.3%) and for the ≥38.0to ≤38.4°C and >40.0°C severity gradings. After Doses 3 and 4, fever rates were generally comparable between study groups with no clear trends.

Fever >38.9 to ≤40.0°C occurred in 0.7 to 2.7% of PCV20 participants and 0.3% to 2.9% of PCV13 participants. Rates of fever >40.0°C, reported in ≤0.2% of PCV20 participants and in ≤0.1% of PCV13 participants, were generally numerically higher in the PCV20 group compared to the PCV13 group.

Table 13. Proportions of Participants with Solicited Systemic Reactions, by Maximum Severity, at the PCV20 or PCV13 Injection Site Within 7 Days After Each Vaccination, Safety Population By Dose, Study B7471011

Graded Systemic Reaction	Dose 1 PCV20 N[a]=993 (%)	Dose 1 PCV13 N[a]=974 (%)	Dose 2 PCV20 N[a]=940 (%)	Dose 2 PCV13 N[a]=924 (%)	Dose 3 PCV20 N[a]=914 (%)	Dose 3 PCV13 N[a]=901 (%)	Dose 4 PCV20 N[a]=826 (%)	Dose 4 PCV13 N[a]=815 (%)
Any Systemic Adverse Reaction[b]	85.9	84.5	82.0	80.5	74.0	72.6	70.8	71.2
Irritability[c]	--	--	--	--	--	--	--	--
Any	70.9	71.7	71.6	68.8	64.4	63.0	61.0	61.1
Mild	23.4	21.6	22.9	21.2	25.2	21.6	23.4	21.8
Moderate	43.0	46.2	44.7	43.4	37.5	39.2	35.0	37.9
Severe	4.5	3.9	4.0	4.2	1.8	2.2	2.7	1.3
Drowsiness[d]	--	--	--	--	--	--	--	--
Any	67.2	66.0	54.7	55.6	44.1	44.1	39.5	39.5
Mild	50.2	49.3	37.0	36.9	31.1	30.1	27.8	28.2
Moderate	16.1	15.6	16.9	17.9	12.5	13.1	11.0	10.7
Severe	0.9	1.1	0.7	0.9	0.5	0.9	0.6	0.6

Graded Systemic Reaction	Dose 1 PCV20 N[a]=993 (%)	Dose 1 PCV13 N[a]=974 (%)	Dose 2 PCV20 N[a]=940 (%)	Dose 2 PCV13 N[a]=924 (%)	Dose 3 PCV20 N[a]=914 (%)	Dose 3 PCV13 N[a]=901 (%)	Dose 4 PCV20 N[a]=826 (%)	Dose 4 PCV13 N[a]=815 (%)
Decreased appetite[e]	--	--	--	--	--	--	--	--
Any	24.4	23.9	26.4	23.5	20.6	22.4	24.8	25.2
Mild	14.5	16.1	16.4	15.3	13.5	13.9	15.9	16.1
Moderate	9.7	7.5	9.8	7.7	6.7	8.2	8.6	8.3
Severe	0.2	0.3	0.2	0.5	0.4	0.3	0.4	0.7
Fever	--	--	--	--	--	--	--	--
≥38.0°C	10.3	7.5	17.3	16.3	12.6	13.7	14.5	14.0
≥38.0°C to 38.4°C	7.3	6.3	10.9	10.0	7.7	7.9	6.5	7.7
>38.4°C to 38.9°C	2.2	0.9	4.0	4.2	3.4	3.9	5.1	3.2
>38.9°C to 40.0°C	0.7	0.3	2.2	2.2	1.4	1.9	2.7	2.9
>40.0°C	0.1	0.0	0.2	0	0.1	0.0	0.2	0.1
Use of antipyretic or pain medication[f]	35.1	33.8	40.7	41.0	36.3	36.1	37.5	36.7

Source: STN 125731/189.0 module 5.3.5.1, B7471011 Clinical Study Report. Table 18, p 83-87.
Note: Systemic reactions and use of antipyretic/pain medication were collected in the e-diary from Day 1 through Day 7 after each dose. No Grade 4 reactions were reported in study B7471011.
a. N = number of participants with any e-diary data reported after the specified dose. This value, which varied for each solicited reaction and severity grading, is the denominator for percentage calculations.
b. Any systemic reaction: any fever ≥38.0°C, any decreased appetite, any drowsiness, or any irritability after the specified dose.
c. Mild: easily consolable; moderate: requiring increased attention; severe: inconsolable; crying cannot be comforted.
d. Mild: increased or prolonged sleeping bouts; moderate: slightly subdued interfering with daily activity; severe: disabling not interested in usual daily activity.
e. Mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed.
f. The numbers in the table reflect yes responses (i.e., number of events reported).

Reviewer Comment: *The numerically higher rates of reported fever overall after doses 1 and 2, fever >38.9°C to ≤40.0°C after Dose 1 and >40.0°C after doses 1 through 4 in the PCV20 group suggest a modest increase in reactogenicity of PCV20 as compared to PCV13. However, the rates of fever are within the range observed following other vaccines licensed for use in infants and toddlers.*

Reviewer Comment: *The clinical study reports for studies B7471003, B7471011, B7471013 and B7471014 present the proportion of participants reporting each solicited local and systemic adverse reactions overall and by maximum severity within 7 days after each study vaccination based on a denominator that reflects the number of study participants with any e-diary data within 7 days after the specified study vaccination. In prior PCV13 clinical trials, the proportions of participants reporting each solicited reaction were based on a denominator that was defined as the number of participants reporting "Yes" for at least 1 day or "No" for all days for each local and systemic reaction. This prior method excluded participants with relevant missing e-diary data (i.e., participants who may have experienced the reaction but did not enter the information in the e-diary). Given that compliance with e-diary completion through all 7 days post-vaccination was <60% in study B7471011 (ranging from 43.8-57.4% overall), CBER performed an internal analysis to determine whether inclusion of participants with missing e-diary data in the denominator impacts study conclusions. We determined that, when using a more conservative denominator that excludes participants with missing relevant e-diary data, the reactogenicity rates were numerically higher in both study groups; however,*

there was no impact on the percent difference in the reactogenicity across study groups. We conclude that any impact of missing data in Wyeth's approach to rate calculation is balanced across study groups due to randomization and does not impact the study conclusions.

Unsolicited Adverse Events (AEs) Reported From Dose 1 Through 30 Days Post-Dose 3
From Dose 1 to 1 month after Dose 3, at least 1 AE was reported in 36.6% of PCV20 participants and 39.4% of PCV13 participants. The most frequently reported AEs by MedDRA System Organ Class (SOC) were: Infections and Infestation (PCV20: 23.2%; PCV13: 24.1%) followed by Skin and Subcutaneous Tissue Disorders (PCV20: 9.9%; PCV13: 10.7%) and Gastrointestinal disorders (PCV20: 7.8%); PCV13: 7.7%). Rates of unsolicited AEs by SOCs and Preferred Terms were similar across study groups.

Unsolicited AEs Reported From Dose 4 through 30 Days Post-Dose 4
From Dose 4 to 1 month after Dose 4, at least 1 AE was reported in 15.1% and 15.0% of participants in the PCV20 and PCV13 groups, respectively. The most frequently reported AEs were in the SOC of infections and infestations (PCV20: 12.4%; PCV13: 10.6%) followed by Respiratory, thoracic and mediastinal disorders (PCV20: 1.9%; PCV13: 1.7%) and Skin and Subcutaneous Tissue Disorders (PCV20: 1.3%; PCV13: 2.0%).

Subgroup Analyses
Descriptive subgroup analyses were conducted for the primary safety endpoints by sex, by race, and by concomitant receipt of influenza vaccine at doses 3 and 4. Rates of solicited local and systemic reactions among PCV20 recipients and among PCV13 recipients were generally similar between females and males (data not shown; ref. CSR Tables 14.51 and 14.54).

Subgroup analyses focused on rates among White vs Black or African American participants. The numbers of participants in the other race subgroups were too small for meaningful analysis. Rates of solicited systemic reaction were generally similar between White and Black or African American participants (data not shown; ref. CSR, Table 14.55). Rates of solicited local injection site redness and injection pain were lower among Black or African American participants compared to White participants; whereas rates of injection site swelling were generally higher among Black or African American participants compared to White participants. (data not shown; ref. CSR Table 14.52). These trends were not observed in the overall safety population.

Within 7 days after dose 3 and dose 4 of PCV20 and PCV13, rates of solicited local reactions were similar in those who did and did not receive a concomitant influenza vaccine (data not shown; ref. CSR Table 15.53). Within 7 days after dose 4 of PCV20 and PCV13, rates of solicited systemic reactions were similar in those who did and did not receive a concomitant influenza vaccine. Within 7 days after study dose 3 of PCV20 and PCV13, rates of solicited systemic reactions, including fever, were generally higher among participants who received concomitant influenza vaccine compared to participants who did not receive concomitant influenza vaccine (data not shown; ref. CSR Table 14.56). In the subgroup that received influenza vaccine with dose 3, 24.3% and 17.9% of PCV20 and PCV13 recipients reported any fever; in the subgroup that did not receive influenza vaccine with dose 3, 11.0% and 13.1% reported any fever (data not shown; ref. CSR Table 14.56). A similar trend was observed with rates of decreased appetite and irritability after dose 3.

The percentages of participants with unsolicited AEs from Dose 1 to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4 were generally similar across each of the sex, race, and

co-administered influenza vaccine subgroups and in the PCV20 and PCV13 study groups within each subgroup (data not shown; ref. Tables 14.57 to 14.62).

> ***Reviewer Comment:***
> *Definitive conclusions could not be made based on the trends noted above for race and concomitant influenza vaccination, as some subgroup sample sizes were small (i.e., Black or African American participants and participants who received concomitant influenza vaccine).*
>
> *The generally higher rate of fever when an influenza vaccine was concomitantly administered with dose 3 of PCV20 or PCV13 was not added to the USPI, because of the inability to draw conclusions from this descriptive data on a small sample size.*

6.1.12.3 Deaths

No deaths were reported in this trial.

6.1.12.4 Nonfatal Serious Adverse Events

The proportion of participants reporting serious adverse events (SAEs) varied based on the follow-up time period:

- Dose 1 thru 6 months after the last study dose: PCV20: 4.5%; PCV13: 3.1%
- Dose 1 thru 1 month post-dose 3: PCV20: 1.2%; PCV13: 0.9%
- Dose 4 thru 1 month post-dose 4: PCV20: 0.7% and PCV13: 0.6%

There were no meaningful imbalances in rates of SAEs by MedDRA preferred terms (PTs) or SOCs (data not shown; ref. CSR Table 21, Supplemental Table 14.49, and Supplemental Table 14.50). No SAEs were considered by the investigator or Applicant to be related to study vaccination.

> ***Reviewer Comment:*** This reviewer considers one serious adverse event (partial seizures) possibly related to the study vaccination (PCV13). This reaction occurred on day 5 after dose 1 of PCV13 in a 2 month old with a family history of seizures. Although a hereditary cause is a likely alternative etiology, the product cannot be ruled out as being possibly related due to the timing of the event following vaccination.

6.1.12.5 Other Significant Adverse Events of Interest

Febrile Seizures

A total of 7 febrile seizures were reported in this study, 5 in the PCV20 group and 2 in the PCV13 group. None of the febrile seizures were considered by the investigator to be related to study vaccination. All but one febrile seizure occurred within 1 month after vaccination; this febrile seizure occurred in a 13 month old on day 7 after dose 4 of PCV20 and was characterized as non-serious by the investigator. The infant's temperature was recorded as 104.0^{o}F in the e-diary on the day of the event. This infant had a concurrent COVID-19 illness with an onset date of Day 3 after Dose 4, which the investigator considered to be the cause of the event.

> ***Reviewer Comment:*** *Th*is reviewer considers the febrile seizure that occurred on day 7 after dose 4 of PCV20 to be possibly related to PCV20 due to the timing following vaccination. I agree the remaining 6 febrile seizure events are not related to study vaccination.

Kawasaki Disease
There was one case of Kawasaki disease, considered unrelated to the study intervention, reported on Day 103 after Dose 3 of PCV20 in a 9 month-old Native Hawaiian/other Pacific Islander male from the US with a positive family history for paternal Kawasaki disease at 2-3 years old. This participant was withdrawn from the trial due to receipt of immunoglobulins which was prohibited by the protocol.

> ***Reviewer Comment:*** *Th*is reviewer concurs with the investigator's assessment that this event is not possibly related to PCV20 due to the positive family history of Kawasaki disease and the timing of the event following vaccination.

Immune Thrombocytopenia
There was one case of immune thrombocytopenia considered unrelated to the study intervention, diagnosed 140 days after Dose 3 of PCV20 in a 10-month old Asian male from the US with nor relevant past medical history. The participant presented to his physician's office after a week of easy bruising and was found to have a low platelet count ($31x10^3/mm^3$) and anemia (hemoglobin 10.5 g/dL, hematocrit 31.4%). Following resolution of the ITP event, treatment was initiated with ferrous sulphate for anemia. The investigator and Applicant did not consider there to be a reasonable possibility that the ITP was related to the investigational product or concomitant vaccines.

> ***Reviewer Comment:*** *Th*is reviewer concurs with the investigator's assessment that this event is not possibly related to PCV20 due to the timing of the event following vaccination.

6.1.12.7 Dropouts and/or Discontinuations

Six participants (2 in the PCV20 group and 4 in the PCV13 group) were withdrawn from study intervention or withdrawn from the study due to an adverse event. One event (urticarial rash) was considered possibly related to PCV13.

- One participant in the PCV13 group was withdrawn prior to study vaccination due to failure to thrive.
- One PCV20 participant with concurrent Norovirus infection and one PCV13 participant with laryngomalacia (a congenital condition) were withdrawn due to an SAE of failure to thrive on Day 49 and Day 63, respectively. Both events were considered unrelated to study intervention.
- One PCV20 participant had an AE of unspecified seizures on Day 39 after Dose 2 and was considered unrelated, although no alternative etiology could be identified. A genetic epilepsy panel showed the presence of a heterozygous phenylalanyl-tRNA synthetase, mitochondrial (FARS2), but the clinical relevance was unknown and no formal diagnosis was made.
- One PCV13 participant had AE of epilepsy on Day 48 after Dose 2 which was considered unrelated to study intervention.
- One PCV13 participant had an AE of urticarial rash based on a photo (no in person visit) which was considered possibly related to study intervention on Day 3 after Dose 1, which resolved after 5 days.

6.1.13 Study Summary and Conclusions

Study B7471011 was designed to demonstrate the safety and immunogenicity of a 4-dose series of PCV20, given at 2, 4, 6, and 12-15 months of age, as compared to PCV13 in healthy

infants. A total of 1997 participants were randomized to PCV20 (N=1004) and PCV13 (N=993). Pediarix and Hiberix were administered concomitantly with each of the 3 infant doses. M-M-R II and VARIVAX were administered with the fourth PCV20 dose.

PCV20 effectiveness against IPD in individuals 6 weeks through 15 months of age was demonstrated from noninferiority comparisons of pneumococcal serotype-specific IgG antibody responses at 1 month after Dose 3 and 1 month after Dose 4 of PCV20 to the responses after vaccination with PCV13 (primary study objectives). For the 13 matched serotypes, IgG antibody responses in the PCV20 group were compared to the corresponding antibody responses after vaccination with PCV13. For the 7 additional serotypes, IgG antibody responses in the PCV20 group were compared to the lowest responding PCV13 serotype (excluding serotype 3) in the PCV13 group. The primary endpoint at the 1 month post-dose 3 timepoint was the proportion of participants meeting the serotype-specific pre-defined IgG antibody concentration. The post-dose 4 co-primary endpoint was the serotype-specific IgG GMC.

The primary objectives also evaluated the immunologic noninferiority of antibody responses to concomitant vaccine antigens following administration of Pediarix and Hiberix vaccines at 2, 4, and 6 months of age concomitantly with PCV20 compared to co-administration with PCV13. Secondary study objectives also assessed the immunologic noninferiority of antibody responses to MMR and Varicella vaccine antigens when M-M-RII and Varivax were administered at 12-15 months of age concomitantly with PCV20 compared to co-administration with PCV13.

The study met the pre-specified statistical noninferiority criterion for the post-dose 3 primary pneumococcal immunogenicity endpoint for 14 of the 20 vaccine serotypes. Six serotypes (5 matched serotypes and 1 additional serotype) failed to meet the post-dose 3 noninferiority criterion. Matched serotypes 1, 3, 4, 9V and 23F did not meet the pre-specified -10% noninferiority criterion; the lower bounds of the 2-sided 95% CIs for the difference in percentages of participants meeting the pre-specified serotype-specific IgG concentrations (PCV20-PCV13) were less than -10% (-12.1%, -20.1%, -12.0%, -11.3%, and -11.4% respectively). Additional serotype 12F also did not meet the post-dose 3 pre-specified -10% noninferiority criterion; the lower bound of the 2-sided 95% CI for the difference in percentages of participants meeting the pre-specified serotype-specific IgG concentration (PCV20-PCV13) was less than -10% (-41.6%). The study met the pre-specified statistical noninferiority criterion for the post-dose 4 primary pneumococcal immunogenicity endpoint for all 20 vaccine serotypes. Additional IgG GMC at 1 month after dose 3 (a key secondary endpoint), and OPA GMTs at 1 month post-dose 3 (an exploratory endpoint in a random subset of participants) support the effectiveness of PCV20 for each of the 6 pneumococcal serotypes that failed to meet the pre-specified post-dose 3 noninferiority criterion. There was no evidence that PCV20, as compared to PCV13, interfered with the antibody responses to the antigens in the concomitantly administered vaccines in this trial.

Overall, the available safety data on the use of a 4-dose series of PCV20 in infants was generally consistent with the safety data available with US-licensed PCV13 (the active control for safety). No safety concerns were identified. One febrile seizure occurred on day 7 after dose 4 of PCV20 in a 13 month old individual with a diagnosis of COVID-19 infection.

6.2 Study B7471013 (NCT04379713)

Study Title: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants

This study was initiated on May 21, 2020 and was completed (last patient last visit) on August 31, 2022.

Data from this study support the safety of the evaluated 4-dose series of PCV20 in individuals 6 weeks through 15 months of age.

6.2.1 Objectives

The primary study objective was to describe the safety profile of PCV20 in study participants receiving at least 1 dose of PCV20 and who have safety data reported after any vaccination.

- Endpoints:
    1. Percentage of participants reporting prompted local reactions within 7 days after each vaccination (injection site redness, swelling, and pain)
    2. Percentage of participants reporting prompted systemic events within 7 days after each vaccination (fever, decreased appetite, irritability, drowsiness/increased sleep, and use of antipyretic/pain medication)
    3. Percentage of participants reporting unsolicited AEs from dose 1 to 1-month PD3 and from dose 4 to 1-month PD4
    4. Percentage of participants reporting SAEs and NDCMCs from dose 1 through 6 months post-dose 4

The exploratory study objective was to describe the safety profile of PCV20 in subgroups based on race and sex. The endpoints are the same as the primary endpoints described above.

6.2.2 Design Overview

This is a Phase 3, multicenter, randomized, double-blind study with a 2-arm parallel design, conducted at sites in the US, Canada, South America and Europe. Approximately 1,500 infants ≥42 days to ≤98 days of age were randomized (2:1) to receive PCV20 or PCV13 at 2, 4, 6 (Doses 1-3) and 12-15 months of age (Dose 4). The protocol permitted other routine pediatric vaccines according to official local recommendations/regulations at any time throughout study participation (i.e., concomitant administration of non-US-licensed vaccines were permitted at non-US sites if given according to local recommendations/regulations). Standard safety monitoring was performed through 6 months after the last study vaccination. This study includes an external data monitoring committee.

> ***Reviewer Comment:*** *This review focuses on the rates of solicited adverse reactions and unsolicited non-serious AEs among the US/Puerto Rico subset of participants. Because participants enrolled at non-US sites were permitted to receive non-US licensed vaccines, this complicates the causality assessment for non-serious adverse events. Consistent with EOP2 agreements, only SAEs among participants enrolled at non-US sites contributed to the PCV20 safety database considered supportive for licensure.*

6.2.3 Population

Individuals were eligible for enrollment if they met all study inclusion criteria and none of the study exclusion criteria. Inclusion criteria 1-4 and exclusion criteria 1-3, 5, 6, 8, 9, 12, and 14-16 described in section 6.1.3 for study B7471011 also applied to study B7471013. In study B7471013, receipt of antibiotic therapy within 72 hours before a blood draw resulted in a temporary delay in a planned immunogenicity blood draw.

6.2.4 Study Treatments or Agents Mandated by the Protocol

- PCV20 and PCV20 lot numbers as described in Section 6.1.4.

- PCV13 and PCV13 lot numbers as described in 6.1.4.

6.2.6 Sites and Centers

Study B7471013 was conducted at a total of 83 sites in 10 countries (Argentina, Canada, Chile, Czech Republic, Finland, Germany, Greece, Hungary, Spain, and the US including the territory of Puerto Rico). US sites enrolled a total of 483 participants (32.0% of all 1,511 participants enrolled across all 10 countries).

6.2.7 Surveillance/Monitoring

Safety monitoring in study B7471013 was identical to study B7471011 safety monitoring. Please refer to Section 6.1.7 for details. For the pre-specified toxicity grading scales, which are identical to those used in study B7471011, are described in the footnotes to Table 16 and Table 17.

6.2.8 Endpoints

The safety endpoints in study B741013 are identical to those described for Study B7471011. Please see Section 6.2.1 of this clinical review.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Safety analyses were descriptive and there were no formal hypothesis tests. Safety analyses included all randomized participants who received at least 1 dose of PCV20 or PCV13 and had safety data after any dose. Participants were analyzed according to the vaccine actually received.

The primary analysis was planned to occur once safety data through the 1 month PD4 visit (Visit 6) were available. Wyeth's study team was unblinded after the last participant completed Visit 6 to allow for the primary analysis. Site staff involved in the conduct of the trial remain blinded to participant vaccine group until the last participant completed the last study visit (visit 7, 6 months PD4) and the database was locked for the final analysis.

6.2.10 Study Population and Disposition

Disposition of Enrolled Participants

A total of 1,511 participants were randomized to PCV20 (N=1006) and PCV13 (N=505). Study visit completion rates were similar across study groups (Table 14).

Table 14. Disposition of all Randomized Participants, Study B7471013.

Disposition	**PCV20 n (%)**	**PCV13 n (%)**
Randomized[a]	1006 (100.0)	505 (100.0)
Not vaccinated	6 (0.6)	1 (0.2)
Vaccinated	--	--
Dose 1	1000 (99.4)	504 (99.8)
Dose 2	972 (96.6)	492 (97.4)
Dose 3	964 (95.8)	483 (95.6)
Dose 4	923 (91.7)	462 (91.5)
Completed 1 month follow-up after Dose 3	961 (95.5)	481 (95.2)
Completed 1 month follow-up after Dose 4	917 (91.2)	460 (91.1)
Completed 6-month follow-up telephone contact[b]	940 (93.4)	468 (92.7)
Completed all visits per protocol	907 (90.2)	450 (89.1)
Total withdrawn	96 (9.5)	54 (10.7)

Source: STN 125731/189.0 module 5.3.5.1, B7471013 Clinical Study Report. Table 2, p 21.
a. This value is the denominator for the percentage calculations.

b. The number of participants in the 6-month follow-up telephone contact includes participants who had previously withdrawn from vaccination but whose parent(s)/legal guardian(s) consented to the safety follow-up.

Overall, a total of 150 randomized participants were withdrawn during the study. The rates of withdrawal were similar by time of withdrawal and withdrawal reason across study groups (data not shown; ref. Table 2 in clinical study report). The most common reason for withdrawal among the 1511 randomized participants included lost to follow-up (3.4%), withdrawal by parent/guardian (3.4%), no longer meets eligibility criteria (1.7%) and protocol deviations (1.1%). Two (0.1%) participants (both in the PCV20 group) were withdrawn from further vaccination and from the study due to an adverse event (see Section 6.2.12.7). Other reasons included physician decision (0.1%).

Populations Analyzed

Section 6.2.9 defines the safety population used for safety analyses. A total of 1504 participants were included in the safety population (1000 in the PCV20 group and 504 in the PCV13 group). Seven randomized participants (6 (0.6%) in the PCV20 group and 1 (0.2%) in the PCV13 group) were excluded from the safety population, because they did not receive the study vaccine. One participant randomized to the PCV13 group actually received PCV13 at Dose 1; this participant was included in the safety population but data from this participant was excluded from analysis summary tables or figures but was included in the listings.

6.2.10.1.1 Demographics

Table 15 summarizes baseline demographic characteristics for the safety population. The two study groups were similar with regard to all baseline demographics. Overall, the safety population included 49.4% females, 87.4% White, 4.7% Black, 3.7% multiracial, 2.1% Asian, 1.6% not reported, and 0.3% each American Indian or Alaska Native and Native Hawaiian or other Pacific Islander, and 37.3% were Hispanic/Latino. By country, 31.8% were from the US, 1.3% Puerto Rico, 21.3% Spain, 17.4% Hungary, 12.6% Canada, 5.3% Argentina, 3.3% Germany, 2.1 Greece, 2.0% Chile, 1.9% Czech Republic, and 1.1% Finland. Overall, the median age at Dose 1 was 64.0 days (range 43, 98) and at Dose 4 was 373 days (range 365, 455). Median gestational age was 39.0 weeks (range 34, 42); 7.4% of participants were born between ≥34 to <37 Weeks gestational age.

Table 15. Demographic Characteristics, Safety Population, Study B7471013

Characteristic	PCV20 N[a]=1000 n[b] (%)	PCV13 N[a]=503 n[b] (%)	Total N[a]=1503 n[b] (%)
Sex	--	--	--
Male	517 (51.7)	244 (48.5)	761 (50.6)
Female	483 (48.3)	259 (51.5)	742 (49.4)
Race	--	--	--
White	868 (86.8)	445 (88.5)	1313 (87.4)
Black or African American	55 (5.5)	15 (3.0)	70 (4.7)
Asian	21 (2.1)	10 (2.0)	31 (2.1)
American Indian or Alaska Native	4 (0.4)	1 (0.2)	5 (0.3)
Native Hawaiian or other Pacific Islander	2 (0.2)	2 (0.4)	4 (0.3)
Multiracial	35 (3.5)	21 (4.2)	56 (3.7)
Not Reported	15 (1.5)	9 (1.8)	24 (1.6)
Ethnicity	--	--	--
Hispanic/Latino	367 (36.7)	193 (38.4)	560 (37.3)
Non-Hispanic/non-Latino	621 (62.1)	303 (60.2)	924 (61.5)

Characteristic	PCV20 N[a]=1000 n[b] (%)	PCV13 N[a]=503 n[b] (%)	Total N[a]=1503 n[b] (%)
Not reported	12 (1.2)	7 (1.4)	19 (1.3)
Geographic region	--	--	--
USA	323 (32.3)	155 (30.8)	478 (31.8)
Puerto Rico	12 (1.2)	7 (1.4)	19 (1.3)
Argentina	51 (5.1)	28 (5.6)	79 (5.3)
Canada	127 (12.7)	62 (12.3)	189 (12.6)
Chile	20 (2.0)	10 (2.0)	30 (2.0)
Czech Republic	20 (2.0)	9 (1.8)	29 (1.9)
Germany	32 (3.2)	17 (3.4)	49 (3.3)
Spain	212 (21.2)	108 (21.5)	320 (21.3)
Finland	11 (1.1)	6 (1.2)	17 (1.1)
Greece	20 (2.0)	11 (2.2)	31 (2.1)
Hungary	172 (17.2)	90 (17.9)	262 (17.4)
Age at Dose 1 (days)	--	--	--
Mean (SD)	64.6 (8.51)	65.0 (8.95)	64.8 (8.66)
Median	64.0	64.0	64.0
Min, max	(43, 98)	(43, 97)	(43, 98)
Age at Dose 4 (days)	--	--	--
Mean (SD)	379.8 (16.69)	380.4 (18.05)	380.0 (17.15)
Median	373.0	372.0	373.0
Min, max	(365, 455)	(366, 455)	(365, 455)
Gestational age (weeks)	--	--	--
Mean (SD)	38.9 (1.50)	38.9 (1.46)	38.9 (1.49)
Median	39.0	39.0	39.0
Min, max	(34, 42)	(34, 42)	(34, 42)
≥34 to <37 Weeks	77 (7.7)	34 (6.8)	111 (7.4)
≥37 Weeks	923 (92.3)	469 (93.2)	1392 (92.6)

Source: STN 125731/189.0 module 5.3.5.1, B7471013 Clinical Study Report. Table 4, p 24-25.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. Participants who received any incorrect study vaccination during the study are excluded.
b. n = Number of participants with the specified characteristic.

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 and monitoring, Section 6.2.1 for a listing of safety endpoints, and Section 6.2.9 for details regarding the safety analysis population.

For solicited local and systemic adverse reactions, if any data were reported for local reactions within 7 days after vaccination, then the e-diary was considered transmitted. E-diary transmission rates were similar between study groups for each of the 7 days following each of the 4 study doses, ranging overall from 83.8% to 94.9% (data not shown; ref. CSR Table 6). Although transmission rates for all 7 days were low, ranging from 50.0% to 63.5% overall, the rates were similar across study groups. Transmission rates by day and across all 7 days generally decreased with each study dose.

6.2.12.2 Overview of Adverse Events

The proportions of participants enrolled at US/Puerto Rico sites with solicited local injection site reactions within 7 days after doses 1 through 4 by maximum severity were generally similar

between the two study groups (Table 16). Injection site pain was the most frequently reported injection site reaction followed by redness and swelling. Most reactions were mild or moderate in severity (≤1.3% locally were severe). The median day of onset for local reactions following doses 1 through 4 was Day 1 or Day 2, and local reactions resolved within a median and median duration of 1 to 3 days.

Table 16. Proportions of United States/Puerto Rico Participants with Solicited Local Reactions, by Maximum Severity, at the PCV20 or PCV13 Injection Site Within 7 Days After Each Vaccination, Safety Population By Dose, Study B7471013

Graded Local Reaction	Dose 1 PCV20 N[a]=329 (%)	Dose 1 PCV13 N[a]=159 (%)	Dose 2 PCV20 N[a]=301 (%)	Dose 2 PCV13 N[a]=151 (%)	Dose 3 PCV20 N[a]=294 (%)	Dose 3 PCV13 N[a]=148 (%)	Dose 4 PCV20 N[a]=264 (%)	Dose 4 PCV13 N[a]=132 (%)
Any local reaction[b]	61.7	62.3	52.8	57.0	52.0	55.4	45.8	50.8
Pain at injection site[c]	--	--	--	--	--	--	--	--
Any	51.1	57.9	43.2	47.0	41.8	45.3	36.4	43.2
Mild	31.6	35.2	25.2	25.2	26.5	27.7	24.6	32.6
Moderate	18.8	22.6	17.3	20.5	15.0	17.6	10.6	10.6
Severe	0.6	0.0	0.7	1.3	0.3	0.0	1.1	0.0
Redness[d]	--	--	--	--	--	--	--	--
Any	25.5	21.4	24.9	24.5	30.3	28.4	25.4	32.6
Mild	21.9	17.0	23.3	22.5	26.2	25.0	19.7	31.1
Moderate	3.6	4.4	1.7	2.0	4.1	3.4	5.7	1.5
Severe	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Swelling[d]	--	--	--	--	--	--	--	--
Any	18.8	19.5	16.3	21.2	18.7	20.9	17.8	22.0
Mild	12.8	13.8	13.0	15.9	15.0	18.9	12.1	20.5
Moderate	6.1	5.7	3.3	5.3	3.7	2.0	5.7	1.5
Severe	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Source: STN 125731/189.0 module 5.3.5.1, B7471013 Clinical Study Report. Table 14.24, p 105-108.
Note: Local reactions were collected in the e-diary from Day 1 through Day 7 after each dose. No Grade 4 reactions were reported in study B7471013.
a. N = number of participants with any e-diary data reported after the specified dose. This value is the denominator for the percentage calculations.
b. Any local reaction: any redness >0.0 cm, any swelling >0.0 cm, or any pain at the injection site after the specified dose.
c. Mild: hurts if gently touched; moderate: hurts if gently touched with crying; severe: causes limitation of limb movement.
d. Mild: >0.0 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm.

The proportions of participants enrolled at US/Puerto Rico sites with solicited irritability, drowsiness, and decreased appetite within 7 days after each vaccination were generally similar across study groups with no clear trends (Table 17). Irritability was the most frequently reported systemic reaction followed by drowsiness and decreased appetite. Most of these reactions were mild or moderate in severity (≤6.6%). The median day of onset for systemic reactions following doses 1 through 4 was Day 1 or Day 2, and systemic reactions resolved within a median duration of 1 to 3 days.

The proportion of participants with fever overall and by severity was highest after dose 3 in both study groups. Rates of fever generally appeared higher in the PCV20 group compared to the PCV13 group. Fever >38.9 to ≤40.0°C occurred in 0.3%-2.3% of PCV20 recipients and 0.0-2.0% of PCV13 recipients. There were no fevers >40.0°C.

Table 17. Proportions of United States/Puerto Rico Participants with Solicited Systemic Reactions, by Maximum Severity, at the PCV20 or PCV13 Injection Site Within 7 Days After Each Vaccination, Safety Population By Dose, Study B7471013

Graded Systemic Reaction	Dose 1 PCV20 N[a]=329 (%)	Dose 1 PCV13 N[a]=159 (%)	Dose 2 PCV20 N[a]=301 (%)	Dose 2 PCV13 N[a]=151 (%)	Dose 3 PCV20 N[a]=294 (%)	Dose 3 PCV13 N[a]=148 (%)	Dose 4 PCV20 N[a]=264 (%)	Dose 4 PCV13 N[a]=132 (%)
Any Systemic Adverse Reaction[b]	84.2	80.5	79.7	76.8	72.1	69.6	61.7	63.6
Irritability[c]	--	--	--	--	--	--	--	--
Any	70.8	74.8	68.1	65.6	59.5	60.8	53.8	56.8
Mild	25.2	23.3	21.9	10.6	20.7	25.7	20.8	25.0
Moderate	42.2	48.4	42.5	48.3	35.7	33.8	30.3	30.3
Severe	3.3	3.1	3.7	6.6	3.1	1.4	2.7	1.5
Drowsiness[d]	--	--	--	--	--	--	--	--
Any	66.6	61.6	55.1	57.0	45.9	41.2	40.2	36.4
Mild	46.8	46.5	36.2	39.1	32.7	28.4	25.8	25.0
Moderate	19.1	15.1	18.6	17.9	12.6	12.8	13.3	11.4
Severe	0.6	0.0	0.3	0.0	0.7	0.0	1.1	0.0
Decreased appetite[e]	--	--	--	--	--	--	--	--
Any	24.9	20.8	22.9	19.2	27.2	16.2	21.6	20.5
Mild	16.4	13.2	11.0	10.6	15.6	10.1	12.5	11.4
Moderate	8.5	6.9	11.6	7.9	10.5	5.4	6.8	8.3
Severe	0.0	0.6	0.3	0.7	1.0	0.7	2.3	0.8
Fever	--	--	--	--	--	--	--	--
≥38.0°C	4.9	3.8	11.6	7.9	12.6	8.8	9.8	6.1
≥38.0°C to 38.4°C	3.0	3.8	6.3	4.6	6.8	6.1	4.5	1.5
>38.4°C to 38.9°C	1.5	0.0	4.3	3.3	4.1	0.7	3.0	3.0
>38.9°C to 40.0°C	0.3	0.0	1.0	0.0	1.7	2.0	2.3	1.5
>40.0°C	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Use of antipyretic or pain medication[f]	38.0	36.5	42.2	47.0	38.4	35.8	38.6	28.8

Source: STN 125731/189.0 module 5.3.5.1, B7471013 Clinical Study Report. Table 14.28, p 121-125.
Note: Systemic reactions and use of antipyretic/pain medication were collected in the e-diary from Day 1 through Day 7 after each dose. No Grade 4 reactions were reported in study B7471013.
a. N = number of participants with any e-diary data reported after the specified dose. This value, which varied for each solicited reaction and severity grading, is the denominator for percentage calculations.
b. Any systemic reaction: any fever ≥38.0°C, any decreased appetite, any drowsiness, or any irritability after the specified dose.
c. Mild: easily consolable; moderate: requiring increased attention; severe: inconsolable; crying cannot be comforted.
d. Mild: increased or prolonged sleeping bouts; moderate: slightly subdued interfering with daily activity; severe: disabling not interested in usual daily activity.
e. Mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed.
f. The numbers in the table reflect yes responses (i.e., number of events reported).

Reviewer Comment: *The rates of solicited irritability, drowsiness and decreased appetite in study B7471013 are generally consistent with the corresponding results in study B7471011 presented in Section 6.1.12.2. Rates of fever generally appear numerically lower in study B7471013, particularly after doses 1, 2 and 4. Reactogenicity rates in study B7471013 may also generally appear more variable across study groups compared to study B7471011, most likely due to the smaller US sample size in study B7471013. Reactogenicity rates in study B7471011 are considered more reliable due to the larger US sample size and are included in the PCV20 prescribing information.*

Unsolicited Adverse Events (AEs) Reported From Dose 1 Through 30 Days Post-Dose 3 in the US/Puerto Rico Subset of Participants

From Dose 1 to 1 month after Dose 3, at least 1 AE was reported in 33.7% of PCV20 participants and 29.6% of PCV13 participants. The most frequently reported AEs by MedDRA System Organ Class (SOC) were: Infections and Infestation (PCV20: 22.7%; PCV13: 14.8%) followed by Skin and Subcutaneous Tissue Disorders (PCV20: 8.1%; PCV13: 5.6%), Gastrointestinal disorders (PCV20: 6.9%); PCV13: 3.7%) and Respiratory, Thoracic, and Mediastinal Disorders (PCV20: 5.7%; PCV13: 6.2%). Rates of unsolicited AEs by SOCs and Preferred Terms were generally similar across study groups (data not shown; ref. CSR Table 14.32).

Unsolicited AEs Reported From Dose 4 through 30 Days Post-Dose 4 in the US/Puerto Rico Subset of Participants

From Dose 4 to 1 month after Dose 4, at least 1 AE was reported in 13.2% and 16.8% of participants in the PCV20 and PCV13 groups, respectively. The most frequently reported AEs were in the SOC of Infections and Infestations (PCV20: 11.5%; PCV13: 16.1%) followed by Respiratory, Thoracic and Mediastinal disorders (PCV20: 1.4%; PCV13: 1.5%), Gastrointestinal Disorders (PCV20: 1.4%; PCV13: 0.7%), and Investigations (PCV20: 1.4%; PCV13: 0.7%) (data not shown; ref. CSR Table 14.36).

Subgroup Analyses
Across each of the sex, race, country/region, and gestational age subgroups, the percentages of participants with unsolicited AEs from Dose 1 to 1 month after Dose 3 and from Dose 4 to 1 month after Dose 4 were generally similar after PCV20 or PCV13 (data not shown; ref. Table 14.30 to 14.37).

> ***Reviewer Comment:*** *Subgroup analyses of solicited local and systemic reactions by sex, race, and gestational age from this study are not relevant to this clinical review, because these analyses included participants from non-US study sites who were eligible to receive non-US-licensed concomitant vaccines. CBER's analysis of reactogenicity data and unsolicited AE data are limited to data from participants receiving US-licensed vaccine administered according to the US-approved schedule only.*

6.2.12.3 Deaths

No deaths were reported in this trial.

6.2.12.4 Nonfatal Serious Adverse Events

The proportion of participants reporting SAEs across all study sites varied based on the follow-up time period:

- Dose 1 thru 6 months after the last study dose: PCV20: 4.4%; PCV13: 5.6%
- Dose 1 thru 1 month post-dose 3: PCV20: 0.8%; PCV13: 2.2%
- Dose 4 thru 1 month post-dose 4: PCV20: 0.7%; PCV13: 0.2%

There were no clinically meaningful imbalances in rates of SAEs by MedDRA PTs or SOCs (data not shown; ref. CSR Table 11, Supplemental Table 14.20 and Supplemental Table 14.21).

No SAEs were considered by the study investigator or Applicant to be related to study vaccination.

> ***Reviewer Comment:*** *This clinical reviewer agrees with the assessments made by the study investigators and Applicant.*

6.2.12.5 Other Significant Adverse Events of Interest

Febrile Seizures

One 12 month old participant from Canada experienced a febrile seizure on Day 14 after Dose 4 of PCV20, which was administered concomitantly with ProQuad (MMR-Varicella vaccine),that resolved after 1 day. The participant had a fever of 39.3°C (rectal) prior to the episode; the event was characterized as serious by the investigator, because it resulted in hospitalization. The investigator considered the event possibly related to ProQuad and not related to study intervention.

> ***Reviewer Comment:*** This reviewer considers this febrile seizure event possibly related to PCV20 due to the timing following vaccination.

6.2.12.7 Dropouts and/or Discontinuations

Two participants (0.1%) in the PCV20 group were withdrawn from further vaccination and from the trial due to an AE (infantile spasms and gaze palsy). One additional participant was withdrawn from further vaccination due to an AE (cerebral hemorrhage). Each of these adverse events were ongoing or unresolved at the time of last report.

- One 3 month old participant from Spain with no medical history had an unrelated SAE of cerebral hemorrhage diagnosed in the hospital 10 days after Dose 1. The participant was withdrawn from further vaccination at 63 days and was lost to follow-up 553 days after Dose 1. The investigator considered this event related to a brain vascular malformation that was a congenital anomaly.
- One 3 month old participant from Spain had an unrelated SAE of infantile spasms 29 days after Dose 1. The participant was withdrawn from further vaccination and was discontinued from the trial 323 days after Dose 1. The participant's MRI showed venous developmental abnormalities in the frontal white matter bilaterally and genetic study results showed chromosome 15 duplication.
- One 11 month old US participant had an unrelated AE of gaze palsy diagnosed 143 days after Dose 3. An electroencephalogram showed the gaze palsy to be epileptic in nature. The participant was withdrawn from further vaccination and from the study.

> ***Reviewer Comment:*** *This reviewer agrees with the investigator's causality assessment for each of the three events leading to withdrawal from vaccination and/or withdrawal from the study.*

6.2.13 Study Summary and Conclusions

Study B7471013 was a Phase 3, randomized, double-blind study conducted in the US, Canada, South America and Europe to demonstrate the safety of a 4-dose series of PCV20 given at 2, 4, 6 and 12-15 months of age, as compared to PCV13. A total of 1,511 participants were randomized to PCV20 (N=1006) and PCV13 (N=505). The protocol permitted other routine pediatric vaccines according to official local recommendations/regulations at any time throughout study participation (i.e., concomitant administration of non-US-licensed vaccines were permitted at non-US sites if given according to local recommendations/regulations). Standard safety monitoring was performed through 6 months after the last study vaccination.

Overall, the safety profile of PCV20 in infants enrolled in study B7471013 was generally consistent with the known safety profile of US-licensed PCV13 (the active control for safety). No safety concerns were identified. One febrile seizure occurred on day 14 after dose 4 of PCV20 given concomitantly with ProQuad (MMR-Varicella) vaccine in a 12 month old individual from Canada.

6.3 Study B7471014 (NCT04642079)

Study Title: A Phase 3, Single-Arm Trial to Evaluate the Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Children 15 Months through 17 Years of Age

This study was initiated in December 2020 and was completed in April 2022.

A single study (study B7471014) evaluated the safety of a single dose of PCV20 when administered to children 15 months through <5 years of age with three or more prior doses of PCV13 and the safety of a single dose of PCV20 when administered to individuals 5 through 17 years of age regardless of prior pneumococcal conjugate vaccination history. During the February 2020 end-of Phase 2 meeting, CBER agreed to Wyeth's proposal that the effectiveness of a catch-up dose of PCV20 in this age group would be based on the effectiveness demonstrated in infants in study B7471011 (i.e., extrapolation). To address European regulatory requirements, this study included primary immunogenicity objectives to demonstrate statistically significantly higher immune responses to the 7 additional serotypes within each age cohort after vaccination compared to baseline. Therefore, this review focuses on the assessments and results pertaining to the safety objective of this study.

6.3.1 Objectives

The primary safety objective was to describe the safety profile of PCV20 in participants from each age cohort receiving PCV20 and having safety data reported after any vaccination.

- Endpoints:
    1. Percentage of participants reporting prompted local reactions within 7 days after each vaccination (injection site redness, swelling, and pain)
    2. Percentage of participants reporting prompted systemic events within 7 days after each vaccination (Cohort 1: fever, decreased appetite, irritability, drowsiness/increased sleep, and use of antipyretic/pain medication; Cohort 2 through 4: fever, fatigue, headache, muscle pain, joint pain, and use of antipyretic/pain medication)
    3. Percentage of participants reporting unsolicited AEs from dose 1 to 1-month post-dose 3 (PD3) and from dose 4 to 1-month post-dose 4 (PD4)
    4. Percentage of participants reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) from dose 1 through 6 months post-dose 4

6.3.2 Design Overview

This is a Phase 3, multicenter, open-label, single-arm US study designed to describe the safety and immunogenicity of a single dose of PCV20 in approximately 800 planned participants ≥15 months to <18 years of age. Participants were enrolled into 4 cohorts based on the age (~200 participants per cohort):

1. ≥15 months to <24 months with at least 3 prior doses of PCV13 (most recent dose >2 months prior to enrollment)

2. ≥2 to <5 years with at least 3 prior doses of PCV13 (most recent dose >2 months prior to enrollment)
3. ≥5 to <10 years regardless of prior vaccination with PCV7 or PCV13
4. ≥10 to <18 years regardless of prior vaccination with PCV7 or PCV13

Other routine pediatric vaccines were permitted to be given at the same time as study vaccination according to local and national recommendations if it was not feasible to separate the vaccination(s) from PCV20 vaccination. The study included an external data monitoring committee.

6.3.3 Population

Participant were eligible for inclusion in the study if all of the following inclusion criteria were met:

1. Male or female children ≥15 months to <18 years of age at the time of consent.
2. Participants' parent(s)/legal guardian(s) were capable of giving signed informed consent. Depending on the age of the participant and according to local requirements, participants were also asked to provide assent as appropriate (verbal or written).
3. Participants' parent(s)/legal guardian(s) and participants, as age appropriate, were willing and able to comply with all scheduled visits and procedures
4. For children ≥15 months to <5 years of age (Cohorts 1 and 2): written documentation of receipt of at least 3 doses of PCV13; the last dose of PCV13 had to have been administered >2 months before enrollment into the trial.
5. Negative urine pregnancy test for menstruating female participants
6. For female participants of childbearing potential or male participants able to father children, willing to use a protocol specified highly effective method of contraception for at least 28 days after the last study dose

Participants were eligible for enrollment if they met none of the study exclusion criteria. Exclusion criteria 1-9 and 12-16 described in section 6.1.3 for study B7471011 also applied to study B7471013. Additional exclusion criteria applicable to study B7471013 cohorts 3 and 4 included pregnant or breastfeeding female participants. Receipt of antibiotic therapy within 72 hours before a blood draw resulted in a temporary delay in a planned immunogenicity blood draw.

6.3.4 Study Treatments or Agents Mandated by the Protocol

PCV20 as described in Section 6.1.4. Vendor/manufacturer lot numbers: CL3157

6.3.6 Sites and Centers

Study B7471014 was conducted at a total of 40 sites in the US.

6.3.7 Surveillance/Monitoring

Safety monitoring in study B7471014 was identical to study B7471011 safety monitoring, with the exception of the list of systemic reactions prompted among children in cohorts 2 through 4 (ages 2 through 17 years of age). The types of solicited systemic reactions collected in the participants ≥15 months to <2 years of age were consistent with those collected in participants 6 weeks through 15 months of age (i.e., irritability, decreased appetite, drowsiness/increased sleep and fever), while the solicited systemic reactions in participants ≥2 years of age required verbal communication by the participant (i.e., fatigue, headache, muscle pain, joint pain and fever). Please refer to Sections 6.1.7 and 6.1.1 for additional details regarding safety monitoring.

6.3.8 Endpoints and Criteria for Study Success

Please see Section 6.1.1 of this clinical review.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Safety analyses were descriptive. Safety analyses included all randomized participants who received a dose of PCV20 and had safety data after vaccination. Participants were analyzed according to the vaccine actually received. Safety data through the 1 month post-vaccination study visit from all participants were planned for analysis by the study team when available. Since all participants eligible for vaccination at visit 1 received PCV20, this was an open-label vaccination.

6.3.10 Study Population and Disposition

Disposition of Enrolled Participants

A total of 839 participants were enrolled, with between 203 and 219 participants in each of the 4 age cohorts (Table 18). A total of 831 participants received a single open-label dose of PCV20. Study visit completion rates were similar across study groups.

Table 18. Disposition of All Enrolled Participants, Study B7471014.

Disposition	≥15 to <24 Months n (%)	≥2 to <5 Years n (%)	≥5 to <10 Years n (%)	≥10 to <18 Years n (%)
Enrolled[a]	210 (100.0)	219 (100.0)	203 (100.0)	207 (100.0)
Not vaccinated	1 (0.5)	3 (1.4)	2 (1.0)	2 (1.0)
Vaccinated	209 (99.5)	216 (98.6)	201 (99.0)	205 (99.0)
Completed 1 month follow-up after vaccination	207 (98.6)	210 (95.9)	200 (98.5)	204 (98.6)
Completed 6-month follow-up telephone contact[b]	207 (98.6)	210 (95.9)	199 (98.0)	203 (98.1)
Completed all visits per protocol	207 (98.6)	210 (95.9)	199 (98.0)	203 (98.1)
Total withdrawn	3 (1.4)	9 (4.1)	4 (2.0)	4 (1.9)

Source: STN 125731/189.0 module 5.3.5.1, B7471014 Clinical Study Report. Table 2, p25.
a. This value is the denominator for the percentage calculations.
b. The number of participants in the 6-month follow-up telephone contact includes participants who had previously withdrawn from vaccination but whose parent(s)/legal guardian(s) provided consented to the safety follow-up.

The rates of withdrawal were generally similar by time of withdrawn and withdrawal reason across age subgroups (data not shown; ref. Table 2 in CSR). The reasons for withdrawal included lost to follow-up (1.0-2.3%), withdrawal by parent/guardian/participant (0.5-1.8%), no longer meets eligibility criteria (0-0.5%) and other (0-0.5%).

Populations Analyzed

Section 6.3.9 defines the safety population used for safety analyses. A total of 831 participants were vaccinated (Table 18) and included in the safety population. Eight enrolled participants were excluded from the safety population, because they did not receive PCV20.

6.3.10.1.1 Demographics

Table 19 summarizes baseline demographic characteristics for the safety population. The two study groups were similar with regard to baseline demographics. The safety population included 43.9-50.9% females, 80.4%-86.8% White, 8.3-12.4% Black, 2.5-6.0% multiracial, and ≤1.4% Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific islander, or not

reported; 15.4%-21.0% were Hispanic/Latino. The median age at vaccination was 18 months, 3 years, 7 years and 14 years for Cohorts 1 through 4, respectively.

Table 19. Demographic Characteristics, Safety Population, Study B7471014.

Characteristic	≥15 to <24 Months N[a]=209 n (%)	≥2 to <5 Years N[a]=216 n (%)	≥5 to <10 Years N[a]=201 n (%)	≥10 to <18 Years N[a]=205 n (%)
Sex	--	--	--	--
Male	117 (56.0)	106 (49.1)	108 (53.7)	115 (56.1)
Female	92 (44.0)	110 (50.9)	93 (46.3)	90 (43.9)
Race	--	--	--	--
White	168 (80.4)	173 (80.1)	174 (86.6)	178 (86.8)
Black or African American	26 (12.4)	26 (12.0)	22 (10.9)	17 (8.3)
Asian	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Multiracial	10 (4.8)	13 (6.0)	5 (2.5)	9 (4.4)
Not Reported	2 (1.0)	3 (1.4)	0 (0.0)	0 (0.0)
Ethnicity	--	--	--	--
Hispanic/Latino	35 (16.7)	45 (20.8)	31 (15.4)	43 (21.0)
Non-Hispanic/non-Latino	172 (82.3)	171 (79.2)	168 (83.6)	161 (78.5)
Not reported	2 (1.0)	0 (0.0)	2 (1.0)	1 (0.5)
Age at vaccination	--	--	--	--
Mean (SD)	18.3 (2.67)	3.0 (0.82)	7.2 (1.38)	13.6 (2.32)
Median	18.1 months	3.0 years	7.0 years	14.0 years
Min, max	(15, 24)	(2, 4)	(5, 9)	(10, 17)

Source: STN 125731/189.0 module 5.3.5.1, B7471014 Clinical Study Report. Table 4, p28.
a. N = number of participants in the specified age cohort. This value is the denominator for the percentage calculations.
b. Age at vaccination in months for participants ≥15 to <24 months of age and in years for participants ≥2 to <18 years of age.

Documentation of at least 3 prior doses of PCV13 was required for children <5 years of age. Although information regarding prior doses of PCV13 or PCV7 was not required for participants ≥5 years of age, it was collected if available. The time since the most recent pneumococcal conjugate vaccination for participants for whom this information was collected, is shown by cohort in Table 20. The majority of participants ≥15 months to <5 years of age received their last PCV13 dose at ≥1 year of age. The majority of participants ≥5 to <10 years and ≥10 to <18 years of age received their last dose of PCV13 or PCV7 five to <10 years prior and ≥10 years prior to enrollment, respectively.

Table 20. Timing of Last PCV13 or PCV7 Dose, All Vaccinated Participants, Study B741014

Timing of Last PCV Dose	≥15 to <24 Months N[a]=209 n (%)	≥2 to <5 Years N[a]=216 n (%)	≥5 to <10 Years N[a]=201 n (%)	≥10 to <18 Years N[a]=205 n (%)
Age at the time of last dose of PCV13	209 (100.0)	216 (100.0)	NA	NA
<1 Year	52 (24.9)	25 (11.6)	NA	NA
≥1 Year	157 (75.1)	191 (88.4)	NA	NA
Time since last dose of PCV13 or PCV7	--	--	--	--

Timing of Last PCV Dose	≥15 to <24 Months N[a]=209 n (%)	≥2 to <5 Years N[a]=216 n (%)	≥5 to <10 Years N[a]=201 n (%)	≥10 to <18 Years N[a]=205 n (%)
2 to <6 Months	80 (38.3)	4 (1.9)	0 (0.0)	0 (0.0)
6 to <12 Months	125 (59.8)	11 (5.1)	0 (0.0)	0 (0.0)
1 to <5 Years	4 (1.9)	201 (93.1)	34 (16.9)	4 (2.0)
5 to <10 Years	NA	NA	145 (72.1)	42 (20.5)
≥10 Years	NA	NA	NA	138 (67.3)

Source: STN 125731/189.0 module 5.3.5.1, B7471014 Clinical Study Report. Table 5, p29.
Abbreviation: NA = not applicable.
Note: Documentation to show receipt of prior pneumococcal vaccination was required for age cohorts 1 and 2 but was optional for age cohorts 3 and 4.
a. N = number of participants in the specified age cohort. This value is the denominator for the percentage calculations.
b. n = number of participants with the specified characteristic.

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 and monitoring, Section 6.3.1 for a listing of safety endpoints, and Section 6.3.9 for details regarding the safety analysis population.

For solicited local and systemic adverse reactions, if any data were reported within 7 days after vaccination, then the e-diary was considered transmitted. E-diary transmission rates were generally similar across cohorts 1-3 (≥15 month to <24 months, ≥2 to <5 years and ≥5 to <10 years cohorts) for each of the 7 days following vaccination (ranging from 83.1% to 91.5%); transmission rates were generally numerically highest in the 10 to <18 years of age cohort (ranging from 89.3% to 95.1%) (data not shown; ref. CSR Table 6). Transmission rates for all 7 days ranged from 53.2% to 65.9%.

6.3.12.2 Overview of Adverse Events

Across all age cohorts, pain at the injection site was the most frequently reported local reaction (Table 21). Rates of injection site pain appeared to increase with age (52.5%, 66.0%, 82.9% and 82.0% of participants reported injection site pain in the ≥15 to <24 months, ≥2 to <5 years, ≥5 to <10 years and ≥10 to <18 years, respectively). Rates of injection site redness and swelling were lowest in the oldest cohort (≥10 to <18 years). Most injection site reactions were mild or moderate in severity (≤2% were severe). Local reactions had a median day of onset of Day 1 or Day 2 (Day 1 was the day of vaccination) and a median duration of 1 or 2 days.

Table 21. Local Reactions, by Maximum Severity, Within 7 Days After Vaccination, Safety Population, Study B7471014

Graded Local Reaction	≥15 to <24 Months N[a]=204 %	≥2 to <5 Years N[a]=215 %	≥5 to <10 Years N[a]=199 %	≥10 to <18 Years N[a]=205 %
Any local reaction[b]	63.2	70.2	86.4	83.9
Pain at injection site[c]	--	--	--	--
Any	52.5	66.0	82.9	82.0
Mild	41.7	47.0	56.8	62.9
Moderate	9.8	17.7	24.6	17.6
Severe	1.0	1.4	1.5	1.5

Graded Local Reaction	≥15 to <24 Months Na=204 %	≥2 to <5 Years Na=215 %	≥5 to <10 Years Na=199 %	≥10 to <18 Years Na=205 %
Redness[d]	--	--	--	--
Any	37.7	39.1	37.2	15.1
Mild	30.4	22.8	16.6	10.7
Moderate	7.4	15.3	18.6	3.9
Severe	0.0	0.9	2.0	0.5
Swelling[d]	--	--	--	--
Any	22.1	23.3	27.1	15.6
Mild	15.7	11.6	10.6	5.4
Moderate	6.4	11.2	15.6	10.2
Severe	0.0	0.5	1.0	0.0

Source: STN 125731/189.0 module 5.3.5.1, B7471014 Clinical Study Report. Table 13, p45-46.
Note: Local reactions were collected in the e-diary from Day 1 through Day 7 after vaccination. No Grade 4 reactions were reported in study B7471014.
a. N = number of participants with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
b. Any local reaction: any redness >0.0 cm, any swelling >0.0 cm, any pain at the injection site.
c. For participants ≥15 to <24 months of age, mild: hurts if gently touched; moderate: hurts if gently touched with crying; severe: causes limitation of limb movement. For participants ≥2 to <18 years of age, mild: does not interfere with activity; moderate: interferes with activity, severe: prevents daily activity.
d. Mild: >0.0 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm.

The most frequently reported systemic reactions varied based on age cohort (Table 22 and Table 23). In Cohort 1 (≥ 15 to <24 months), irritability was the most frequently reported systemic reaction (61.8%) followed by drowsiness/increased sleep (41.7%). In Cohort 2 (≥2 to <5 years), fatigue was most frequently reported solicited reaction (27.8-37.2%) followed by muscle pain (26.5%). In Cohorts 3 and 4 (≥ 5 to <18 years), muscle pain was the most frequently reported solicited reaction (39.2-48.3%) followed by fatigue (27.8-28.1%) and headache (18.6-29.3%). Most systemic events were mild or moderate in severity (≤2.0% were severe).

Fever rates and rates of antipyretic or pain medication in Cohort 1 (≥ 15 to <24 months) were similar to rates reported in the infant trials. Fever rates in Cohorts 2 through 4 (≥2 to <5 years, ≥5 to <10 years, and ≥10 to <18 years) were low (≤3.3%). Fever >38.9°C to 40.0°C ranged from 0%-2.9% across all age cohorts. There were no fevers >40.0°C.

Systemic events had a median day of onset between Day 1 and Day 2 and a median duration of 1 or 2 days.

Table 22. Systemic Reactions, by Maximum Severity, Within 7 Days After Vaccination, Cohort 1 (≥15 Months to <24 Months of Age) Safety Population, Study B7471014

Graded Systemic Reaction	≥15 Months to <24 Months Na=204 %
Any Systemic Adverse Reaction[b]	75.0
Irritability[c]	
Any	61.8
Mild	22.5
Moderate	37.3
Severe	2.0

Graded Systemic Reaction	≥15 Months to <24 Months N[a]=204 %
Drowsiness[d]	
Any	41.7
Mild	31.4
Moderate	9.3
Severe	1.0
Decreased appetite[e]	
Any	25.0
Mild	17.6
Moderate	6.4
Severe	1.0
Fever	
≥38.0°C	11.8
≥38.0°C to 38.4°C	5.9
>38.4°C to 38.9°C	2.9
>38.9°C to 40.0°C	2.9
>40.0ºC	0.0
Use of antipyretic or pain medication[f]	31.4

Source: STN 125731/189.0 module 5.3.5.1, B7471014 Clinical Study Report. Table 14, p47.
Note: Systemic events and use of antipyretic/pain medication were collected in the e-diary from Day 1 through Day 7 after vaccination. No Grade 4 reactions were reported in study B7471014.
a. N = number of participants with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
b. Any systemic event: any fever ≥38.0°C, any decreased appetite, any drowsiness, any irritability.
c. Mild: easily consolable; moderate: requiring increased attention; severe: inconsolable; crying cannot be comforted.
d. Mild: increased or prolonged sleeping bouts; moderate: slightly subdued interfering with daily activity; severe: disabling not interested in usual daily activity.
e. Mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed.
f. The numbers in the table reflect yes responses (i.e., number of events reported).

Table 23. Systemic Reactions, by Maximum Severity, Within 7 Days After Vaccination, Cohorts 2 through 4 (≥2 to <5 Years, ≥5 to <10 Years, and ≥10 to <18 Years) Safety Population, Study B7471014

Graded Systemic Reaction	≥2 to <5 Years N[a]=215 %	≥5 to <10 Years N[a]=199 %	≥10 to <18 Years N[a]=205 %
Any systemic reaction[b]	50.2	58.3	68.3
Muscle Pain[c]	--	--	--
Any	26.5	39.2	48.3
Mild	17.7	26.6	34.6
Moderate	8.4	11.1	13.2
Severe	0.5	1.5	0.5
Fatigue[c]	--	--	--
Any	37.2	28.1	27.8
Mild	21.9	19.1	15.6
Moderate	14.4	8.5	12.2
Severe	0.9	0.5	0.0
Headache[c]	--	--	--
Any	5.6	18.6	29.3
Mild	3.3	14.6	20.0
Moderate	1.9	3.0	7.8
Severe	0.5	1.0	1.5
Joint Pain[c]	--	--	--
Any	3.7	6.5	8.3

Graded Systemic Reaction	≥2 to <5 Years Na=215 %	≥5 to <10 Years Na=199 %	≥10 to <18 Years Na=205 %
Mild	2.3	3.0	3.4
Moderate	1.4	3.0	4.9
Severe	0.0	0.5	0.0
Fever	--	--	--
≥38.0°C	3.3	0.5	0.0
≥38.0°C to 38.4°C	1.4	0.5	0.0
>38.4°C to 38.9°C	1.4	0.0	0.0
>38.9°C to 40.0°C	0.5	0.0	0.0
>40.0°C	0.0	0.0	0.0
Use of antipyretic or pain medication[d]	16.7	25.6	14.6

Source: STN 125731/189.0 module 5.3.5.1, B7471014 Clinical Study Report. Table 15, p48-49.
Note: Systemic events and use of antipyretic/pain medication were collected in the e-diary from Day 1 through Day 7 after vaccination. No Grade 4 reactions were reported in study B7471014.
a. N = number of participants with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
b. Any systemic event: any fever ≥38.0°C, any fatigue, any headache, any muscle pain, or any joint pain.
c. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily routine activity.
d. The numbers in the table reflect yes responses (ie, number of events reported).

Subgroup Analyses
Safety results were generally comparable across subgroups based on sex and race within each of the study's age-based cohorts, with no clear or consistent trends (data not shown; ref. CSR Tables 14.33 to 14.56).

6.3.12.3 Deaths

No deaths were reported in this trial.

6.3.12.4 Nonfatal Serious Adverse Events

A total of five (0.6%) participants experienced SAEs during the trial: two in the 15 to <24 month cohort and 3 in the 10 to <18 year cohort. No SAE was assessed by the investigator as related to study intervention. One SAE occurred within 30 days of vaccination (near drowning). The four remaining SAEs were reported between 1 month and 6 months post-vaccination and included appendicitis (Day 112), papillary thyroid cancer (Day 68), febrile convulsion (Day 46) and headache (Day 49). The febrile convulsion occurred in a 16 month old male on Day 46 after receiving PCV20; the participant had a fever of 104.8°F and decreased oral intake due to an unspecified infectious process. One Cohort 4 participant (10 to <18 years) was noted to have a thyroid nodule on physical exam at Visit 1 was subsequently diagnosed with papillary thyroid cancer.

> ***Reviewer Comment:*** *This reviewer agrees with the investigator's causality assessment regarding the five SAEs that occurred in study B7471014.*

6.3.12.5 Other Significant Adverse Events of Interest

Please see Section 6.3.12.4 regarding one febrile convulsion event reported as a SAE. There were no other reported significant adverse events.

6.3.12.7 Dropouts and/or Discontinuations

No participants were withdrawn from the trial due to an adverse event.

6.3.13 Study Summary and Conclusions

Study B7471014 was a Phase 3, single-arm, open-label trial conducted in the US to describe the safety and immunogenicity of a single dose of PCV20 when administered to children 15 months through <5 years of age with three or more prior doses of PCV13 and the safety of a single dose of PCV20 when administered to individuals 5 through 17 years of age regardless of prior pneumococcal conjugate vaccination history (N=831). Other routine pediatric vaccines were permitted to be given at the same time as study vaccination according to local and national recommendations if it was not feasible to separate the vaccination(s) from PCV20 vaccination. This review focused on the safety assessments and results in this study. CBER previously agreed to Wyeth's proposal that the effectiveness of a catch-up dose of PCV20 in this age group would be based on the effectiveness demonstrated in infants in study B7471011 (i.e., extrapolation).

Standard safety monitoring was performed through 6 months after vaccination. Overall, the safety evaluations of PCV20 when given as a single catch-up or supplemental (i.e., 5th) pneumococcal conjugate vaccine in individuals 15 months through 17 years of age revealed no safety concerns.

6.4 Study B7471003 (NCT03512288)

Study Title: A Phase 2, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a Multivalent Pneumococcal Conjugate Vaccine in Healthy Infants

This study was initiated in April 2018 and was completed (last participant last visit) in February 2020.

Safety and immunogenicity data from this study supported initiation of the Phase 3 clinical trials evaluating PCV20 in pediatric populations. Safety data from this study contributed towards the total safety database supporting PCV20 licensure in infants and toddlers 6 weeks through 15 months of age. This review will focus on the safety results from this study, as study B7471011 provided the formal comparative immunogenicity analyses supporting PCV20 effectiveness (i.e., pre-specified hypothesis testing).

6.4.1 Objectives

The primary safety objective was to describe the safety profile of PCV20 in healthy infants.

- Endpoints:
    1. Percentage of participants reporting prompted local reactions within 7 days after each vaccination (injection site redness, swelling, and pain)
    2. Percentage of participants reporting prompted systemic events within 7 days after each vaccination (fever, decreased appetite, irritability, drowsiness/increased sleep, and use of antipyretic/pain medication)
    3. Percentage of participants reporting unsolicited AEs from dose 1 to 1-month post-dose 3 (PD3) and from dose 4 to 1-month post-dose 4 (PD4)
    4. Percentage of participants reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) from dose 1 through 6 months post-dose 4

6.4.2 Design Overview

This was a Phase 2, multicenter, randomized, active-controlled, double-blind study conducted in the US. Wyeth planned to enroll approximately 460 infants to receive PCV20 or PCV13 active control at 2, 4, 6 and 12-15 months of age. Participants were administered Pediarix (DTaP-

HBV-IPV) concomitantly at 2, 4 and 6 months of age. Other routine pediatric vaccines (polio, hepatitis B, Hib, MMR, rotavirus, meningococcal, influenza) were permitted as specified in the study protocol. This study included an external data monitoring committee.

6.4.3 Population

Study eligibility criteria were as described in Section 6.1.3.

6.4.4 Study Treatments or Agents Mandated by the Protocol

- PCV20 as described in Section 6.1.4. Vendor/Manufacturer Lot Numbers: T82474, W73014
- PCV13 as described in Section 6.1.4: Vendor/Manufacturer Lot Number: T82473
- Pediarix as described in Section 6.1.4. Vendor/Manufacturer Lot Number: 9A2KC

6.4.6 Sites and Centers

Study B7471003 was conducted at a total of 33 sites in the US.

6.4.7 Surveillance/Monitoring

Safety monitoring in study B7471003 was identical to study B7471011 safety monitoring. Please refer to Section 6.1.7. The toxicity grading scales using to assess severity of solicited adverse reactions were also identical to those used in study B7471011 and are described in the footnotes to Table 12 and Table 13.

6.4.8 Endpoints and Criteria for Study Success

Please see Section 6.4.8 of this clinical review.

6.4.9 Statistical Considerations & Statistical Analysis Plan

Safety analyses were descriptive. The safety population includes all randomized participants who received at least 1 dose of the investigational product and who had safety follow-up after any dose. Participants were analyzed according to the vaccine actually received.

Safety data from dose 1 through the 1 month after dose 3, from 1 month post-dose 3 through Dose 4, and from 1 month after Dose 4 through 6 months after Dose 4 were evaluated when available.

Wyeth personnel directly involved in evaluating participant data were blinded to vaccine assignment until the planned analysis of safety and immunogenicity results using 1 month after Dose 3 data from all subjects. Laboratory personnel performing the immunologic assays were blinded until all assays had been completed and assay results finalized. Investigator personnel remained blinded to participant treatment assignments until after the safety follow-up was completed 6 months after the last dose.

6.4.10 Study Population and Disposition

A total of 460 participants were randomized to PCV20 (N=232) and PCV13 (N=228). One participant in each study group was randomized but not vaccinated (data not shown; ref. Table 6 of CSR). A similar proportion of participants in each group completed each study visit. Overall, 99.6%, 94.6%, 90.4%, and 85.0% completed vaccinations of dose 1, 2, 3, and 4, respectively. Overall, the most common reason for withdrawal before the 1 month post-dose 3 visit and between the 1 month post-dose 3 visit and the dose 4 visit was withdrawal by parent/guardian (5.7% and 1.5%, respectively). The most common reason for withdrawal between the dose 4

and 1 month post-dose 4 visit and between the 1 month post-dose 4 and 6 months post-dose follow-up visit was lost to follow-up (1.5% and 0.9%, respectively).

6.4.10.1 Populations Enrolled/Analyzed

Section 6.4.9 defines the safety population used for safety analyses. A total of 458 participants (231 from the PCV20 group and 227 from the PCV13 group) were in the overall safety population. The Dose 1 to Dose 3 safety population was identical to the overall safety population. The Dose 4 safety population included a total of 391 participants (197 from the PCV20 group and 194 from the PCV13 group).

> ***Reviewer Comment:*** *Participants in study B7471003 were permitted to receive other routine pediatric vaccines, including influenza and rotavirus vaccines, concomitantly with PCV20 or PCV13 according to local or national recommendations. The proportion of participants receiving a concomitant influenza vaccine and the proportion of participants receiving a concomitant rotavirus vaccine were similar across the two study groups in Study B7471003. Among PCV20 recipients, 21.4% received an influenza vaccine with Dose 3 of PCV20; 65.3% to 94.8% received a rotavirus vaccine with each of the first 3 doses of PCV20.*

6.4.10.1.1 Demographics

The two study groups were similar with regard to all baseline demographics for the safety population. Overall, the safety population included 49.3% females, 72.2% White, 13.9% Black, 8.0% multiracial, 3.0% Asian, 1.5% Asian Indian or Alaskan Native, 0.9% Native Hawaiian or other Pacific Islander, and 0.4% not reported; 17.6% were Hispanic/Latino. The median age at Dose 1 was 64 days (range 44, 95)

6.4.12 Safety Analyses

6.4.12.1 Methods

Safety analyses were descriptive. Please see Section 6.4.7 for details regarding safety surveillance and monitoring, Section 6.4.1 for a listing of safety endpoints, and Section 6.4.9 for details regarding the safety analysis population.

E-diary transmission rates for doses 1-4 was above 72.6% for each day. Daily transmission rates were similar across study groups. Transmission rates for all 7 days were similar across study groups and ranged from 35.3% to 51.5% overall.

6.4.12.2 Overview of Adverse Events

The proportion of participants who reported solicited adverse reactions and unsolicited adverse events generally followed the trends reported in Phase 3 studies in prior sections of this memo. One pertinent reaction involved a PCV20 recipient who experienced isolated injection site hypersensitivity (redness) within approximately 30 minutes after each of the first 3 doses which resolved on the same day; this reaction was not observed after the fourth dose in this participant. This reaction is included in Section 6 of the PCV20 prescribing information.

6.4.12.3 Deaths

No deaths were reported in this trial.

6.4.12.4 Nonfatal Serious Adverse Events

SAEs were reported by 12 (5.2%) of PCV20 recipients and 5 (2.2%) of PCV13 recipients. No SAEs were considered related to the study vaccine. One 10-week old participant in the PCV20 group with a history of poor weight gain and laryngomalacia was withdrawn during the study due to a SAE (worsening failure to thrive resulting in hospitalization) on Day 290.

> ***Reviewer Comment:*** *This reviewer agrees with the investigator's causality assessments of the SAEs reported in this study.*

6.4.12.5 Adverse Events of Special Interest (AESI)

There were no significant adverse events of interest reported in this study.

6.4.12.7 Dropouts and/or Discontinuations

Please see Section 6.4.12.4 regarding the one participant who was withdrawn from the study due to a SAE.

6.4.13 Study Summary and Conclusions

Study B7471003 was a Phase 2, randomized, double-blind, active-controlled study conducted in the US to describe the safety and immunogenicity of a 4-dose series of PCV20 given at 2, 4, 6 and 12-15 months of age, as compared to PCV13. A total of 460 participants were randomized to PCV20 (N=232) and PCV13 (N=228). Participants were administered Pediarix (DTaP-HBV-IPV) concomitantly at 2, 4 and 6 months of age. Other routine pediatric vaccines (polio, hepatitis B, Hib, MMR, rotavirus, meningococcal, influenza) were permitted as specified in the study protocol). This study included an external data monitoring committee. Standard safety monitoring was performed through 6 months after the last study vaccination. One participant experienced isolated injection site hypersensitivity (redness) within approximately 30 minutes of Prevnar 20 after each of the first 3 doses resolving on the same day, this was not observed after the fourth dose.

Overall, the safety results of PCV20 in infants enrolled in study B7471003 were generally consistent with safety results observed in Phase 3 studies described in prior sections of this memo. No safety concerns were identified.

7. Integrated Overview of Efficacy

This submission included one study with immunogenicity data to support PCV20 vaccine effectiveness (study B7471011). Please refer to Section 6.1 for details regarding the study design and results.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

The integrated summary of safety includes results from the single Phase 2 study (B7471003) and from the three Phase 3 studies (B7471011, B7471013 and B7471014) submitted to this sBLA. The methods for safety data collection and analysis were the same in the three infant studies B7471003, B7471011 and B7471013 and are described in Section 6.1.7. Safety monitoring in study B7471014 was identical to the infant studies with the exception of the list of

systemic reactions prompted among participants 2 through 17 years of age (see Section 6.3.7 for details).

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of PCV20 in individuals from 6 weeks through 17 years of age was evaluated in 3 randomized, double-blind, active-controlled, clinical trials and one single-arm clinical trial. Table 1 in Section 5.3 includes a brief description of the three Phase 3 studies included in the integrated summary of safety.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Overall Safety Database
Across the 4 pediatric trials (B7471003, B7471011, B7471013, and B7471014) conducted in the Americas and Europe, 3063 participants received at least one dose of PCV20, and 1720 participants received at least one dose of PCV13.

Safety Database in Individuals 6 Weeks of Age Through 15 Months of Age
Globally, 2232 participants who received at least one dose of a 4-dose series of PCV20 and 1717 participants who received at least one dose of a 4-dose series of PCV13 were included in the infant safety analysis. In the US (including the US territory of Puerto Rico), 1567 participants received at least one dose of a 4-dose series of PCV20 and 1376 participants received at least one dose of a 4-dose series of PCV13.

Safety Database in Individuals 15 Months of Age Through 17 Years of Age
The safety of a single dose of PCV20 in individuals 15 months through 17 years of age was assessed in a single study conducted in the US (B7471014). A total of 831 participants received a single dose of PCV20 among the 4 age groups (≥15 to <24 months, ≥2 to <5 years, ≥5 to <10 years, and ≥10 to <18 years).

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

Wyeth pooled SAE safety data for Studies B7471003, B7471011, and B7471013, because of comparable study design (randomized, double-blind, active-controlled), study population (healthy infants ≥42 days to ≤98 days of age days at enrollment), and dosing regimens (4-dose series at 2, 4, 6, 12-15 months of age). Study B7471014 SAEs were not pooled with the infant study SAEs in the integrated analyses due to differences in the cited study elements.

8.4 Safety Results

8.4.1 Deaths

No deaths were reported in the four clinical studies submitted to this sBLA.

8.4.2 Nonfatal Serious Adverse Events

SAEs Among All Study Participants 6 Weeks of Age Through 15 Months of Age
Globally, across the 3 infant trials, the proportion of participants reporting 1 or more SAEs within 6 months after the fourth dose of PCV20 was 4.5% (101 of 2232 participants). This was similar to the proportion of participants with SAEs after vaccination with PCV13 (3.7%; 64 of 1717 participants). The proportions of SAEs observed from the first dose to 1 month after the third dose were 1.1% and 1.2% for PCV20 and PCV13 groups respectively. The proportions of SAEs

observed from the fourth dose to 1 month after the fourth dose were 0.7% and 0.5% for PCV20 and PCV13 groups, respectively. There were no notable patterns or imbalances between vaccine groups for specific categories of SAEs that would suggest a causal relationship to PCV20. Participants in these studies may have received other US-licensed (B7471003, B7471011, and B7471013) or non-US-licensed concomitant (Study B7471013) vaccines according to their local recommended schedule.

In the PCV20 group, two febrile seizures considered possibly related to vaccination with PCV20 were reported. One case was serious and occurred 14 days after the fourth dose given with MMR and varicella vaccine. One case was categorized as non-serious by the investigator and occurred 7 days after the fourth dose of PCV20 in an individual with diagnosis of COVID-19 infection.

SAEs Among Study B7471014 Participants 15 Months of Age Through 17 Years of Age
Five participants (5.2%) reported SAEs within 6 months after vaccination (2 participants [1.0%] ≥15 to <24 months of age and 3 participants [1.5%] ≥10 to <18 years of age). One participant (0.5%) ≥15 to <24 months of age reported an SAE within 1 month after vaccination. No SAEs were considered related to the vaccination.

8.4.3 Study Dropouts/Discontinuations

Subject disposition data were summarized separately for each of the studies in Sections 6.1.12.7, 6.2.12.7, 6.3.12.7, and 6.4.12.7.

8.4.4 Common Adverse Events

In individuals 2, 4, 6, and 12 through 15 months of age vaccinated with a 4-dose schedule, the most commonly reported solicited adverse reactions >10% were irritability (>60%), pain at the injection site (>30%), drowsiness (>30%), decreased appetite and injection site redness (>20%), injection site swelling (>10%), and fever (>10%).

In individuals 15 months through 17 years of age vaccinated with a single dose, the most commonly reported solicited adverse reactions >10% were irritability (>60% in individuals less than 2 years of age), pain at the injection site (>50%), drowsiness (>40% in individuals less than 2 years of age), fatigue and muscle pain (>20% in individuals 2 years of age and older), decreased appetite (>20% in individuals less than 2 years of age), injection site swelling and injection site redness (>10%), headache (>10% in individuals 5 years of age and older), and fever (>10% in individuals less than 2 years of age).

In individuals 18 through 59 years of age, the most commonly reported solicited adverse reactions >10% were pain at the injection site (>70%), muscle pain (>50%), fatigue (>40%), headache (>30%), and arthralgia and injection site swelling (>10%).

In individuals 60 years of age and older, the most commonly reported solicited adverse reactions >10% were pain at the injection site (>50%), muscle pain and fatigue (>30%), headache (>20%), and arthralgia (>10%).

8.6 Safety Conclusions

The safety of PCV20 in individuals from 6 weeks through 17 years of age was evaluated in 3 randomized, double-blind, active-controlled, clinical trials (B7471003, B7471011, and B7471013) and one single-arm clinical trial (B7471014). Across the 4 pediatric trials conducted in the Americas and Europe, 3063 participants received at least one dose of PCV20, and 1720

participants received at least one dose of PCV13. Reported rates of local and systemic adverse reactions were generally comparable between PCV20 and PCV13 recipients. The reactogenicity profile of PCV20 is similar to that observed with other licensed childhood vaccines. No serious safety concerns were identified for any of the evaluated age groups. In the Prevnar 20 group, two febrile seizures considered possibly related to vaccination with Prevnar 20 were reported. One case was serious and occurred 14 days after the fourth dose given with MMR and varicella vaccine. One case was non-serious and occurred 7 days after the fourth dose of Prevnar 20 in an individual with diagnosis of COVID-19 infection. One participant experienced isolated injection site hypersensitivity (redness) within approximately 30 minutes of Prevnar 20 after each of the first 3 doses resolving on the same day, this was not observed after the fourth dose.

9. Additional Clinical Issues

9.1 Special Populations

Section 8.4 of the USPI was edited to include the information in Section 9.1.3.

9.1.1 Human Reproduction and Pregnancy Data

Please refer to Section 8.1 of the PCV20 prescribing information. No new information was available in this submission pertaining to human reproduction and pregnancy.

9.1.2 Use During Lactation

Please refer to Section 8.2 of the PCV20 prescribing information. No new information was available in this submission pertaining to use during lactation.

9.1.3 Pediatric Use and PREA Considerations

Pediatric Use and PREA Considerations for the Invasive Pneumococcal Indication
Studies B7471011, B7471013, and B7471014, included in this sBLA submission, fulfill the 3 post-marketing requirements (PMRs) identified under PREA in the initial BLA approval (June 10, 2021) for the deferred evaluation of PCV20 in individuals 6 weeks through 17 years of age for the IPD indication. Data from these three PMR studies support the safety and effectiveness of PCV20 for the proposed IPD indication in the included age groups as follows:

- Data from studies B7471011 and B7471013 support the safety of a 4-dose series of PCV20 when administered to infants and toddlers 6 weeks through 15 months of age as well as the safety of the proposed catch-up vaccination schedules in individuals 7 months of age and older.

- Data from study B7471014 support the safety of the proposed catch-up/supplemental vaccination with a single dose of PCV20 in certain individuals 15 months of age and older.

- Immunogenicity data from study B7471011 support the effectiveness of a 4-dose series of PCV20 for the prevention of vaccine-type IPD in infants and toddlers 6 weeks through 15 months of age.

- The effectiveness of PCV20 when administered according to the proposed catch-up vaccination schedules in individuaols initiating vaccination at 7 months through 17 years of age and in individuals 15 months through 17 years of age previously vaccinated or incompletely vaccinated with a pneumococcal conjugate vaccine is supported by

evidence from clinical studies in younger children who received a 4-dose series of PCV20. The PCV20 proposed catch-up vaccination schedules are supported by evidence from clinical studies of catch-up vaccination with PCV13 and PCV7.

These 3 studies were presented to the FDA's Pediatric Review Committee on March 14, 2023. The committee agreed that Wyeth's PMRs for individuals 6 weeks through 17 years of age were fulfilled by the included studies.

Pediatric Use and PREA Considerations for the Otitis Media Indication

The sBLA submission triggered PREA for the new indication of otitis media. Partial waiver requests of pediatric studies for the otitis media indication were submitted in Module 1.9 of the sBLA. Wyeth requested a partial waiver of the pediatric study requirement in individuals from birth through <6 weeks of age for the otitis media indication, because the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

Wyeth requested a partial waiver of the pediatric study requirement for the otitis media indication in individuals 6 years through 17 years of age, because the necessary studies are impossible or highly impracticable due to the low incidence of acute otitis media in this age group.

The pediatric assessment for the otitis media indication in individuals 6 weeks through 5 years of age consists of data from two previously conducted well-controlled clinical endpoint efficacy studies with PCV7: the Finnish Otitis Media trial and the Northern California Kaiser Permanente trial. These studies supported the effectiveness of PCV13 in children 6 weeks through 5 years of age for the prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, are described in detail in the PCV13 prescribing information, and are included in the PCV20 prescribing information. The pediatric assessment for the otitis media indication also consists of safety data in infants and children 6 weeks through 5 years of age from the three IPD PMR studies noted above.

9.1.4 Immunocompromised Patients

The safety and effectiveness of PCV20 have not been established in immunocompromised individuals.

10. Conclusions

Wyeth Pharmaceuticals, LLC submitted a sBLA for PCV20 on October 26, 2022. With the sBLA, Wyeth is seeking approval of PCV20 for the following proposed indications:

- In individuals 6 weeks through 17 years: active immunization for the prevention of 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 individuals 6 weeks through 5 years of age: active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

PCV20 is currently indicated for active immunization for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older. The June 10, 2021 approval letter included three deferred PREA PMRs (PMRs 2, 3, and 4

representing studies B7471011, B7471013, and B7471014, respectively) for the IPD indication. This sBLA contains safety and immunogenicity data from these three PMR studies and Phase 2 infant study B7471003 provide evidence to support the safety and effectiveness of a 4-dose series of PCV20 in individuals 6 weeks through 15 months of age and the proposed catch-up vaccination schedules of PCV20 in individuals 7 months of age and older as follows:

- Data from studies B7471011 and B7471013 support the safety of a 4-dose series of PCV20 when administered to infants and toddlers 6 weeks through 15 months of age as well as the safety of the proposed catch-up vaccination schedules in individuals 7 months of age and older.

- Data from study B7471014 support the safety of the proposed catch-up/supplemental vaccination with a single dose of PCV20 in certain individuals 15 months of age and older.

- Immunogenicity data from study B7471011 support the effectiveness of a 4-dose series of PCV20 for the prevention of vaccine-type IPD in infants and toddlers 6 weeks through 15 months of age.

- The effectiveness of the PCV20 when administered according to the proposed catch-up vaccination schedules in infants and individuals initiating vaccination at 7 months through 17 years of age and in individuals 15 months through 17 years of age previously vaccinated or incompletely vaccinated with a pneumococcal conjugate vaccine is supported by evidence from clinical studies in younger children who received a 4-dose series of PCV20. The PCV20 proposed catch-up vaccination schedules are supported by evidence from clinical studies of catch-up vaccination with PCV13 and PCV7.

The pediatric assessment for the otitis media indication consists of data from two previously conducted well-controlled clinical endpoint efficacy studies with PCV7: the Finnish Otitis Media (FinOM) trial and the Northern California Kaiser Permanente trial. These studies supported the effectiveness of PCV13 in children 6 weeks through 5 years of age for the prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, are described in detail in the PCV13 prescribing information, and are included in the PCV20 prescribing information. PCV20 effectiveness against AOM due to serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in children 6 weeks through 5 years of age is anticipated to be similar to PCV7 effectiveness, because the vaccines are manufactured and formulated similarly and contain 7 of the same polysaccharide conjugates. The pediatric assessment for the otitis media indication also consists of safety data in infants and children 6 weeks through 5 years of age from the three IPD PMR studies noted above.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 24 summarizes PCV20 risk-benefit considerations in individuals 6 weeks through 17 years of age.

Table 24. Risk Benefit Considerations of Vaccination with Prevnar 20 (PCV20) in Individuals 6 Weeks of Age and Older

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *S. pneumoniae* can cause invasive pneumococcal disease (IPD) in individuals <18 years of age, including meningitis and bacteremia. IPD can result in significant morbidity, permeant sequelae, and death. The incidence of IPD during 2018-2019 was 7.2 per 100,000 children aged <5 years and individuals 5-18 years, respectively. The 7 additional serotypes covered by PCV20 but not PCV13 (8, 10A, 11A, 12F, 15B, 22F, and 33F) of which 5 serotypes are unique to PCV20 (i.e., those not included in current US PCV15) caused 15% and 13% of IPD cases in individuals <5 years and 5-18 years, respectively. • *S. pneumoniae* is also a common cause of acute otitis media (AOM). It is the second most common cause of acute otitis media (following non-b *Haemophilus influenzae)*, accounting for 15-20% of cases. AOM occurs primarily in children <5 years of age. The peak age for AOM in the US is between 6 and 12 months of age. • Conditions that increase the risk of IPD among individuals 6 weeks through 17 years of age include functional/anatomic asplenia, immunocompromising conditions, chronic heart disease, lung disease, liver disease, CSF leak, and having a cochlear implant. Rates are also increased among individuals in certain racial and ethnic groups, including Alaska Natives, African Americans, and certain American Indian groups (Navajo and White Mountain Apache).	• IPD is a serious and life-threatening condition that can result in significant morbidity and mortality in individuals <18 years of age. • AOM caused by *S. pneumoniae* is a major cause of morbidity in children <5 years of age. • The risk of serious pneumococcal disease is greatest in individuals with certain underlying medical conditions or in certain racial and ethnic groups are at particularly higher risk of IPD.
Unmet Medical Need	• PCV13 and Vaxneuvance are two pneumococcal vaccines approved for use in the US in pediatric populations 6 weeks through 17 years of age. Pneumovax 23 is approved for use in the US in pediatric populations 2 years through 17 years of age (PPSV23 does not elicit a protective antibody response in children <2 years of age). PCV20 includes 13 serotypes in common with PCV13, 15 serotypes in common with PCV13, and 19 serotypes in common with PPSV23. • The 5 serotypes unique to PCV20 are responsible for approximately 15 % of IPD cases in individuals <5 years and 5-18 years, respectively. • According to US multistate surveillance, the incidence of IPD during 2018-2019 was 7.2 per 100,000 children aged <5 years and 1.5 per 100,000 individuals 5-18 years, respectively (Kobayashi 2022). Additional serotypes unique to PCV20 accounted for 15% and 13% of IPD cases in individual <5 years and 5-18 years, respectively (Gierke 2023). • There has been no evidence of an indirect (population-level) impact of PCV13 vaccination on the incidence of serotype 3 IPD in the US or in other countries using PCV13. PCV13 elicits a relatively lower immunogenic response to this serotype compared to the other vaccine serotypes. • Effective antibiotic is available for the treatment of IPD in adults; however, antibiotic resistance is increasingly common making treatment more difficult.	• In individuals <18 years of age, there is an unmet medical need for effective prevention of IPD caused by the 5 additional serotypes uniquely included in PCV20 (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.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons

Clinical Benefit	• PCV20 effectiveness against IPD was demonstrated from serotype-specific IgG antibody responses as compared to PCV13.
	  • For 14 of the 20 vaccine serotypes, the IgG responses elicited by PCV20 at 1 month post-dose 3 met the pre-specified post-dose 3 noninferiority criterion. Six serotypes did not meet this noninferiority criterion. Serotype 3 and 12F failed to meet the noninferiority criterion by a large margin.
	  • For each of the 20 vaccine serotypes, the IgG responses elicited by PCV20 at 1 month post-dose 4 met the pre-specified post-dose 4 noninferiority criterion.
	  • Additional IgG GMC data at one month after Dose 3 and OPA data at one month after Dose 3, support the effectiveness of PCV20 for each of the 6 serotypes that failed to meet the pre-specified post-dose 3 non-inferiority criterion.
	• Immunological interference was not observed when PCV20 was administered concomitantly with ACIP-recommended routine US vaccines (i.e., Pediarix, Hiberix, Varivax, and M-M-R II).
	• PCV20 effectiveness against AOM due to serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in children 6 weeks through 5 years of age is supported by evidence from two previously conducted well-controlled clinical endpoint efficacy studies with PCV7.
		• The totality of the submitted immunogenicity data support the effectiveness of PCV20 to prevent vaccine-serotype IPD and lack of immune interference when administered concomitantly with Pediarix, Hiberix, Varivax and M-M-R II infant vaccines.
		• PCV20 vaccine effectiveness against serotype 3 invasive disease is anticipated to be similar to PCV13 effectiveness, based on the totality of the available immunogenicity data.
		• PCV20 vaccine effectiveness against serotype 12F invasive disease is anticipated to be similar to that of the PCV13 serotype with the lowest IgG antibody response based on the totality of the available immunogenicity data.
		• PCV20 effectiveness against AOM due to serotypes 4, 6B, 9V, 14, 18C, 19F and 23F in children 6 weeks through 5 years of age is anticipated to be similar to PCV7 effectiveness, because the vaccines are manufactured and formulated similarly and contain 7 of the same polysaccharide conjugates.

Risk	• In individuals 2, 4, 6, and 12 through 15 months of age vaccinated with a 4-dose schedule, the most commonly reported solicited adverse reactions >10% were irritability (>60%), pain at the injection site (>30%), drowsiness (>30%), decreased appetite and injection site redness (>20%), injection site swelling (>10%), and fever (>10%). • In individuals 15 months through 17 years of age vaccinated with a single dose, the most commonly reported solicited adverse reactions >10% were irritability (>60% in individuals less than 2 years of age), pain at the injection site (>50%), drowsiness (>40% in individuals less than 2 years of age), fatigue and muscle pain (>20% in individuals 2 years of age and older), decreased appetite (>20% in individuals less than 2 years of age), injection site swelling and injection site redness (>10%), headache (>10% in individuals 5 years of age and older), and fever (>10% in individuals less than 2 years of age). • The vast majority of solicited reactions in all age groups were mild or moderate in severity and resolve quickly. Severe reactions were infrequent (≤4.5%) • No other safety signals were apparent in individuals 6 weeks through 17 years of age.	• All the evidence indicates that the safety profile of PCV20 is acceptable in individuals 6 weeks through 17 years of age.
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 PCV20 were approved for individuals 6 weeks through 17 years of age, routine pharmacovigilance measures would be adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of PCV20 in preventing IPD caused by twenty *S. pneumoniae* serotypes contained in the vaccine in individuals 6 weeks through 17 years of age and preventing otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in individuals 6 weeks through 5 years of age is favorable compared to the risks associated with vaccination. Data submitted to this sBLA establish the safety and effectiveness of a 4-dose series of PCV20 in infants, and a 1 to 3 catch-up vaccination series in individuals 7 months through 17 years of age. The safety of PCV20 is adequately described in the prescribing information, and Wyeth's routine pharmacovigilance is adequate for monitoring AEs postmarketing. There was no evidence of immune interference when routine infant vaccines were administered concomitantly with PCV20 as compared to PCV13.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of this efficacy supplement application as the clinical data provided support the safety and effectiveness of PCV20 in individuals 6 weeks through 17 years of age in preventing IPD caused by the twenty pneumococcal vaccine serotypes and the safety and effectiveness of PCV20 in individuals 6 weeks through 5 years of age in preventing otitis media caused by vaccine serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

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.