Application Type	BLA Supplement
STN	125731/189
CBER Received Date	October 26, 2022
PDUFA Goal Date	April 27, 2023
Division / Office	DVRPA/OVRR
Committee Chair	Christina Houck
Clinical Reviewer(s)	Tina Mongeau
Project Manager	Tatiana Claro da Silva Susan DeRocco-Keller
Priority Review	Yes
Reviewer Name(s)	Ruoxuan Xiang
Review Completion Date / Stamped Date	
Concurrence	Ye Yang Team Lead, Vaccine Evaluation Branch (VEB), Division of Biostatistics (DB), Office of Biostatistics and Pharmacovigilance (OBPV)
	Tsai-Lien Lin Branch Chief, VEB/DB/OBPV
Applicant	Pfizer Inc.
Established Name	20-valent Pneumococcal Conjugate Vaccine
(Proposed) Trade Name	Prevnar20
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	2.2 µg of each of 20 saccharides, except for 4.4 µg of 6B, (b) (4) succinate buffer, (b) (4) sodium chloride, (b) (4) polysorbate 80, and 0.125 mg aluminum as aluminum phosphate
Dosage Form(s) and Route(s) of Administration	0.5 mL suspension for intramuscular injection, supplied in a single-dose pre-filled syringe
Dosing Regimen	Four doses
Indication(s) and Intended Population(s)	In infants and children 6 weeks through 17 years of age, for the active immunization for the prevention of 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 infants and children 6 weeks through 5 years of age, for the active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F

Table of Contents

1. Executive Summary

Pfizer, the applicant, submitted a Biologics License Application efficacy supplement (sBLA), STN 125731/189, for the 20-valent Pneumococcal Conjugate Vaccine (20vPnC) Prevnar 20® to support the addition of the following proposed pediatric indications:

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

Prevnar 20® was approved under the original BLA, STN 125731, on June 08, 2021 for active immunization for the prevention of pneumonia and invasive disease caused by the *S. pneumoniae* vaccine serotypes in adults ≥18 years of age.

This supplement includes data obtained from 4 clinical trials (one Phase 2 and three Phase 3 studies) performed in 3952 participants enrolled as infants and 831 participants enrolled between 15 months to <18 years of age. Study B7471011 is the pivotal Phase 3, double-blind, active-controlled trial of safety and immunogenicity in infants randomized to receive either 20vPnC or 13vPnC in a 4-dose series. Study B7471013 is the Phase 3, double-blind trial of safety in infants randomized to receive either 20vPnC or 13vPnC in a 4-dose series. Study B7471014 is the Phase 3, single-arm trial of safety and immunogenicity in children 15 months through 17 years of age receiving a single dose of 20vPnC.

Study B7471011

In the pivotal trial B7471011, approximately 2000 heathy infants, ≥ 42 to ≤ 98 days of age at the time of consent, were enrolled. Participants were randomized (1:1) to receive either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age. The primary objective was to evaluate non-inferiority (NI) of immune responses after 20vPnC to those after 13vPnC. A total of 40 comparisons were performed for the co-primary objectives: comparison of the IgG geometric mean concentrations (GMCs) after Dose 4 for each of the 20 serotypes and comparison of the percentages of participants with a predefined IgG concentration after Dose 3 for each of the 20 serotypes. For any serotype that missed the statistical NI criteria, the totality of data, including the margin by which NI was missed and the secondary and exploratory analyses, were considered.

IgG GMCs after Dose 4 of 20vPnC for all 13 matched serotypes were noninferior to those in the 13vPnC group, as demonstrated by the lower bounds (LBs) of the two-sided 95% confidence intervals (CIs) of IgG geometric mean ratios (GMRs, 20vPnC/13vPnC) >0.5. IgG GMCs after Dose 4 of 20vPnC for all 7 additional serotypes were noninferior to the lowest IgG GMC among the vaccine serotypes in the 13vPnC group, excluding Serotype 3 (i.e., Serotype 1), as the lower bounds of the two-sided 95% CIs of IgG GMRs (20vPnC / lowest 13vPnC) were >0.5.

The percentages of participants with predefined serotype-specific IgG concentrations after Dose 3 of 20vPnC for 8 of the 13 matched serotypes were noninferior to those in the 13vPnC group, as the lower bounds of the two-sided 95% CIs for the percentage differences (20vPnC – 13vPnC) were >-10%. Serotypes 1, 4, 9V, and 23F missed the statistical NI criterion by small margins (LBs of the two-sided 95% CI for the difference ranged from -12.1% to -11.3%). The majority of participants (77.9% to 81.9%) had predefined IgG concentrations to these four serotypes after Dose 3 of 20vPnC. These IgG concentrations all increased at 1 month after Dose 4 of 20vPnC (94.3% to 98.9%) and were comparable to 13vPnC. Serotype 3 missed the statistical NI criterion with an observed percentage difference of -15.5% (95% CI: -20.1% to -10.8%). There were 52.1% and 73.6% of participants who had the predefined IgG concentration for Serotype 3 after Dose 3 and Dose 4 of 20vPnC, respectively. The percent difference after Dose 4 between the 20vPnC and 13vPnC groups still missed the NI criterion of -10% but was reduced to -12.1% (95% CI: -16.2% to -8.1%).

The percentages of participants with predefined serotype-specific IgG concentrations after Dose 3 of 20vPnC for 6 of the 7 additional serotypes were noninferior to the lowest percentage among the vaccine serotypes in the 13vPnC group, excluding Serotype 3 (i.e., Serotype 23F). Serotype 12F missed the statistical NI criterion with an observed percentage difference of -18.1% (95% CI: -22.1% to -14.0%). The percentage of participants with predefined IgG concentrations to 12F after Dose 4 increased to 95.2% from 67.5% after Dose 3.

For the key secondary objective, IgG GMCs after Dose 3 of 20vPnC for all 13 matched serotypes were noninferior to those in the 13vPnC group. IgG GMCs after Dose 3 of 20vPnC for all 7 additional serotypes were noninferior to the lowest IgG GMC among the vaccine serotypes in the 13vPnC group, excluding Serotype 3 (i.e., Serotype 19A).

NI was demonstrated for immune responses to the co-administered diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib vaccine antigens one month after three infant doses of 20vPnC compared with 13vPnC.

Study B7471014

Approximately 800 healthy children ≥15 months to <18 years of age were enrolled into 4 cohorts based on age. For Cohorts 1 and 2, documentation of at least three prior doses of 13vPnC was required for children <5 years of age. For Cohorts 3 and 4, children ≥ 5 years could be enrolled regardless of previous vaccination with a pneumococcal conjugate vaccine (7vPnC or 13vPnC). All participants received a single dose of 20vPnC.

The observed IgG geometric mean fold rises (GMFRs) from pre- to post-20vPnC vaccination ranged from 27.9 (Serotype 12F) to 1847.7 (Serotype 22F), with lower bounds of the two-sided 95% CIs being 22.9-fold (Serotype 12F) or higher in participants ≥15 to <24 months of age (Cohort 1). The observed IgG GMFRs ranged from 36.6 (Serotype 12F) to 796.2 (Serotype 22F), with lower bounds of the two-sided 95% CIs being 30.1-fold (Serotype 12F) or higher in participants ≥2 to <5 years of age (Cohort 2).

The observed GMFRs ranged from 11.6 (Serotype 11A) to 463.6 (Serotype 12F), with lower bounds of the two-sided 95% CIs being 7.6 (Serotype 11A) or higher in participants ≥5 to <10 years of age (Cohort 3). The observed GMFRs ranged from 11.5 (Serotype 33F) to 499.0 (Serotype 15B), with lower bounds of the two-sided 95% CIs being 8.9 (Serotype 33F) or higher in participants ≥10 to <18 years of age (Cohort 4).

Overall Safety

No notable differences in the percentages of subjects reporting solicited adverse reactions, adverse events (AEs), and newly diagnosed chronic medical conditions (NDCMCs) were observed in the studies. The percentages of participants with SAEs at any time after Dose 1 through the 6-month follow-up period after the last dose were 4.5% (n=45) in the 20vPnC group and 3.1% (n=31) in the 13vPnC group in Study B7471011.

Conclusion

The pre-specified success criteria were met for 34 of the 40 primary immunogenicity comparisons, with six serotypes missing the NI margin for the difference in percentages of participants with predefined serotype-specific IgG concentrations after Dose 3 between 20vPnC and 13vPnC in the pivotal study B7471011. NI success criteria were met for key secondary immunogenicity endpoints (i.e., IgG GMCs post Dose 3), and for immune responses to the co-administered diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, Hib, measles, mumps, rubella, and varicella vaccine antigens. No significant safety concerns were identified in the study populations. I defer to the clinical reviewer on the acceptability of the totality of the immunogenicity and safety data.

2. CLINICAL AND REGULATORY BACKGROUND

Pfizer submitted a sBLA, STN 125731/189, for Prevnar 20® to support the addition of the following proposed pediatric indications:

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

Prevnar 20® was approved under the original BLA, STN 125731, on June 08, 2021 for active immunization for the prevention of pneumonia and invasive disease caused by the *S. pneumoniae* vaccine serotypes in adults ≥18 years of age.

At End-of-Phase 2 (EoP2) interactions in 2020, the FDA agreed that licensure for the proposed indications could be granted based on the demonstration of an adequate safety profile of 20vPnC and noninferior immunogenicity compared with the predecessor vaccine (13vPnC), rather than conducting an efficacy trial.

FDA granted priority review designation for this sBLA, and the action due date (ADD) is April 27, 2023.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues in the pivotal studies were identified.

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

I defer to reviewers from other disciplines.

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

5.1 Review Strategy

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

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

The following submissions were reviewed:

- STN 125731/189.0 Module 2.5 Clinical Overview
- STN 125731/189.0 Module 2.7 Clinical Summary
- STN 125731/189.0 Module 5 Clinical Study Reports
- STN 125731/189.22, 125731/189.23, 125731/189.24 Module 1.11.3 Clinical Information Amendment

5.3 Table of Studies/Clinical Trials

Table 1 provides an overview of the clinical trials providing immunogenicity and safety data to support this application.

Table 1. Overview of 20vPnC Pediatric Trials

Protocol No.	Study Design and Primary Objectives	No. of Subjects (By Treatment Group)	Vaccine Schedule
B7471011	Pivotal Phase 3, randomized, double-blind, active-controlled trial of safety and immunogenicity in infants **Primary Objective**: To describe the safety profile of 20vPnC in infants; To demonstrate NI of immune responses to 20vPnC with those to 13vPnC; To demonstrate NI of immune responses to specific concomitant vaccines administered with 20vPnC or 13vPnC	20vPnC: 1001 13vPnC: 990	Vaccination at approximately 2, 4, 6, and 12–15 months of age DTaP-IPV-HBV (Pediarix) and Hib (Hiberix) vaccines were co-administered with Doses 1–3; MMR (M-MR II) and varicella (Varivax) vaccines were co-administered with Dose 4.
B7471013	Phase 3, randomized, double-blind trial of tolerability and safety in infants **Primary Objective**: To describe the safety profile of 20vPnC in infants	20vPnC: 1000 13vPnC: 504	Vaccination at approximately 2, 4, 6, and 12–15 months of age
B7471014	Phase 3, single-arm trial of safety and immunogenicity in children ≥15 months − 17 years of age with a 4-cohort design based on age **Primary Objective**: To describe the safety profile of 20vPnC; To evaluate the immune responses to the 7 additional serotypes	Cohort 1 (15–24 months): 209 Cohort 2 (2−5 years): 216 Cohort 3 (5−10 years): 201 Cohort 4 (10−18 years): 205	Single dose of 20vPnC
B7471003	Phase 2, randomized, active-controlled, double-blind trial of safety and immunogenicity in infants **Primary Objective**: To describe the safety and immunogenicity of a vaccine series of 20vPnC in infants	20vPnC: 231 13vPnC: 227	Vaccination at approximately 2, 4, 6, and 12 months of age DTaP-IPV-HBV (Pediarix) was co-administered with Doses 1-3.

Source: Adapted from Table 4 in Clinical Overview submitted to BLA 125731/189.0.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1: B7471011

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

6.1.1 Objectives

Primary Objectives:

- To describe the safety profile of 20vPnC.
- To demonstrate that the percentages of participants with predefined serotype specific IgG concentrations for the 13 serotypes in the 20vPnC group are noninferior to the percentages for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3.
- To demonstrate that the percentages of participants with predefined serotype specific IgG concentrations for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest percentage among the 13 serotypes in the 13vPnC group at 1 month after Dose 3.
- To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 4.
- To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC group at 1 month after Dose 4.
- To demonstrate that percentages of participants with prespecified antibody levels to specific concomitant vaccine antigens (diphtheria toxoid, tetanus toxoid, pertussis antigens [PT, FHA, PRN], HBsAg, poliovirus strains, and Hib) when given with 20vPnC are noninferior to the corresponding percentages when the antigens are given with 13vPnC at 1 month after Dose 3.

Key Secondary Pneumococcal Immunogenicity Objectives:

- To demonstrate that the serotype-specific IgG GMCs for the 13 serotypes in the 20vPnC group are noninferior to the GMCs for the corresponding serotypes in the 13vPnC group at 1 month after Dose 3.
- To demonstrate that the serotype-specific IgG GMCs for the 7 additional serotypes in the 20vPnC group are noninferior to the lowest IgG GMC among the 13 serotypes in the 13vPnC group at 1 month after Dose 3.

Secondary Pneumococcal Immunogenicity Objectives:

- To further describe the immunogenicity of 20vPnC using percentages of participants with the predefined serotype-specific IgG concentration in each group at 1 month after Dose 4.

Secondary Concomitant Immunogenicity Objectives:

- To demonstrate that GMCs to specific concomitant vaccine antigens when given with 20vPnC are noninferior to the corresponding GMCs when the antigens are given with 13vPnC at 1 month after Dose 4.

6.1.2 Design Overview

This Phase 3, multicenter, randomized, double-blind trial was conducted in the United States (US) and the territory of Puerto Rico (PR). The purpose of this study was to describe the safety profile of 20vPnC and conduct the noninferiority immunogenicity

comparison of 20vPnC to the licensed pneumococcal conjugate vaccine, 13vPnC, in infants receiving a 4-dose series. Data were also generated on responses to key routine pediatric vaccines given concomitantly with 20vPnC. 13vPnC served as an active comparator.

Approximately 2000 infants ≥42 to ≤98 days of age at the time of consent, by their parents/legal guardians, were planned to be enrolled. Participants were randomized in a 1:1 ratio to receive either 20vPnC or 13vPnC (control vaccine) at 2, 4, 6, and 12 to 15 months of age (Doses 1, 2, 3, and 4, respectively) by site-based randomization. Participants received the same vaccine (20vPnC or 13vPnC) for all 4 doses. The study was initiated on May 20, 2020 and completed on September 02, 2022.

6.1.3 Population

The study population consisted of infants ≥42 to ≤98 days of age at the time of consent.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Participants received a single dose (0.5 mL) of 20vPnC or 13vPnC intramuscularly at each vaccination visit (Doses 1, 2, 3, and 4 at Visits 1, 2, 3, and 5, respectively). Participants also received a dose of a DTaP-containing vaccine in combination with other antigens including poliovirus and hepatitis B (PEDIARIX) and a dose of a Hib vaccine (HIBERIX) at Visits 1, 2, and 3. MMR (M-M-RII) and varicella (VARIVAX) vaccines were administered concomitantly with 20vPnC or 13vPnC at Visit 5 with Dose 4.

6.1.5 Directions for Use

Please refer to Dr. Tina Mongeau's clinical review memo.

6.1.6 Sites and Centers

One hundred and seven sites in the United States and five sites in Puerto Rico participated in the study.

6.1.7 Surveillance/Monitoring

Please refer to Dr. Tina Mongeau's clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

Primary Safety Endpoints:

- Prompted local reactions within 7 days after each vaccination.
- Prompted systemic events within 7 days after each vaccination.
- AEs from Dose 1 to one month after Dose 3.
- AEs from Dose 4 to one month after Dose 4.
- SAEs up to 6 months after Dose 4.
- NDCMCs up to 6 months after Dose 4.

Primary Immunogenicity Endpoint:

- Pneumococcal serotype-specific IgG concentration 1 month after Dose 3 and 1 month after Dose 4.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Success criteria and statistical methods for the primary immunogenicity analysis
For IgG GMCs, NI was declared if the lower bound of the two-sided 95% CI for the GMR (20vPnC/13vPnC) for each of the 20 serotypes was greater than 0.5 (2-fold criterion). IgG GMC or GMR was calculated by exponentiating the mean or the mean differences of logarithmically transformed IgG concentrations. The CI was derived based on the Student's t-distribution.

For percentages of participants with a predefined IgG concentration, NI was declared if the lower bound of the two-sided 95% CI for the difference in percentages (20vPnC – 13vPnC) for each of the 20 serotypes was greater than -10%. The Miettinen and Nurminen method was used to derive the CI for the difference in percentages between vaccine groups.

The NI comparisons of percentage of participants with prespecified antibody level to each concomitant vaccine antigen was performed similarly to that for the percentage of participants with predefined serotype-specific IgG concentrations.

The overall primary pneumococcal immunogenicity objectives were achieved if noninferiority of 20vPnC compared to 13vPnC based on both the percentage of participants with predefined serotype-specific IgG concentration levels at 1 month after Dose 3 and the serotype-specific IgG GMCs at 1 month after Dose 4 was demonstrated for all 20 serotypes. Therefore, the overall type I error rate for the primary immunogenicity assessment of the pneumococcal immune response of 20vPnC was controlled at the 0.05 level. The noninferiority evaluations of concomitant immunogenicity results comparing the 20vPnC group to the 13vPnC group were meaningful only if the criteria for achieving the pneumococcal immunogenicity objectives were met. Consequently, no type I error adjustments were needed for the concomitant immunogenicity assessments.

Sample size estimation
A total of approximately 2000 enrolled participants would yield approximately 1600 evaluable participants assuming a 20% non-evaluable rate for the study, resulting in approximately 800 evaluable participants for each vaccine group. Sample size and power for the primary pneumococcal immunogenicity objectives associated with IgG concentration results at 1 month after Dose 3 and 1 month after Dose 4 were assessed based on simulations with assumptions supported by IgG results from an internal Pfizer Phase 2 infant study of 20vPnC (B7471003) following multivariate log-normal distributions.

Assuming the true GMCs and variance-covariance matrices for the 20 serotype-specific IgG concentrations from both 20vPnC and 13vPnC groups were the same as those observed from Study B7471003, the study had approximately 93% and 81% probabilities

to show at least 37 and 38 (out of 40 total) positive noninferiority assessments, respectively.

For the primary concomitant immunogenicity objectives, evaluable sample sizes needed to achieve 99% power to detect noninferiority for each antigen ranged from ~36 to ~367 per vaccine group.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The randomized population included all participants who were assigned a randomization number in the interactive response technology (IRT) system.

The safety population included all participants who received at least 1 dose of the intervention with safety follow-up after any dose. Participants were grouped according to the vaccine as administered in the safety analysis.

The Dose 3 evaluable immunogenicity population included all participants who:

1. were eligible and randomized,
2. were 42 to 98 days of age, inclusive, on the day of Dose 1,
3. received the first 3 vaccinations to which they were randomized,
4. had at least 1 valid immunogenicity result within 27 to 56 days, inclusive, after Dose 3, and
5. had no other major protocol deviations as determined by the clinician.

The Dose 3 evaluable immunogenicity population was the primary analysis population for the pneumococcal immunogenicity results from blood collected up to and before Dose 4.

The Dose 4 evaluable immunogenicity population included all participants who:

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

The Dose 4 evaluable immunogenicity population was the primary analysis population for the pneumococcal immunogenicity results after Dose 4.

Table 2 below lists the numbers of participants in these populations. Overall, 361 (18.1%) participants were excluded from the Dose 3 evaluable immunogenicity population (171 [17.0%] from the 20vPnC group and 190 [19.1%] from the 13vPnC group). The most common reason for exclusion was not having blood drawn within 27 to 56 days after Dose 3. Four hundred and ninety-seven (24.9%) participants were excluded from the

Dose 4 evaluable immunogenicity population (249 [24.8%] from the 20vPnC group and 248 [25.0%] from the 13vPnC group). The most common reason for exclusion was not receiving all 4 vaccinations as randomized.

Table 2. Analysis Populations

	20vPnC	**13vPnC**	**Total**
	n (%)	n (%)	n (%)
Randomized population	1004 (100.0)	993 (100.0)	1997 (100.0)
Safety population	1001 (99.7)	990 (99.7)	1991 (99.7)
Dose 3 evaluable immunogenicity population	833 (83.0)	803 (80.9)	1636 (81.9)
Dose 4 evaluable immunogenicity population	755 (75.2)	745 (75.0)	1500 (75.1)

Source: Adapted from Table 4 in the CSR for Study B7471011.

Demographic and baseline characteristics of sex, race, geographic region (US/ Puerto Rico), and age for the safety population were similar in the 20vPnC and 13vPnC groups. Although most participants were White and non-Hispanic/non-Latino, approximately 25% of the study population was non-White, with approximately 11% Black or African American and 7% multiracial.

6.1.11 Efficacy and Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoints

Table 3 shows that the percentages of participants with predefined serotype-specific IgG concentrations 1 month after Dose 3 of 20vPnC for 8 of the 13 matched serotypes were noninferior to those in the 13vPnC group, as the lower bounds of the two-sided 95% CIs for the percentage differences (20vPnC – 13vPnC) were >-10%. The percentages of participants with predefined serotype-specific IgG concentrations 1 month after Dose 3 of 20vPnC for 6 of the 7 additional serotypes were noninferior to the lowest percentage among the 13 serotypes excluding Serotype 3 (i.e., Serotype 23F) in the 13vPnC group, using the same criterion as the 13 matched serotypes.

For the serotypes that met NI, the observed differences (20vPnC – 13vPnC) in percentage of participants with predefined serotype-specific IgG concentrations ranged from -4.3% (Serotype 5) to 12.8% (Serotype 22F). Serotypes 1, 4, 9V, and 23F missed the statistical NI criterion by small margins. The lower bounds of the two-sided 95% CIs for the difference in percentages of participants with predefined serotype-specific IgG concentrations ranged from -12.1% to -11.3% for these serotypes. Serotype 3 and Serotype 12F missed the statistical NI criterion with an observed percentage difference of -15.5% (95% CI: -20.1% to -10.8%) and -18.1% (95% CI: -22.1% to -14.0%), respectively.

Reviewer's Comment:

Although there is no established correlate of protection for pneumococcal conjugate vaccines that directly predicts protection for an individual, an IgG concentration of 0.35 μg/ml as measured by the World Health Organization (WHO) standardized enzyme-linked immunosorbent assay (ELISA), developed from a meta-analysis of the results from efficacy studies, is accepted by the FDA as a reference level for comparing new pneumococcal conjugate vaccines to existing ones. For the 13 matched serotypes, the direct-binding Luminex immunoassay (dLIA), which was used to measure the pneumococcal IgG concentrations, was bridged to the WHO ELISA using incurred samples from historical 13vPnC Phase 3 pediatric studies. The bridging study determined that the predefined IgG concentration levels by dLIA corresponding to the IgG concentrations of 0.35 μg/ml established by the WHO ELISA were 0.35 μg/mL, except for Serotypes 5, 6B, and 19A, which had corresponding dLIA predefined levels at 0.23 μg/mL, 0.10 μg/mL, and 0.12 μg/mL, respectively.

During this sBLA review, the product reviewer requested a bridging study to establish dLIA-specific threshold values corresponding to the 0.35 μg/mL IgG antibody threshold established by the WHO ELISA for the seven additional serotypes. In response, the applicant submitted the bridging study data to BLA 125731/189.16. Based on the data, the review team determined that the dLIA-specific threshold for Serotype 12F be increased to 0.69 μg/mL, and the NI analysis in the clinical trial be revised to reflect this change. However, revisions of the NI analyses are not necessary for the remaining six serotypes at this point. Please refer to my clinical assay review memo for details.

The revised primary NI analysis for Serotype 12F using the dLIA threshold of 0.69 μg/mL was submitted to BLA 125731/189.22. Serotype 12F missed the statistical NI criterion by a larger margin, with an observed percentage difference of -37.5% (95% CI: -41.6% to -33.3%).

Table 3. Comparison of the Percentage of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

Serotype	PCV20 N=831-833 %	PCV13 N=801-802 %	Difference (95% CI) (PCV20-PCV13) %
1	79.8	88.4	-8.6 (-12.1, -5.1)
3	52.1	67.6	-15.5 (-20.1, -10.8)
4	79.7	88.2	-8.4 (-12.0, -4.9)
5	82.5	86.8	-4.3 (-7.8, -0.8)
6A	93.5	95.9	-2.4 (-4.6, -0.2)
6B	88.3	92.4	-4.1 (-7.0, -1.2)
7F	96.6	97.6	-1.0 (-2.7, 0.7)
9V	81.9	89.8	-7.9 (-11.3, -4.6)
14	93.4	94.1	-0.8 (-3.1, 1.6)
18C	92.6	93.1	-0.6 (-3.1, 1.9)
19A	97.1	98.1	-1.0 (-2.6, 0.5)
19F	96.9	96.6	0.2 (-1.5, 2.0)
23F	77.9	85.5	-7.6 (-11.4, -3.9)
Seven Additional	-	-	-
8	96.8	85.5	11.2 (8.6, 14.0)
10A	82.2	85.5	-3.3 (-6.9, 0.3)
11A	92.7	85.5	7.1 (4.2, 10.2)
12F	67.5	85.5	-18.1 (-22.1, -14.0)
15B	98.2	85.5	12.7 (10.2, 15.4)
22F	98.3	85.5	12.8 (10.3, 15.5)
33F	86.7	85.5	1.1 (-2.2, 4.5)

Source: Adapted from Table 9 in the CSR for Study B7471011.

Table 4 shows that the IgG GMCs 1 month after Dose 4 of 20vPnC for all 13 matched serotypes were noninferior to those in the 13vPnC group, as the lower bounds of the two-sided 95% CIs for the IgG GMRs (20vPnC/13vPnC) were >0.5. The observed GMRs for the 13 matched serotypes ranged from 0.64 (Serotype 23F) to 0.90 (Serotype 14). IgG GMCs 1 month after Dose 4 of 20vPnC for all 7 additional serotypes were noninferior to the lowest IgG GMC among the 13 serotypes, excluding Serotype 3 (i.e., Serotype 1) in the 13vPnC group, using the same criterion as for those 13 matched serotypes (Table 4). The observed GMRs ranged from 0.88 (Serotype 12F) to 5.95 (Serotype 15B).

Table 4. Pneumococcal IgG GMCs and GMRs – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

Serotype	PCV20 N=753-755 GMC (µg/mL)	PCV13 N=744-745 GMC (µg/mL)	GMC Ratio (95% CI) (PCV20/PCV13)
1	1.5	2.1	0.69 (0.63, 0.76)
3	0.6	0.9	0.66 (0.61, 0.73)
4	3.8	4.8	0.78 (0.70, 0.86)
5	1.9	2.5	0.74 (0.67, 0.82)
6A	9.0	11.7	0.77 (0.70, 0.85)
6B	4.0	5.7	0.70 (0.62, 0.79)
7F	3.9	5.2	0.76 (0.70, 0.82)
9V	3.4	4.3	0.80 (0.73, 0.88)
14	5.7	6.3	0.90 (0.81, 1.00)
18C	3.5	4.7	0.74 (0.67, 0.82)
19A	3.5	4.1	0.85 (0.77, 0.94)
19F	5.0	5.8	0.86 (0.78, 0.96)
23F	4.0	6.2	0.64 (0.57, 0.72)
Seven Additional			
8	3.97	2.1	1.87 (1.71, 2.06)
10A	6.22	2.1	2.94 (2.64, 3.26)
11A	3.53	2.1	1.67 (1.51, 1.84)
12F	1.85	2.1	0.88 (0.79, 0.97)
15B	12.59	2.1	5.95 (5.39, 6.55)
22F	10.60	2.1	5.01 (4.54, 5.52)
33F	9.31	2.1	4.40 (3.99, 4.85)

Source: Adapted from Table 8 in the CSR for Study B7471011.

NI was demonstrated for immune responses to the co-administered diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, and Hib vaccine antigens 1 month after Dose 3 of 20vPnC compared with 13vPnC based on the lower bounds of the two-sided 95% CIs for the differences in the percentages of participants with prespecified antibody levels >-10% (Table 5).

Table 5. Comparison of the Percentage of Participants With Prespecified Antibody Levels for Concomitant Vaccine Antigens 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

Antigen	Predefined Level	PCV20 N[a]	PCV20 %	PCV13 N[a]	PCV13 %	Difference (95% CI) (PCV20-PCV13) %
Diphtheria	≥0.1 IU/mL	370	93.5	363	97.8	-4.3 (-7.5, -1.4)
Tetanus	≥0.1 IU/mL	370	99.7	363	99.4	0.3 (-1.0, 1.7)
Pertussis	-	-	-	-	-	-
PT	≥14.40 EU/mL	370	94.9	363	95.0	-0.2 (-3.5, 3.1)
FHA	≥26.60 EU/mL	370	95.7	363	95.0	0.6 (-2.5, 3.9)
PRN	≥13.00 EU/mL	370	93.8	363	95.0	-1.3 (-4.7, 2.2)
HBsAg	≥10 mIU/mL	118	100.0	127	100.0	0.0 (-3.2, 2.9)
Poliovirus	-	-	-	-	-	-
Type 1	≥1:8	111	100.0	117	100.0	0.0 (-3.4, 3.2)
Type 2	≥1:8	115	100.0	120	99.2	0.8 (-2.4, 4.6)
Type 3	≥1:8	115	100.0	120	100.0	0.0 (-3.2, 3.1)
Hib	≥0.15 µg/mL	124	100.0	125	100.0	0.0 (-3.0, 3.0)

a. N = number of participants with valid assay results for the specified antigen. These values are the denominators for the percentage calculations.
Source: Adapted from Table 14.30 in the CSR for Study B7471011.

6.1.11.2 Analyses of Secondary Endpoints

For the key secondary pneumococcal objectives, IgG GMCs 1 month after Dose 3 of 20vPnC for all 13 matched serotypes were noninferior to those in the 13vPnC group, as the lower bounds of the two-sided 95% CIs for the IgG GMRs (20vPnC/13vPnC) were >0.5 (Table 6). The observed GMRs (20vPnC/13vPnC) for the 13 matched serotypes ranged from 0.60 (Serotype 6B) to 0.79 (Serotypes 14, 19A, and 19F). IgG GMCs 1 month after Dose 3 of 20vPnC for all 7 additional serotypes were noninferior to the lowest IgG GMC among the 13 serotypes, excluding Serotype 3 (i.e., Serotype 19A) in the 13vPnC group. The observed GMRs (20vPnC/13vPnC) for the 7 additional serotypes ranged from 0.60 (Serotype 12F) to 4.82 (Serotype 15B).

Table 6. Pneumococcal IgG GMCs and GMRs – 1 Month After Dose 3 – Dose 3 Evaluable Immunogenicity Population

Serotype	PCV20 N=831-833 GMC (µg/mL)	PCV13 N=801-803 GMC (µg/mL)	GMC Ratio (95% CI) (PCV20/PCV13)
1	0.74	1.14	0.65 (0.59, 0.72)
3	0.36	0.51	0.70 (0.64, 0.76)
4	0.75	1.08	0.70 (0.63, 0.78)
5	0.66	0.96	0.69 (0.61, 0.77)
6A	1.95	2.69	0.72 (0.65, 0.81)
6B	0.61	1.02	0.60 (0.51, 0.70)
7F	1.71	2.29	0.75 (0.69, 0.81)
9V	0.87	1.21	0.72 (0.65, 0.80)
14	2.16	2.72	0.79 (0.71, 0.89)
18C	1.31	1.71	0.77 (0.70, 0.84)
19A	0.72	0.91	0.79 (0.72, 0.86)
19F	1.59	2.00	0.79 (0.73, 0.86)
23F	0.82	1.25	0.66 (0.58, 0.75)
Seven Additional			
8	1.80	0.91	1.98 (1.81, 2.16)
10A	1.21	0.91	1.32 (1.18, 1.49)
11A	1.39	0.91	1.52 (1.39, 1.67)
12F	0.55	0.91	0.60 (0.54, 0.67)
15B	4.40	0.91	4.82 (4.39, 5.30)
22F	3.71	0.91	4.06 (3.68, 4.48)
33F	1.49	0.91	1.64 (1.46, 1.83)

Source: Adapted from Table 12 in the CSR for Study B7471011.

Table 7 presents the observed differences (20vPnC – 13vPnC) in percentages of participants with predefined serotype-specific IgG concentrations 1 month after Dose 4, which ranged from -12.1% (Serotype 3) to 0.3% (Serotype 18C), for the 13 matched serotypes. For the 7 additional serotypes, the observed differences in percentage of participants with predefined serotype-specific IgG concentrations 1 month after Dose 4 ranged from -1.9% (Serotype 12F) to 2.6% (Serotype 15B), between the 20vPnC group and the lowest percentage among the 13 serotypes, excluding Serotype 3 (i.e., Serotype 1) in the 13vPnC group.

Reviewer's Comment:
Based on the submitted data, I calculated the difference in percentages of participants with an updated IgG concentration ≥0.69 µg/mL for Serotype 12F one month after Dose 4 to be -10.8% (95% CI: -13.7% to -8.2%).

Table 7. Comparison of the Percentage of Participants With Predefined Pneumococcal IgG Concentrations for Vaccine Serotypes – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

Serotype	PCV20 N=831-833 %	PCV13 N=801-802 %	Difference (95% CI) (PCV20-PCV13)
1	94.3	97.2	-2.9 (-5.0, -0.8)
3	73.6	85.8	-12.1 (-16.2, -8.1)
4	98.9	99.1	-0.1 (-1.3, 1.0)
5	97.9	97.7	0.2 (-1.4, 1.7)
6A	99.5	99.7	-0.3 (-1.1, 0.5)
6B	99.1	99.5	0.4 (-1.4, 0.6)
7F	99.5	99.9	-0.4 (-1.2, 0.3)
9V	98.5	98.9	-0.4 (-1.6, 0.8)
14	98.9	99.5	-0.5 (-1.6, 0.4)
18C	98.9	98.7	0.3 (-0.9, 1.5)
19A	99.9	99.7	0.1 (-0.5, 0.9)
19F	98.8	98.9	0.1 (-1.3, 1.1)
23F	97.2	98.1	-0.9 (-2.5, 0.7)
Seven Additional			
8	99.5	97.2	2.3 (1.1, 3.8)
10A	97.7	97.2	0.6 (-1.1, 2.3)
11A	98.8	97.2	1.6 (0.2, 3.2)
12F	95.2	97.2	-1.9 (-4.0, 0.0)
15B	99.7	97.2	2.6 (1.4, 4.0)
22F	99.6	97.2	2.4 (1.3, 3.9)
33F	99.5	97.2	2.3 (1.1, 3.8)

Source: Adapted from Table 13 in the CSR for Study B7471011.

NI was demonstrated for immune responses to the co-administered measles, mumps, rubella, and varicella virus vaccine antigens 1 month after Dose 4 of 20vPnC compared with 13vPnC based on the lower bounds of the two-sided 95% CIs for GMRs (20vPnC/13vPnC) >0.5 (Table 8).

Table 8. Concomitant Vaccine Antigen GMs and GMRs – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

Antigen	PCV20 N[a]	PCV20 GM	PCV13 N[a]	PCV13 GM	GMR (95% CI) (PCV20/PCV13)
Measles (AU/mL)	234	277.74	232	215.41	1.29 (1.05, 1.58)
Mumps (AU/mL)	234	36.96	232	34.19	1.08 (0.85, 1.38)
Rubella (IU/mL)	234	49.63	232	40.44	1.23 (1.02, 1.48)
Varicella (mIU/mL)	231	233.05	229	234.78	0.99 (0.84, 1.17)

a. n = Number of participants with valid assay results for the specified antigen.
Source: Adapted from Table 14.32 in the CSR for Study B7471011.

Reviewer's Comment:
At the request of the assay reviewer, I reviewed the validation report for the Measles, Mumps, Rubella II and Varicella (MMRV) Quantitative IgG assays. Please refer to my clinical assay review memo for details. Although several issues with dilutional linearity were identified for the MMRV IgG assays, they would not change the NI conclusions for these secondary concomitant endpoints.

6.1.11.3 Subpopulation Analyses

Slightly higher IgG responses in female participants were observed for each serotype (Table 9) compared to male participants. The trend was consistent across the vaccine groups, resulting in generally similar GMRs between 20vPnC and 13vPnC groups within each sex.

In addition, there was a trend of slightly higher observed responses among Black or African American participants (not shown in table). However, the sample sizes were too small to draw meaningful inference for the non-White population.

Table 9. Pneumococcal IgG GMCs by Sex – 1 Month After Dose 4 – Dose 4 Evaluable Immunogenicity Population

Serotype	PCV20, Male N=377-378 GMC (µg/mL)	PCV13, Male N=373-383 GMC (µg/mL)	PCV20, Female N=376-377 GMC (µg/mL)	PCV13, Female N=347-362 GMC (µg/mL)
1	1.26	1.92	1.71	2.35
3	0.49	0.78	0.65	0.93
4	3.30	4.29	4.32	5.52
5	1.67	2.27	2.08	2.78
6A	7.90	10.40	10.29	13.23
6B	3.37	4.73	4.77	7.03
7F	3.53	4.77	4.34	5.65
9V	2.98	3.93	3.98	4.72
14	4.86	5.55	6.64	7.29
18C	3.02	4.21	3.97	5.25
19A	2.91	3.56	4.28	4.84
19F	4.07	4.79	6.16	7.08
23F	3.36	5.22	4.66	7.40
Seven Additional	-	-	-	-
8	3.51	0.03	4.48	0.04
10A	5.72	0.01	6.76	0.01
11A	3.02	0.02	4.14	0.02
12F	1.62	0.01	2.13	0.01
15B	10.94	0.02	14.49	0.03
22F	9.21	0.01	12.20	0.00
33F	8.39	0.01	10.35	0.01

Source: Adapted from Table 14.26 in the CSR for Study B7471011.

6.1.11.4 Exploratory and Post Hoc Analyses

No exploratory and post-hoc analyses are considered in this review.

6.1.12 Safety Analyses

The percentages of participants with local reactions after Doses 1 through 4 were generally similar in the 20vPnC and 13vPnC groups (Table 10). The most frequently reported local reaction after any dose was pain at injection site (35.7% to 49.1% in the 20vPnC group and 35.8% to 45.3% in the 13vPnC group). Most local reactions were mild or moderate in severity.

The percentages of participants with systemic events after Doses 1 through 4 were generally similar in the 20vPnC and 13vPnC groups (Table 11). The most frequently

reported systemic event was irritability (61.0% to 71.6% in the 20vPnC group and 61.1% to 71.7% in the 13vPnC group), followed by drowsiness (39.5% to 67.2% in the 20vPnC group and 39.5% to 66.0% in the 13vPnC group, which decreased in frequency in both groups after each subsequent dose). Most systemic events were mild or moderate in severity.

Table 10. Percentage of Participants With Solicited Local Adverse Reactions Within 7 Days After Each Vaccination

-	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3	Dose 4	Dose 4
-	PCV20 (N[a]=993) %	PCV13 (N[a]=974) %	PCV20 (N[a]=940) %	PCV13 (N[a]=924) %	PCV20 (N[a]=914) %	PCV13 (N[a]=901) %	PCV20 (N[a]=826) %	PCV13 (N[a]=815) %
Redness[b]	-	-	-	-	-	-	-	-
Any	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[b]	-	-	-	-	-	-	-	-
Any	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
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
Any local reaction[d]	59.8	56.5	53.1	52.7	50.8	49.1	44.8	45.9

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. Mild: >0.0 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm.
c. Mild: hurts if gently touched; moderate: hurts if gently touched with crying; severe: causes limitation of limb movement.
d. Any local reaction: any redness >0.0 cm, any swelling >0.0 cm, or any pain at the injection site after the specified dose.
Source: Adapted from Table 17 in the CSR for Study B7471011.

Table 11. Percentage of Participants With Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination

	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) %
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	0.2	0	0.1	0	0.2	0.1
Decreased Appetite[b]	-	-	-	-	-	-	-	-
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
Drowsiness[c]	-	-	-	-	-	-	-	-
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
Irritability[d]	-	-	-	-	-	-	-	-
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
Any systemic reaction[e]	85.9	84.5	82.0	80.5	74.0	72.6	70.8	71.2
Use of antipyretic or pain[f]	35.1	33.8	40.7	41.0	36.3	36.1	37.5	36.7

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. Mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed.
c. Mild: increased or prolonged sleeping bouts; moderate: slightly subdued interfering with daily activity; severe: disabling not interested in usual daily activity.
d. Mild: easily consolable; moderate: requiring increased attention; severe: inconsolable; crying cannot be comforted.
e. Any systemic reaction: any fever ≥38.0°C, any decreased appetite, any drowsiness, or any irritability after the specified dose.
f. The numbers in this row reflect yes responses (i.e., number of events reported).
Source: Adapted from Table 18 in the CSR for Study B7471011.

From Dose 1 to one month after Dose 3, at least one AE was reported in 36.6% of participants in the 20vPnC group and 39.4% of participants in the 13vPnC group. AEs in the system organ class (SOC) of infections and infestations were reported most frequently in the 20vPnC (23.2%) and 13vPnC (24.1%) groups and included upper respiratory tract infection (9.5% and 9.7%, respectively) and otitis media (3.9% and 3.2%, respectively). From Dose 4 to one month after Dose 4, at least 1 AE was reported in 15.1% and 15.0%

of participants in the 20vPnC and 13vPnC groups, respectively. As with the AEs from Dose 1 to one month after Dose 3, AEs in the SOC of infections and infestations were reported most frequently in participants in the 20vPnC (12.4%) and 13vPnC (10.6%) groups.

The percentages of participants with SAEs at any time after Dose 1 through the 6-month follow-up period after the last dose were 4.5% (n=45) in the 20vPnC group and 3.1% (n=31) in the 13vPnC group. The percentages of participants with NDCMCs after Dose 1 were similar in the 20vPnC (n=50; 5.0%) and 13vPnC (n=58; 5.9%) groups. There were no deaths during the trial.

6.2 Trial #2: B7471013

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

6.2.1 Objectives

Primary Objective: To describe the safety profile of 20vPnC.

6.2.2 Design Overview

This Phase 3, multicenter, randomized, double-blind study with a 2-arm parallel design was conducted in Europe, South America, and North America, including the United States and the US territory of PR.

Approximately 1500 infants ≥42 to ≤98 days of age were randomized (2:1) to receive either 20vPnC or 13vPnC at 2, 4, and 6 months of age (Doses 1 through 3) and 12 to 15 months of age (Dose 4). Participants received the same vaccine (20vPnC or 13vPnC) for all 4 doses.

6.2.3 Population

The study population comprised infants born at >34 weeks of gestation and 2 months of age (≥42 to ≤98 days of age) at the time of consent.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Participants received a single 0.5-mL dose of either 20vPnC or 13vPnC at each vaccination visit (Doses 1, 2, 3, and 4 at Visits 1, 2, 3, and 5, respectively) administered intramuscularly into the anterolateral thigh muscle of the left leg.

6.2.5 Directions for Use

Please refer to Dr. Tina Mongeau's clinical review memo.

6.2.6 Sites and Centers

Ninety-nine sites in Europe, South America, and North America, including the US and PR, participated in the study.

6.2.7 Surveillance/Monitoring

Please refer to Tina Mongeau's clinical review memo.

6.2.8 Endpoints and Criteria for Study Success

Primary Safety Endpoints:

- Prompted local reactions within 7 days after each vaccination.
- Prompted systemic events within 7 days after each vaccination.
- AEs from Dose 1 to one month after Dose 3.
- AEs from Dose 4 to one month after Dose 4.
- SAEs up to 6 months after Dose 4.
- NDCMCs up to 6 months after Dose 4.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The study size in each vaccine group was not based on any formal hypothesis test for any safety endpoints. All statistical analyses were descriptive.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Overall, a total of 1511 participants were randomized, of whom 1504 (99.5%) participants completed at least one dose and were included in the safety population (Table 12). Of the 150 (9.9%) participants that were withdrawn from the trial, the two most common reasons were lost to follow-up (52 [3.4%] participants) and withdrawal by parent/legal guardian (51 [3.4%] participants). Disposition of all randomized participants was similar in the 20vPnC and 13vPnC groups.

Table 12. Analysis Populations

-	20vPnC	13vPnC	Total
-	n (%)	n (%)	n (%)
Randomized population	1006 (100.0)	505 (100.0)	1511 (100.0)
Vaccinated (Dose 1)	1000 (99.4)	504 (99.8)	1504 (99.5)
Safety population	1000 (99.4)	504 (99.8)	1504 (99.5)
Total withdrawn	96 (9.5)	54 (10.7)	150 (9.9)
Withdrawn before Dose 1	6 (0.6)	1 (0.2)	7 (0.5)

Source: Adapted from Table 2 in the CSR for Study B7471013.

6.2.11 Immunogenicity Analyses

No immunogenicity analyses were performed.

6.2.12 Safety Analyses

The percentages of participants with local reactions at the injection site within 7 days after Doses 1 through 4 of 20vPnC or 13vPnC are presented in Table 13. The percentages of participants with any local reactions after Doses 1 through 4 were generally similar in the 20vPnC group (51.6%, 45.8%, 38.6%, and 40.6%, respectively) and 13vPnC group

(53.6%, 49.1%, 40.0%, and 42.3%, respectively). The most frequently reported local reaction after any dose was pain at injection site (24.7% to 40.5% in the 20vPnC group and 26.8% to 42.0% in the 13vPnC group). Most local reactions were mild or moderate in severity.

Table 13. Percentage of Participants With Solicited Local Adverse Reactions Within 7 Days After Each Vaccination

-	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3	Dose 4	Dose 4
-	PCV20 (N[a]=992) %	PCV13 (N[a]=498) %	PCV20 (N[a]=952) %	PCV13 (N[a]=485) %	PCV20 (N[a]=940) %	PCV13 (N[a]=477) %	PCV20 (N[a]=892) %	PCV13 (N[a]=454) %
Redness[b]	-	-	-	-	-	-	-	-
Any	21.8	19.5	23.5	23.3	23.2	20.3	21.2	21.8
Mild	18.0	16.5	20.4	19.4	19.4	17.0	15.1	19.4
Moderate	3.7	3.0	3.2	3.9	3.8	3.1	5.9	2.4
Severe	0	0	0	0	0	0.2	0.1	0
Swelling[b]	-	-	-	-	-	-	-	-
Any	20.0	16.7	17.9	19.0	16.4	16.4	14.8	14.3
Mild	13.8	11.2	13.4	13.4	12.2	13.0	10.1	11.5
Moderate	6.1	5.4	4.4	5.6	4.1	3.1	4.7	2.9
Severe	0	0	0	0	0	0.2	0	0
Pain at injection site[c]	-	-	-	-	-	-	-	-
Any	40.5	42.0	32.2	32.8	24.7	26.8	30.8	31.9
Mild	24.8	25.3	20.8	20.2	16.3	16.6	19.8	21.8
Moderate	15.5	16.7	10.7	11.8	8.3	10.3	10.2	10.1
Severe	0.2	0	0.7	0.8	0.1	0	0.8	0
Any local reaction[d]	51.6	53.6	45.8	49.1	38.6	40.0	40.6	42.3

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. Mild: >0.0 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm.
c. Mild: hurts if gently touched; moderate: hurts if gently touched with crying; severe: causes limitation of limb movement.
d. Any local reaction: any redness >0.0 cm, any swelling >0.0 cm, or any pain at the injection site after the specified dose.
Source: Adapted from Table 7 in the CSR for Study B7471013.

The percentages of participants with systemic events after Doses 1 through 4 were generally similar in the 20vPnC and 13vPnC groups (Table 14). The most frequently reported systemic event was irritability (54.8 % to 68.2% in the 20vPnC group and 54.7% to 68.5% in the 13vPnC group), followed by drowsiness (35.3% to 64.8% in the 20vPnC group and 35.9% to 62.2% in the 13vPnC group). The percentages of participants with any fever of ≥38.0°C were similar in the 20vPnC and 13vPnC groups (9.3%–18.0% in the 20vPnC group and 9.8%–17.0% in the 13vPnC group). Fever of >38.9°C to 40°C was reported infrequently in both groups (≤3.7% and ≤3.1 % in the 20vPnC and 13vPnC groups, respectively), and fever of >40°C was reported only at Dose 4 (1 participant in each vaccine group).

Table 14. Percentage of Participants With Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination

-	Dose 1	Dose 1	Dose 2	Dose 2	Dose 3	Dose 3	Dose 4	Dose 4
-	PCV20 (N[a]=992) %	PCV13 (N[a]=498) %	PCV20 (N[a]=952) %	PCV13 (N[a]=485) %	PCV20 (N[a]=940) %	PCV13 (N[a]=477) %	PCV20 (N[a]=892) %	PCV13 (N[a]=454) %
Fever	-	-	-	-	-	-	-	-
≥38.0°C	9.3	9.8	15.5	11.3	11.6	9.9	18.0	17.0
≥38.0°C to 38.4°C	6.3	7.8	10.6	8.5	7.4	8.2	9.8	9.5
>38.4°C to 38.9°C	2.3	1.8	3.6	2.7	2.9	0.6	4.5	4.2
38.9°C to 40.0°C	0.7	0.2	1.4	0.2	1.3	1.0	3.7	3.1
>40.0°C	0	0	0	0	0	0	0.1	0.2
Decreased Appetite[b]	-	-	-	-	-	-	-	-
Any	25.0	23.7	23.7	20.6	23.6	17.2	28.4	25.8
Mild	14.2	14.7	13.4	12.0	15.0	10.5	16.1	12.3
Moderate	10.3	8.6	9.6	8.2	8.2	6.3	10.5	11.7
Severe	0.5	0.4	0.7	0.4	0.4	0.4	1.7	1.8
Drowsiness[c]	-	-	-	-	-	-	-	-
Any	64.8	62.2	49.2	50.3	35.3	36.3	37.1	35.9
Mild	48.5	47.4	35.3	35.3	26.6	27.3	24.2	25.1
Moderate	15.8	14.5	13.4	13.8	8.5	9.0	12.2	10.6
Severe	0.5	0.4	0.4	1.2	0.2	0	0.7	0.2
Irritability[d]	-	-	-	-	-	-	-	-
Any	68.2	68.5	64.7	67.6	54.8	54.7	55.3	55.1
Mild	22.7	22.9	23.2	19.8	22.3	22.2	21.4	22.0
Moderate	41.2	41.4	37.3	42.7	30.1	29.8	31.4	29.7
Severe	4.3	4.2	4.2	5.2	2.3	2.7	2.5	3.3
Any systemic reaction[e]	84.4	83.1	78.6	79.4	68.6	67.3	66.1	68.1
Use of antipyretic or pain medication[f]	30.2	28.9	35.5	34.8	25.9	27.7	37.1	33.3

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. Mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed.
c. Mild: increased or prolonged sleeping bouts; moderate: slightly subdued interfering with daily activity; severe: disabling not interested in usual daily activity.
d. Mild: easily consolable; moderate: requiring increased attention; severe: inconsolable; crying cannot be comforted.
e. Any systemic reaction: any fever ≥38.0°C, any decreased appetite, any drowsiness, or any irritability after the specified dose.
f. The numbers in this row reflect yes responses (i.e., number of events reported).
Source: Adapted from Table 8 in the CSR for Study B7471013.

From Dose 1 to one month after Dose 3, at least 1 AE was reported in 29.6% of participants in the 20vPnC group and 27.6% of participants in the 13vPnC group. AEs in the SOC of infections and infestations were reported most frequently in the 20vPnC (18.2%) and 13vPnC (15.9%) groups. From Dose 4 to one month after Dose 4, AEs were reported in 15.1% of participants in the 20vPnC group and 15.8% of participants in the 13vPnC group. As with the AEs from Dose 1 to one month after Dose 3, AEs in the SOC

of infections and infestations were reported most frequently in participants in the 20vPnC (11.6%) and 13vPnC (13.4%) groups.

The percentages of participants with SAEs at any time after Dose 1 through the 6-month follow-up period after the last dose were similar in the 20vPnC (n=44; 4.4%) and 13vPnC (n=28; 5.6%) groups. The percentages of participants with NDCMCs after Dose 1 were the same (2.8%) in both groups. There were no deaths during the trial.

6.3 Trial #3: B7471014

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

6.3.1 Objectives

Primary Objectives:

- To describe the safety profile of 20vPnC.
- Cohort 1 and Cohort 2: To demonstrate that the serotype-specific IgG concentrations for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding IgG concentrations before 20vPnC.
- Cohort 3 and Cohort 4: To demonstrate that the serotype-specific OPA titers for the 7 additional serotypes 1 month after 20vPnC are superior to the corresponding OPA titers before 20vPnC.

6.3.2 Design Overview

This Phase 3, multicenter, single-arm trial was conducted in the US as part of the Phase 3 clinical development program to support the use of 20vPnC in the pediatric population (up to <18 years of age). Approximately 800 children ≥15 months to <18 years of age at the time of consent (provided by a parent/legal guardian) and assent were enrolled into 4 cohorts based on age (Cohort 1: ≥15 to <24 months, Cohort 2: ≥2 to <5 years, Cohort 3: ≥5 to <10 years, and Cohort 4: ≥10 to <18 years) with approximately 200 participants in each cohort. Documentation of at least 3 prior doses of 13vPnC was required in children <5 years of age (Cohorts 1 and 2).

6.3.3 Population

The study population consisted of children ≥15 months to <18 years of age at the time of consent (provided by a parent/legal guardian) and assent. Documentation of at least 3 prior doses of 13vPnC was required in children <5 years of age (Cohorts 1 and 2).

6.3.4 Study Treatments or Agents Mandated by the Protocol

A single, 0.5-mL dose of 20vPnC was administered intramuscularly into the left leg (option for participants ≥15 to <24 months of age [Cohort 1] only) or left arm by a designated site staff member at Visit 1.

6.3.5 Directions for Use

Please refer to Tina Mongeau's clinical review memo.

6.3.6 Sites and Centers

Forty-four sites in the United States participated in the study.

6.3.7 Surveillance/Monitoring

Please refer to Tina Mongeau's clinical review memo.

6.3.8 Endpoints and Criteria for Study Success

Primary Safety Endpoints:

- Prompted local reactions (redness, swelling, and pain at the injection site) within 7 days after vaccination.
- Prompted systemic events (Cohort 1: Fever, decreased appetite, drowsiness/increased, sleep, and irritability; Cohorts 2 through 4: fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination.
- AEs within 1 month after vaccination.
- SAEs and NDCMCs within 6 months after vaccination.

Primary Immunogenicity Endpoint:

- Cohort 1 and Cohort 2: Pneumococcal serotype-specific IgG concentrations one month after vaccination.
- Cohort 3 and Cohort 4: Pneumococcal serotype-specific OPA titers one month after vaccination.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Statistical method and success criteria:
For the primary immunogenicity objective for Cohorts 1 and 2, hypothesis testing was used to assess superiority of the IgG concentrations for the 7 additional pneumococcal serotypes 1 month after 20vPnC vaccination to the IgG concentrations before 20vPnC vaccination within each cohort. Superiority would be declared for a serotype if the lower bound of the two-sided 95% CI for the IgG GMFR was greater than 1.0. Two-sided CIs were obtained based on the Student's t-distribution for the mean difference of logarithmically transformed assay results and exponentiating the limits.

For the primary immunogenicity objective for Cohorts 3 and 4, hypothesis testing was used to assess superiority of the OPA titers for the 7 additional pneumococcal serotypes 1 month after 20vPnC vaccination to the OPA titers before 20vPnC vaccination within each cohort in a randomly selected subset of participants. Superiority would be declared for a serotype if the lower bound of the two-sided 95% CI for the OPA GMFR was greater than 1.0. Two-sided CIs were obtained in the same way as the IgG GMFRs.

Sample size determination:
For IgG concentrations with 180 evaluable participants in each cohort (Cohort 1 or

Cohort 2), there was a >99% probability that superiority would be declared for all 7 additional serotypes, if the true GMFRs from before 20vPnC vaccination to 1 month after 20vPnC vaccination were at least 50% of the observed GMFRs in the B7471003 study.

For OPA titers with 90 evaluable participants in each cohort (Cohort 3 or Cohort 4), the probability that superiority would be declared for the 7 additional serotypes ranged from 64% (11A) to ≥98% if the true GMFRs from before 20vPnC vaccination to 1 month after 20vPnC vaccination were 75% of the observed GMFRs from participants 18 through 29 years of age in the B7471007 study. If the assumed number of evaluable participants were increased to 180 and GMFR assumptions were unchanged, the probability to demonstrate superiority for 11A would increase to 91%.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

The safety population included all participants who received 20vPnC and had safety follow-up after vaccination.

The evaluable immunogenicity population included all participants who:

- Were eligible,
- Received 20vPnC,
- Had at least 1 valid immunogenicity result from 1 month after vaccination collected within 27 to 56 days after vaccination for Cohorts 1-2 or within 27 to 49 days after vaccination for Cohorts 3-4, and
- Had no other major protocol deviations as determined by the clinician.

Table 15 below lists the numbers of participants in these populations. Overall, 82 participants were excluded from the evaluable immunogenicity population (20 [9.5%] , 36 [19.1%], 17 [8.4%], and 9 [4.3%] for Cohorts 1-4, respectively).

Table 15. Analysis Populations

-	≥15 to <24 Months (Cohort 1)	≥2 to <5 Years (Cohort 2)	≥5 to <10 Years (Cohort 3)	≥10 to <18 Years (Cohort 4)
-	n (%)	n (%)	n (%)	n (%)
Enrolled	210 (100.0)	219 (100.0)	203 (100.0)	207 (100.0)
Safety population	209 (99.5)	216 (98.6)	201 (99.0)	205 (99.0)
Evaluable immunogenicity population	190 (90.5)	183 (83.6)	186 (91.6)	198 (95.7)

Source: Adapted from Table 3 in the CSR for Study B7471014.

Demographic and baseline characteristics of sex, race, and ethnicity for the safety population were generally similar across the 4 age cohorts. There were slightly more male participants in each age cohort, except in participants ≥2 to <5 years of age (Cohort 2, which had an approximately equal distribution). The majority of the study population was White (80.1% to 86.8%) and non-Hispanic/non-Latino (78.5% to 83.6%) across all age cohorts. Demographic and baseline characteristics for the evaluable immunogenicity population were similar to those in the safety population.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoints

The IgG concentrations for all 7 additional serotypes after 20vPnC vaccination were superior to those before vaccination in participants ≥15 months to <5 years of age (Cohorts 1 and 2), as the lower bound of the two-sided 95% CI for each of the IgG GMFRs was >1.0 (Table 16). The observed IgG GMFRs ranged from 27.9 (Cohort 1 Serotype 12F) to 1847.7 (Cohort 1 Serotype 22F), with the lower bounds of the two-sided 95% CIs being 22.9-fold (Cohort 1 Serotype 12F) or higher.

Table 16. Pneumococcal IgG GMFRs for the 7 Additional Serotypes – Evaluable Immunogenicity Population Among Participants ≥15 Months to <5 Years of Age

Serotype	Age Cohort	n	GMC Before Vaccination	GMC 1 Month After Vaccination	GMFR	95% CI
8	≥15 to <24 Months	186	0.04	4.67	113.4	(93.2, 137.9)
8	≥2 to <5 Years	178	0.05	5.04	107.0	(86.1, 133.0)
10A	≥15 to <24 Months	188	0.01	1.23	83.2	(69.1, 100.2)
10A	≥2 to <5 Years	181	0.03	2.76	106.7	(86.2, 132.0)
11A	≥15 to <24 Months	188	0.03	1.61	62.7	(49.9, 78.8)
11A	≥2 to <5 Years	182	0.06	2.64	43.6	(33.2, 57.1)
12F	≥15 to <24 Months	188	0.01	0.23	27.9	(22.9, 34.1)
12F	≥2 to <5 Years	182	0.01	0.38	36.6	(30.1, 44.7)
15B	≥15 to <24 Months	188	0.02	1.16	52.1	(43.2, 62.8)
15B	≥2 to <5 Years	180	0.05	3.99	73.3	(58.7, 91.5)
22F	≥15 to <24 Months	188	0.01	9.61	1847.7	(1481.3, 2304.5)
22F	≥2 to <5 Years	182	0.02	12.46	796.2	(577.1, 1098.4)
33F	≥15 to <24 Months	188	0.02	1.90	113.5	(92.5, 139.2)
33F	≥2 to <5 Years	182	0.04	3.16	78.3	(61.6, 99.5)

Source: Adapted from Table 7 in the CSR for Study B7471014.

The OPA GMTs for all 7 additional serotypes after 20vPnC vaccination were superior to those before vaccination in participants ≥5 to <18 years of age (Cohorts 3 and 4), as the lower bound of the two-sided 95% CI for each of the OPA GMFRs was >1.0 (Table 17). The observed OPA GMFRs ranged from 11.5 (Cohort 4, Serotype 33F) to 499.0 (Cohort 4, Serotype 15B), with the lower bounds of the two-sided 95% CIs being 7.6 (Cohort 3, Serotype 11A) or higher.

Table 17. Pneumococcal OPA GMFRs for the 7 Additional Serotypes – Evaluable Immunogenicity Population Among Participants ≥5 to <18 Years of Age

Serotype	Age Cohort	n	GMT Before Vaccination	GMT 1 Month After Vaccination	GMFR	95% CI
8	≥5 to <10 Years	153	35	3755	106.5	(79.9, 142.0)
8	≥10 to <18 Years	174	36	3091	86.3	(64.2, 115.9)
10A	≥5 to <10 Years	134	657	20127	30.6	(20.1, 46.6)
10A	≥10 to <18 Years	142	459	15360	33.5	(22.3, 50.1)
11A	≥5 to <10 Years	136	1423	16464	11.6	(7.6, 17.7)
11A	≥10 to <18 Years	155	808	12021	14.9	(10.2, 21.8)
12F	≥5 to <10 Years	154	50	23210	463.6	(332.3, 646.7)
12F	≥10 to <18 Years	164	43	19645	454.1	(333.3, 618.7)
15B	≥5 to <10 Years	142	68	26060	380.8	(228.3, 635.2)
15B	≥10 to <18 Years	164	44	21780	499.0	(338.7, 735.3)
22F	≥5 to <10 Years	137	270	34717	128.5	(76.7, 215.3)
22F	≥10 to <18 Years	168	240	26678	111.2	(67.1, 184.3)
33F	≥5 to <10 Years	144	3210	45518	14.2	(10.9, 18.4)
33F	≥10 to <18 Years	158	2896	33315	11.5	(8.9, 14.9)

Source: Adapted from Table 11 in the CSR for Study B7471014.

6.3.11.2 Analyses of Secondary Endpoints

No secondary endpoint analyses are considered in this review.

6.3.11.3 Subpopulation Analyses

For the 7 additional serotypes, IgG GMFRs in participants ≥15 months to <5 years of age (Cohorts 1 and 2) and OPA GMFRS in participants ≥5 to <18 years of age (Cohorts 3 and 4) were generally similar in male and female participants and in each of the race subgroups.

6.3.11.4 Exploratory and Post Hoc Analyses

No exploratory or post-hoc analyses are considered in this review.

6.3.12 Safety Analyses

Across all age cohorts, the most frequently reported local reaction was pain at injection site (52.5%, 66.0%, 82.9%, and 82.0% in Cohort 1, 2, 3, and 4, respectively), followed by redness and swelling. Most local reactions were mild or moderate in severity (Table 18).

Table 18. Percentage of Participants With Solicited Local Adverse Reactions Within 7 Days After Vaccination

-	≥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) %
Redness[b]	-	-	-	-
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	0.9	2.0	0.5
Swelling[b]	-	-	-	-
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	0.5	1.0	0
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
Any local reaction[d]	63.2	70.2	86.4	83.9

a. N = number of participants with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
b. Mild: >0.0 to 2.0 cm; moderate: >2.0 to 7.0 cm; severe: >7.0 cm.
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. Any local reaction: any redness >0.0 cm, any swelling >0.0 cm, or any pain at the injection site after the specified dose.
Source: Adapted from Table 13 in the CSR for Study B7471014.

The most frequently reported systemic event in participants ≥15 to <24 months of age was irritability (61.8%), followed by drowsiness/increased sleep (41.7%) and decreased appetite (25.0%; Table 19). Most systemic events were mild or moderate in severity. Fever of ≥38.0°C was reported by 11.8% of participants.

Table 19. Percentage of Participants ≥15 to <24 Months of Age with Solicited Systemic Adverse Reactions Within 7 Days After Vaccination

-	≥15 to <24 Months (N[a]=204) %
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
>40.0°C	0
Decreased Appetite[b]	-
Any	25.0
Mild	17.6
Moderate	6.4
Severe	1.0
Drowsiness[c]	-
Any	41.7
Mild	31.4
Moderate	9.3
Severe	1.0
Irritability[d]	-
Any	61.8
Mild	22.5
Moderate	37.3
Severe	2.0
Any systemic reaction[e]	75.0
Use of antipyretic or pain medication[f]	31.4

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. Mild: decreased interest in eating; moderate: decreased oral intake; severe: refusal to feed.
c. Mild: increased or prolonged sleeping bouts; moderate: slightly subdued interfering with daily activity; severe: disabling not interested in usual daily activity.
d. Mild: easily consolable; moderate: requiring increased attention; severe: inconsolable; crying cannot be comforted.
e. Any systemic reaction: any fever ≥38.0°C, any decreased appetite, any drowsiness, or any irritability after the specified dose.
f. The numbers in this row reflect yes responses (i.e., number of events reported).
Source: Adapted from Table 14 in the CSR for Study B7471014.

The most frequently reported systemic events in participants ≥2 to <18 years of age varied by age cohort (Table 20). Fatigue was most frequently reported in participants ≥2 to <5 years of age (Cohort 2), and muscle pain was most frequently reported in participants ≥5 to <18 years of age (Cohorts 3 and 4). Most systemic events were mild or moderate in severity. Fever was reported for 3.3% of participants ≥2 to <5 years of age and only one participant ≥5 to <18 years of age.

Table 20. Percentage of Participants ≥2 to <18 Years of Age with Solicited Systemic Adverse Reactions Within 7 Days After Vaccination

-	≥2 to <5 Years (N[a]=215) %	≥5 to <10 Years (N[a]=199) %	≥10 to <18 Years (N[a]=205) %
Fever	-	-	-
≥38.0°C	3.3	0.5	0
≥38.0°C to 38.4°C	1.4	0.5	0
>38.4°C to 38.9°C	1.4	0	0
38.9°C to 40.0°C	0.5	0	0
>40.0°C	0	0	0
Fatigue[b]	-	-	-
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
Headache[b]			
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
Muscle pain[b]	-	-	-
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
Joint pain[b]	-	-	-
Any	3.7	6.5	8.3
Mild	2.3	3.0	3.4
Moderate	1.4	3.0	4.9
Severe	0	0.5	0
Any systemic reaction[c]	50.2	58.3	68.3
Use of antipyretic or pain[d]	16.7	25.6	14.6

a. N = number of participants with any e-diary data reported after vaccination. This value is the denominator for the percentage calculations.
b. Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily routine activity.
c. Any systemic reaction: any fever ≥38.0°C, any fatigue, any headache, any muscle pain, or any joint pain.
d. The numbers in this row reflect yes responses (i.e., number of events reported).
Source: Adapted from Table 15 in the CSR for Study B7471014.

The percentage of participants reporting any AE was highest in participants ≥15 to <24 months of age (23.9%) and was lower in the older age cohorts (≤7.9%). Five participants had SAEs during the trial. No SAE was assessed by the investigator as related to study intervention. Few participants (≤3.3% in any cohort) had NDCMCs at any time after 20vPnC vaccination. No NDCMC was considered by the investigator as related to study intervention. No participant died during the trial.

7. INTEGRATED OVERVIEW OF EFFICACY

Integrated analysis of immunogenicity data pooled across trials was not conducted because B7471011 was designed as the single pivotal Phase 3 immunogenicity trial conducted in infants that compared 20vPnC with 13vPnC using the 4-dose series. B7471014 was conducted in participants ≥15 months to <18 years of age; all participants received a single dose of 20vPnC.

8. INTEGRATED OVERVIEW OF SAFETY

Integrated summary of local reactions and systemic events was not provided for the overall cross-trial infant population.

Among US/PR participants enrolled as infants (Studies B7471003, B7471011, and B7471013 [US/PR only]), AEs from Dose 1 to one month after Dose 3 and from Dose 4 to one month after Dose 4 occurred at similar frequencies (43.8% and 46.3%, respectively) among 20vPnC (N=1567) and 13vPnC (N=1376) recipients. Related AEs as assessed by the investigator were reported in ≤1.1% of 20vPnC and 13vPnC recipients. Severe AEs were reported in 1.4% of 20vPnC recipients and 1.1% of 13vPnC recipients.

The percentages of infant participants with SAEs were similar for 20vPnC (4.5%) and 13vPnC (3.7%) recipients from Dose 1 to the end of the trial, among all participants (N=2232 for 20vPnC; N=1717 for 13vPnC) from Studies B7471003, B7471011, and B7471013. No SAEs reported were assessed as related to study vaccination by the investigator. There were no deaths in the trials.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

The pre-specified NI success criteria were met for 34 of the 40 primary immunogenicity comparisons, with six serotypes missing the NI margin for the difference in percentages of participants with predefined serotype-specific IgG concentrations after Dose 3 between 20vPnC and 13vPnC in the pivotal study B7471011. NI success criteria were met for key secondary immunogenicity endpoints (i.e., IgG GMCs post Dose 3), and for immune responses to the co-administered diphtheria, tetanus, acellular pertussis, hepatitis B virus, poliovirus, Hib, measles, mumps, rubella, and varicella vaccine antigens. No significant safety concerns were identified in the study populations. I defer to the clinical reviewer on the acceptability of the totality of the immunogenicity and safety data.