Vaccines and Related Biological Products Advisory Committee

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FDA Briefing Document

Prevnar 13™ (13vPnC): Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) Manufactured by Wyeth Pharmaceuticals Inc.

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CBER/FDA

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1.0 General Information

Product name:

Proper name: Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]

Proposed trade name: Prevnar 13

Product composition: Each 0.5 ml dose contains

- 2.2 µg of polysaccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4 µg polysaccharide for 6B individually conjugated to diphtheria cross-reacting material 197 (CRM_{197}). The total concentration of CRM_{197} is ~32 µg.
- 5 mM succinate buffer
- 0.125 mg aluminum as $AlP0_4$
- 0.02% polysorbate 80

The vaccine contains no preservative.

Sponsor: Wyeth Pharmaceuticals Inc.

Proposed indication: Active immunization of infants and toddlers for the prevention of invasive disease and otitis media caused by *Streptococcus pneumonia*e serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

Proposed age group: 6 weeks to 5 years

Dosing regimen and Route of administration: 4 doses, intramuscularly, given at 2, 4, 6, and 12-15 months of age

2.0 Executive Summary

Wyeth Pharmaceuticals Inc. has submitted a Biologics License Application (BLA) for their 13vPnC vaccine, which is a successor to Prevnar. The 13vPnC vaccine is composed of capsular polysaccharides derived from the seven pneumococcal serotypes contained in Prevnar (4, 6B, 9V, 14, 18C, 19F, and 23F) and from six additional pneumococcal serotypes (1, 3, 5, 6A, 7F, and 19A). Consistent with Prevnar manufacturing, each capsular polysaccharide is individually conjugated to diphtheria CRM_{197} protein. The proposed indications for the 13vPnC vaccine are for the active immunization of infants and toddlers for the prevention of invasive disease and otitis media caused by *Streptococcus pneumonia*e serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The proposed regimen consists of four doses, with a single intramuscular injection at ages 2, 4, 6, and 12-15 months.

Prevnar, the first pneumococcal conjugate vaccine licensed in the United States (U.S.), was approved by the FDA for active immunization to prevent invasive pneumococcal disease (IPD) in February 2000. The serotypes in the vaccine were originally selected because, at that time, they accounted for approximately 80% of IPD in young children in North America. A high level of efficacy (aggregated for the 7 serotypes) in preventing vaccine serotype IPD was demonstrated in a clinical endpoint vaccine efficacy trial in infants. In October, 2002, an additional Prevnar indication was approved for active immunization of infants and toddlers against otitis media caused by vaccine serotypes. Efficacy against otitis media was supported by data from an acute otitis media efficacy trial, which involved tympanocentesis, as well as information on health care utilization for otitis media.

In October 2000, the Advisory Committee on Immunization Practices (ACIP) recommended Prevnar for all children aged < 2 years and for older children at increased risk of IPD. Since the introduction of Prevnar in 2000, the rates of IPD caused by vaccine serotypes declined among U.S. children in the age group targeted by vaccination (direct effects) and among unimmunized older children and adults (indirect or herd immunity). By 2007, in children aged < 5 years, rates of IPD caused by serotypes contained in Prevnar declined by 99%. Although the overall rate of IPD caused by all pneumococcal serotypes was 76% lower in 2007 compared with the years preceding Prevnar introduction, overall IPD rates began to level off in 2002. This leveling off was due to an increase in the incidence of IPD caused by non-Prevnar serotypes, particularly serotype 19A. The six additional pneumococcal serotypes contained in 13vPnC vaccine were responsible for approximately 62% of IPD cases in children < 5 years of age in 2007. In this same age group, the thirteen serotypes contained in the 13vPnC vaccine were responsible for approximately 64% of IPD cases in 2007.

Following universal recommendations for Prevnar in infants in the U.S., parts of Europe and other countries, a placebo-controlled clinical endpoint efficacy study for 2nd generation pneumococcal conjugate vaccines in infants and toddlers less than 2 years of age was no longer feasible. On March 8, 2001, the Vaccine and Related Biological Products Advisory Committee (VRBPAC) was convened to consider alternate approaches for licensure of 2nd generation pneumococcal conjugate vaccines indicated for children less than 2 years of age. VRBPAC recommended that noninferiority immunogenicity studies conducted in the U.S. comparing a pneumococcal conjugate candidate vaccine to Prevnar based on an antibody response quantified by Enzyme Linked Immunosorbent Assay (ELISA) would be an acceptable approach for inferring efficacy against IPD for the candidate vaccine. Of note, the committee did not provide conclusive advice about whether noninferiority would have to be demonstrated for all 7 serotypes contained in Prevnar, or whether specific serotypes should be weighed more heavily, based on the disease impact of those serotypes. For additional serotypes not contained in Prevnar, the Committee also recommended use of immunological parameters to infer efficacy. Consequently, the clinical development for the 13vPnC vaccine involved an approach in which vaccine efficacy against IPD was to be inferred from immunologic parameters.

In a pivotal U.S. study, immunologic noninferiority of 13vPnC vaccine relative to Prevnar was evaluated. Primary immunogenicity endpoints, as agreed upon by the Center for Biologics Evaluation and Research (CBER), were based on immunoglobulin (IgG) antibody responses using an ELISA. Consistent with World Health Organization (WHO) recommendations, for each serotype, the proportion of subjects achieving serum IgG antibody concentrations ≥ 0.35 µg/mL four weeks after the third dose was one primary endpoint. For each serotype, the IgG geometric mean antibody concentration (GMC) measured 4 weeks after the fourth dose was a second primary endpoint. A single-antibody reference value of 0.35 µg/mL after the third dose was used for all pneumococcal serotypes, although this value does not necessarily predict protection in an individual subject. This antibody value was based on pooled efficacy estimates from three clinical efficacy trials that evaluated Prevnar or a 9-valent CRM_{197} conjugate vaccine against IPD. For new serotypes not included in Prevnar, noninferiority comparisons of the 13vPnC vaccine were made to the lowest response rate observed among the Prevnar serotypes in Prevnar recipients. In the absence of an established correlate of protection, CBER acknowledged that the clinical relevance of missed endpoints for one or more serotypes may not be clear. Thus, additional pneumococcal immunogenicity endpoints, including functional antibody responses, were also evaluated.

For three serotypes in the 13vPnC vaccine, the noninferiority criterion was not met for the proportion of subjects with an IgG antibody concentration ≥ 0.35 µg/mL one month after the third dose. The lower limit of the 95% confidence interval (CI) for the difference in proportions (13vPnC vaccine – Prevnar) exceeded CBER's agreed upon pre-specified noninferiority margin of -10% and was -10.9%, -12.4%, and -36.2% for serotypes 6B, 9V, and 3 respectively (Table 3). For serotype 3, the noninferiority criterion was not met for the IgG GMC after the fourth dose; the lower limit of the 95% CI for the GMC ratio (13vPnC vaccine/Prevnar), 0.22, was less than CBER's agreed upon noninferiority margin of 0.5 (Table 9). Otherwise, the noninferiority criteria for the primary endpoints were met. Additional immunogenicity endpoints for all serotypes are presented in tables 5, 7, 8, 11, and 12.

Across 14 studies, safety was evaluated in 5084 infants and young children who received 13vPnC vaccine and 2760 infants and young children who received Prevnar as the control vaccine. Analysis of safety outcomes after the 13vPnC vaccine relative to Prevnar are described in section 6.

CBER requests that the discussion and voting items for the Committee focus on whether the data submitted in the BLA support the safety and effectiveness of 13vPnC vaccine for the proposed indications. With regard to the effectiveness of 13vPnC vaccine against IPD, CBER is specifically seeking the Committee's input regarding the missed primary noninferiority immunogenicity criteria for serotypes 6B, 9V, and 3 in the pivotal U.S. study. CBER is also requesting the Committee's input on the proposed postmarketing IPD effectiveness studies. With regard to the effectiveness of 13vPnC vaccine against otitis media, it is important to note that the 0.35µg/mL value applies only to IPD and not to otitis media or other non-invasive disease endpoints. Moreover, the relevance of circulating IgG in preventing otitis media is unclear. Currently, there is no consensus regarding the serologic criteria for assessing efficacy of new pneumococcal conjugate vaccines against otitis media. Thus, CBER is seeking the Committee's advice on (1) whether the Prevnar efficacy data against otitis media can be used to support an otitis media indication for the 13vPnC vaccine for the 7 common serotypes and/or the 6 additional serotypes, and (2) the sponsor's proposed postmarketing otitis media effectiveness studies.

3.0 Introduction and Background

3.1 Epidemiology of pneumococcal infections in children up to 5 years of age

Streptococcus pneumoniae is a common bacterial cause of meningitis, bacteremia, pneumonia, and otitis media. In 1998, the U.S. Centers for Disease Control and Prevention's (CDC) Active Bacterial Core surveillance (ABCs) showed that invasive pneumococcal disease (bacteremia, meningitis, or other infection of a normally sterile site) rates in U.S. children aged < 12 months and 12-23 months were 165 and 203 cases per 100,000 population, respectively. After U.S. licensure of Wyeth Lederle's 7-valent pneumococcal conjugate vaccine, Prevnar (PCV7), in the year 2000, the incidence of invasive pneumococcal disease (IPD) caused by vaccine serotypes declined among U.S. children in the age group targeted by vaccination (direct effects) and among unimmunized older children and adults (indirect or herd immunity).[1] By 2007, seven years after routine PCV7 use in children aged < 23 months and in certain older children at high-risk for IPD, the incidence rates of IPD caused by serotypes contained in Prevnar declined by 99%.[2] PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) accounted for 1.9% of IPD in children less than 5 years of age.[2]

Although the overall IPD rate in children aged < 5 years was 76% lower in 2007 compared with the years preceding Prevnar introduction, this rate began to level off in 2002. The overall IPD rate (IPD caused by all pneumococcal serotypes) in this age group remained unchanged during 2003-2006 due to emerging non-PCV7 serotype IPD, especially antimicrobial-resistant *S. pneumoniae* serotype 19A.[2] In 2007, serotype 19A alone accounted for 42% of IPD cases. Of cases caused by these six additional serotypes, serotypes 19A, 7F and 3 accounted for 98% of IPD; serotypes 1 and 5 together accounted for 0.9%.[2] Overall IPD incidence rates are highest among children < 12 months of age (43 cases per 100,000).[2] In 2007, the IPD rate was 23.6 and 12.2 cases/100,000 population in Blacks and Whites, respectively.[3]

The incidence of acute otitis media (AOM) peaks at 6 to 12 months of age[4], and declines after 5 years of age.[5] More than 80% of healthy children have experienced at least one otitis media (OM) episode by age 3 years.[4] Prior to the U.S. introduction of Prevnar, approximately 25 million ambulatory care visits by children aged < 13 years[6] and 490,000 procedures for myringotomy with tube placement[7] were attributed to OM. In 2005, OM accounted for 10.4 million ambulatory care visits by children aged < 13 years. Reductions in tube placement showed similar trends.[6] The incidence of PCV7 vaccine serotypes in OM middle ear fluid (MEF) declined after routine PCV7 immunization; increases in non-PCV7 serotypes that are pertinent to the 13vPnC vaccine include 1, 3, 6A, 7, and 19A.[6,8,9,10] The most frequent MEF serotypes in children who received two to four PCV7 doses were serotypes 3 (13%), 19A (14%), and 19F (28%), which are all serotypes included in the 13vPnC vaccine.[6,8]

3.2 Regulatory background

Licensure of PCV7

Approved in the U.S. on February 17, 2000, Prevnar was initially indicated for active immunization of infants as a four dose series at 2, 4, 6, and 12-15 months of age to prevent IPD caused by vaccine serotypes. On October 1, 2002, an additional Prevnar indication was approved for active immunization of infants and toddlers against otitis media caused by vaccine serotypes. Vaccine efficacy for IPD and otitis media indications were demonstrated in well-controlled clinical trials with clinical disease endpoints.

PCV7: IPD Preventive Efficacy

A clinical efficacy trial conducted at Northern California Kaiser Permanente (NCKP) demonstrated 97.4% (95% CI, 82.7, 99.9) vaccine efficacy in preventing PCV7 serotype IPD among all infants

receiving at least 1 dose. Licensure of Prevnar was based on aggregate efficacy for all 7 serotypes; insufficient IPD cases accrued for some serotypes to determine efficacy for each serotype individually.[11]

PCV7: Otitis Media Preventive Efficacy
An otitis media indication for PCV7 was supported by (1) data on the effect of PCV7 on all-cause otitis media from the Prevnar NCKP trial[12] and (2) an acute otitis media efficacy trial that evaluated PCV7 in Finland and involved tympanocentesis.[13] Efficacy of PCV7 for vaccine serotype AOM was 57% (95% CI 44, 67), 34% (95% CI 21, 45) for all pneumococcal AOM, and 7% (95% CI 4.1, 9.7) for all-cause AOM. Vaccine efficacy estimates for individual serotypes ranged from 25% (for serotype 19F) to 84% (for serotype 6B). The number of otitis media episodes attributed to cross-reactive serotypes (serotypes 6A, 9N, 18B, 19A, and 23A) was reduced by 51 percent, whereas the number of episodes due to all other pneumococcal serotypes (non-PCV7 and non-PCV7 cross-reacting serotypes) increased by 33 percent in the pneumococcal vaccine group compared to the control-vaccine group.[13]

PCV7: Postmarketing Safety Surveillance
Safety outcomes were evaluated in an observational study that included 65,927 infants. Among the primary safety outcomes analyses, no elevated risk of healthcare utilization for croup, gastroenteritis, allergic reactions, seizures, wheezing diagnoses, or breath-holding was observed consistently across doses, health care settings, or multiple time windows. As in pre-licensure trials, fever was associated with PCV7 administration.

3.3 IPD Primary immunogenicity endpoints: 7 common and 6 non-Prevnar serotypes

Immunoglobulin (IgG) antibody reference value for comparing immune responses in infant pneumococcal conjugate vaccine trials

Licensure approaches for new pneumococcal conjugate vaccines were discussed at a Vaccines and Related Biological Products Advisory Committee Meeting held March 8, 2001. The committee advised that a noninferiority comparison of candidate pneumococcal conjugate vaccine immune responses to Prevnar was an acceptable licensure approach for an IPD indication. The advisory committee did not comment on specific immunogenicity criteria to use in comparative analyses.

A series of expert consultations, which included Food and Drug Administration (FDA) participation, were convened by the WHO. One of the meeting objectives was to establish a pnuemococcal IgG antibody reference value that related back to the demonstrated clinical efficacy outcome. Comparison of immune responses thus pertained to licensure approaches for preventing vaccine serotype IPD in infants, but not to other pneumococcal disease manifestations or age groups. A summary of the meeting outcomes, which pertain to the IgG antibody reference value, are as follows:

A single pneumococcal IgG antibody reference value for immunogenicity comparisons for all vaccine serotypes 1 month after three doses is, in part, based on the aggregate vaccine clinical efficacy estimate observed in the Prevnar NCKP trial. The pneumococcal IgG antibody concentration, determined in an ELISA, was derived from pooled vaccine efficacy estimates from three clinical studies conducted in NCKP [11], American Indians [14], and South Africa.[15] A pooled efficacy estimate of 93% (95% CI: 81.0%, 98.2%) corresponded to an IgG antibody concentration of 0.35 µg/mL (i.e., 93% of children in the clinical efficacy trials who provided blood samples after three doses achieved an antibody concentration of 0.35 µg/mL).[16] The ELISA assay used to establish the 0.35ug/mL reference value included a C-PS pre-adsorption step. Subsequent ELISA assays included pre-adsorption with both C-PS and serotype 22F polysaccharide. The effect of 22F pre-adsorption on estimated IgG concentrations in vaccinated infant sera was minimal.[17]

Limitations of the statistical modeling used to determine a single 0.35 μg/mL IgG antibody reference value include uncertain applicability across all serotypes, across different geographic regions, and among higher risk groups.[16] In addition, the 0.35 μg/mL IgG antibody reference value applies only to (1) comparisons among infants after receipt of three doses of a pneumococcal conjugate vaccine, (2) the prevention of IPD, and (3) populations rather than to individuals.[16]

Pneumococcal IgG antibody primary endpoints
The proportion of subjects achieving a serum IgG antibody concentration ≥ 0.35 μg/mL by ELISA one month after the third dose was chosen as a primary endpoint. In part, this time point was chosen because the highest age-specific risk for IPD occurs at 6 to 12 months of age, which also corresponds to the interval between the third and fourth pneumococcal vaccine doses. Thus, demonstration of noninferiority at this time point was considered of primary importance.

IgG GMCs one month after the fourth dose were chosen as a co-primary endpoint. Since most children in the Prevnar NCKP efficacy trial received a fourth PCV7 dose and cases contributing to the efficacy evaluation accrued after the 4th dose, post-dose 4 antibody data provide information about antibody persistence and duration of protection beyond 1 year of age.

Immunogenicity criteria to demonstrate noninferior immune responses to the 6 additional serotypes in the 13vPnC vaccine were based on comparisons to the lowest immune response elicited by a PCV7 vaccine serotype in PCV7 recipients. This approach is supported by IPD efficacy data from clinical trials for some PCV7 serotypes, and postmarketing effectiveness data from observational studies for the remaining serotypes. An estimate of the average response rate from each of the 7 common serotypes in the Prevnar group at the pre-specified threshold was not viewed as a feasible regulatory pathway, since antibody responses to some serotypes would be expected to be below the average.

Pneumococcal opsonophagocytic antibody exploratory endpoint
Evaluation of functional antibodies, as measured in an opsonophagocytic antibody (OPA) assay might be considered a preferable outcome measure because opsonophagocytosis is the main protective response in vivo. However, the OPA assay is more variable than the ELISA assay, and standardized OPA assay protocols are not yet available. Nevertheless, a functional antibody assessment was recognized as important, and was thus included as an exploratory objective. OPA geometric mean titers (GMTs) and the proportion of subjects achieving an OPA titer ≥ 1:8 were included as exploratory endpoints. Data from the three efficacy trials used to establish the pneumococcal IgG antibody reference value showed that an ELISA antibody concentration in the range of 0.20 – 0.35 μg/mL correlated with an OPA titer of 1:8.[17]

Because the OPA assays are not controlled by an external standard, the 1:8 titer may not have equivalent biological meaning for all serotypes, particularly for the additional 6 serotypes for which there are no direct clinical efficacy data. The lack of a standard against which OPA results can be normalized also precludes comparisons of OPA GMTs across different serotypes. Therefore, comparisons of serotype-specific OPA GMTs between 13vPnC and PCV7 recipients were viewed as a more meaningful expression of the ability of the 13vPnC vaccine to elicit opsonic activity.[18]

3.4 Otitis media endpoints

There is no consensus regarding the serologic criteria for assessing effectiveness of new pneumococcal conjugate vaccines against otitis media. IgG antibody levels were not indicative of prevention of vaccine serotype otitis media in clinical trials. For example, in the NCKP PCV7 efficacy trial, the type 19F

estimate for preventing IPD was 85% (95% CI 32,98); but serotype 19F was the most frequent pneumococcal vaccine type isolated from spontaneously ruptured tympanic membranes (vaccine failures) in the NCKP study. In the Finnish otitis media trial, efficacy was not demonstrated for type 19F despite it being the most common pneumococcal isolate from middle ears. Yet, IgG GMCs for 19F are comparable to those of the other vaccine serotypes.

4.0 Overview of Clinical Studies

The clinical section of the application contains study reports for 15 clinical studies. An integrated clinical summary is also provided.

Table 1. Clinical Studies Included in the 13vPnC Biologics License Application

Study No. / Country	Description	Schedule (months)	Control	Concomitant Vaccine Schedule (months)	Number Vaccinated (as randomized)	
					13vPnC	PCV7
Final Formulation						
6096A1-009 (Poland)	13vPnC +/- Polysorbate 80	2,3,4,12	13vPnC-P80	Pentaxim[b], ActHIB (2,3.4) Engerix-B[b] (2), Priorix[b] (12)	500[a]	-
Pivotal Studies						
6096A1-004 (USA)	Safety and immunogencity (Pivotal U.S.) Evaluation for concomitant antigens: Diphtheria, PT, FHA, PRN, Hib, and MMRV	2,4,6,12-15	PCV7	Pediarix, ActiHIB (2.4.6) PedvaxHib, ProQuad, and VAQTA (12-15)	332	331
6096A1-3005 (USA)	U.S. Lot consistency Evaluation for concomitant antigens: Tetanus, IPV, and HBV	2,4,6,12	PCV7	Pediarix, ActHIB (2,4,6) MMR II, Varivax, Havrix (12)	1455	244
Catch-up vaccination						
6096A1-3002 (Poland)	Assessment of catch-up schedule in unvaccinated children	Catch-up	None	N/A	354	-
6096A1-008 (France)	Immunogenicity of 13vPnC/13vPnC and PCV7/PCV7 and PCV7/13vPnC vaccination regimens for children with incomplete routine PCV7 infant immunization series Evaluation for concomitant antigens: (French routine childhood vaccination)	2,3,4,12	PCV7	Pentavac[b] (2,3,4,12)	302	309

Supporting Studies						
6096A1-002 (USA)	Phase I adult safety (18-50y)	Single dose	23vPS	N/A	15	15
6096A1-003 (USA)	Phase 2 safety and immunogenicity in infants/toddlers	2,4,6,12-15	PCV7	Pediarix (2,4,6) ActiHIB (2,4,6,12-15)	121	126
6096A1-006 (Germany)	Safety and immungenicity; Evaluation for concomitant antigens: Diphtheria, HBV, and Hib	2,3,4,11-12	PCV7	Infanrix hexa[b] (2,3,4,11-12)	300	303
6096A1-500 (Italy)	Safety and immunogenicity; Evaluation for concomitant antigens	3,5,11	PCV7	Infanrix hexa[b] (3,5,11)	302	302
6096A1-3000 (Poland)	Lot consistency (Europe)	2,3,4,12	None	Pentaxim[b] (2,3,4) Engerix-B[b] (2), Priorix[b] (12)	269	-
6096A1-3008 (Canada)	Safety and immunogenicity; Evaluation for concomitant antigens: NeisVac-C and Pentacel vaccine antigens	2,4,6,12	PCV7[c]	NeisVac-C[b] (2,6,12) Pentacel (2,4,6) MMR II and Varicella (12)	300	303
6096A1-501 (Spain)	Safety and immunogenicity; Evaluation for concomitant antigens: Meningitec, PT, FHA, PRN, Diphtheria, Tetanus, and IPV	2,4,6,15	PCV7[c]	Infanrix hexa[b] (2,4,6) Meningitec[b] (2,4,15) Infanrix-IPV+Hib[b] (15) MMR II (12)	314	302
6096A1-3007 (Spain)	Safety and immunogenicity; Evaluation for concomitant antigens: NeisVac-C and Infanrix hexa vaccine antigens	2,4,6,15	PCV7[c]	Infanrix hexa[b] (2,4,6) NeisVac-C[b] (2,4,15) Priorix[b] (12) Infanrix-IPV+Hib[b] (15)	218	226
6096A1-007 (UK)	Safety and immunogenicity; Evaluation for concomitant antigens	2,4,12	PCV7[c]	NeisVac[b] (2,4) Pediacel[b] (2,3,4) Menitorix[b] (12)	139	139
6096A1-011 (India)	Safety and immunogenicity; Evaluation for concomitant antigens: Easyfive vaccine antigens	6,10,14 wks, 12 months	PCV7	Easyfive[b]: DTP-Hib-HBV (6,10,14 wks) Biopolio[b] (6,10,14 wks)	178	175

[a] 250 subjects were randomized to receive 13vPnC with P80 and 250 subjects were randomized to receive 13vPnc without P80.
[b] Vaccine not licensed in the U.S.
[c] For concomitant antigen and safety assessments only.

5.0 Pivotal Clinical Studies

Two studies, 6096A1-004 and -3005, comprised the pivotal studies to demonstrate immunologic noninferiority (inferred efficacy) and lot consistency, respectively. Study results also provided the safety data for solicited and unsolicited adverse events, including serious adverse events.

5.1 Study 6096A1-004: immunogenicity and safety study

Title: A phase 3, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunologic noninferiority of a 13-valent Pneumococcal Conjugate Vaccine in healthy infants when given with routine pediatric vaccinations in the U.S.

5.1.1 Study design

Table 2. Study 6096A1-004 Trial Design: Randomized, active-controlled, double-blind, multicenter study

Population n= 640	Vaccine	Dosing Schedule	Concomitant Vaccines	Blood Draws
n= 320	13vPnC	2, 4, 6, and 12-15 mo	DTaP-HBV-IPV (Pediarix) at 2, 4, and 6 mo PRP-T (ActHIB) at 2, 4, and 6 mo PRP-OMP (PedvaxHIB) at 12-15 mo MMRV (ProQuad) at 12-15 mo HAV (VAQTA) at 12-15 mo	1 mo post-dose 3 Pre-dose 4 1 mo post-dose 4
n= 320	PCV7 (Prevnar)			

HBV (birth dose), rotavirus, and influenza vaccines permitted during the study period

5.1.2 Study objectives

Primary objectives

1. To demonstrate that the immune responses to the 7 common pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) induced by 13vPnC are noninferior to the immune responses induced by PCV7 when measured one month after the 3rd dose.
2. To demonstrate that the immune responses to the 6 additional pneumococcal serotypes (1, 3, 5, 6A, 7F, and 19A) induced by 13vPnC are noninferior to the lowest immune response elicited by a pneumococcal serotype contained in PCV7 when measured one month after the 3rd dose.
3. To demonstrate that the geometric mean IgG concentration for the 7 common pneumococcal conjugates induced by 13vPnC are noninferior to the geometric mean IgG concentration induced by PCV7 when measured one month after the 4th dose.
4. To demonstrate that the geometric mean IgG concentration to the 6 additional pneumococcal conjugates induced by 13vPnC are noninferior to the lowest geometric mean IgG concentration elicited by a pneumococcal serotype contained in PCV7 when measured 1 month after the 4th dose.
5. To demonstrate that the immune responses induced by DTaP-HBV-IPV (Pediarix; GSK) given with 13vPnC are noninferior to the immune responses induced by DTaP-HBV-IPV given with PCV7 when measured 1 month after the 3rd dose. Responses to the following antigens in Pediarix will be assessed: diphtheria and pertussis antigens (pertussis toxoid (PT), filamentous hemagglutinin (FHA), and pertactin (PRN)).
6. To demonstrate that the immune response induced by PRP-T [ActHIB; Sanofi Pasteur SA] given with 13vPnC is noninferior to the immune response induced by PRP-T [ActHIB] given with PCV7 when measured 1 month after the 3rd dose.

Secondary objectives

1. To assess in a subset (n=100 participants/per study group) the opsonophagocytic activity (OPA) one month after study dose 3 and 4.
2. To compare, one month post-vaccination, the immune responses induced by MMRV [ProQuad; Merck], when coadministered with 13vPnC, are noninferior to immune responses induced by ProQuad when given with PCV7.
3. To assess the immune response to PRP induced by PedvaxHIB given with 13vPnC, compared to the immune response induced by PedvaxHIB given with PCV7 when measured 1 month after the toddler dose.

Exploratory objective

To assess the opsonophagocytic activity (OPA) one month after dose 3 and one month after dose 4 following 13vPnC relative to the OPA level elicited by PCV7 in a subset of subjects (n=100 subjects per treatment group).

Primary immunogenicity endpoints

- % with pneumococcal serotype-specific IgG antibody concentration ≥ 0.35 µg/mL 1 month post-dose 3
- Pneumococcal serotype-specific IgG GMC ratio 1 month post-dose 4
- % with seroresponse cutoff value to pertussis antigens (PT, FHA, and PRN) 1 month post-dose 3
- % with anti-PRP antibody concentration ≥ 0.15 µg/mL 1 month post-dose 3
- % with anti-diphtheria ELISA antibody concentration ≥ 0.1 IU/mL 1 month post-dose 3

Secondary immunogenicity endpoints

- % with anti-measles antibody concentration ≥ 1.10 index value (I.V.) units one month post-dose 4
- % with anti-mumps antibody concentration ≥ 1.10 I.V. units one month post-dose 4
- % with anti-rubella antibody concentration ≥ 15.0 IU/mL one month post-dose 4
- % with anti-varicella antibody concentration ≥ 1.09 I.V. units by ELISA one month post-dose 4
- % with anti-PRP antibody concentration ≥ 1.0 µg/mL one month post-dose 3
- % with anti-PRP antibody concentration ≥ 1.0 µg/mL one month post-dose 4

Exploratory endpoint

- % with pneumococcal serotype-specific OPA antibody titer ≥ 1:8 one month post-doses 3 and 4
  OPA GMT one month post-doses 3 and 4

5.1.3 Populations analyzed

Evaluable infant/toddler population for immunogenicity

Infant: all eligible, randomized participants who received vaccine according to the treatment assignment, who complied with scheduled visits for blood specimens, who have at least 1 valid and determinate assay result for the proposed analysis, and have no protocol violations as determined by the clinical team leader/medical monitor. Entry criterion for age was 41 to 99 days of age, inclusive, on the day of first vaccination. Blood samples collected 27 to 56 days after the third vaccination. The blood sampling interval differed from the pre-specified blood sampling interval 28 to 42 days. The statistical analysis plan, which included this revision, was updated after study completion.

Toddler: all eligible, randomized participants who received vaccine according to the treatment assignment, who complied with scheduled visits for blood specimens, who have at least 1 valid and determinate assay result for the proposed analysis, and have no protocol violations as determined by the clinical team leader/medical monitor. Criterion for age was 334 to 396 days of age, inclusive, on the day of 4th dose vaccination. Blood samples collected 27 to 56 days after the third vaccination. The blood sampling interval differed from the pre-specified blood sampling interval 28 to 42 days. The statistical analysis plan, which included this revision, was updated after study completion.

All available infant/toddler population for immunogenicity
All enrolled participants who received study vaccine and have at least 1 valid and determinate assay result related to a planned analysis. Immunogenicity analyses were performed according to subjects' randomized treatment assignment.

5.1.4 Pneumococcal immunogenicity results

Primary immunogenicity analysis: post-dose 3 IgG seroresponse rates ≥ 0.35 µg/mL *with comparisons to the lowest PCV7 seroresponse rate for the 6 additional serotypes*

The criterion for demonstrating noninferiority based on post-dose 3 IgG seroresponse rates ≥ 0.35µg/mL was a lower limit of the 2-sided 95% CI for the difference in two proportions (13vPnC group – PCV7 reference value) > -0.1. The PCV7 reference value for the 6 additional serotypes is serotype 6B from the PCV7 group (the lowest response among the 7 serotypes contained in PCV7 achieved by subjects who received PCV7). Serotypes 6B, 9V, and 3 did not meet the pre-specified noninferiority criterion. The lower limits of the 95% CI for serotypes 6B, 9V were -10.9% and -12.4% respectively. For serotype 3, the lower limit of the 95% CI was -36.2%.

Table 3. Study 6096A1-004. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL after Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized									
	13vPnC				PCV7					
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**Difference[d]**	**(95% CI)[e]**
PCV7										
4	252	238	94.4	(90.9, 96.9)	251	246	98.0	(95.4, 99.4)	-3.6	(-7.3, -0.1)
6B	252	220	87.3	(82.5, 91.1)	250	232	92.8	(88.9, 95.7)	-5.5	(**-10.9**, -0.1)
9V	252	228	90.5	(86.2, 93.8)	252	248	98.4	(96.0, 99.6)	-7.9	(**-12.4**, -4.0)
14	251	245	97.6	(94.9, 99.1)	252	245	97.2	(94.4, 98.9)	0.4	(-2.7, 3.5)
18C	252	244	96.8	(93.8, 98.6)	252	248	98.4	(96.0, 99.6)	-1.6	(-4.7, 1.2)
19F	252	247	98.0	(95.4, 99.4)	251	245	97.6	(94.9, 99.1)	0.4	(-2.4, 3.4)
23F	252	228	90.5	(86.2, 93.8)	252	237	94.0	(90.4, 96.6)	-3.6	(-8.5, 1.2)
Additional										
1	252	241	95.6	(92.3, 97.8)	250	232	92.8	(88.9, 95.7)	2.8	(-1.3, 7.2)
3	249	158	63.5	(57.1, 69.4)	250	232	92.8	(88.9, 95.7)	-29.3	(**-36.2**, -22.4)
5	252	226	89.7	(85.2, 93.1)	250	232	92.8	(88.9, 95.7)	-3.1	(-8.3, 1.9)
6A	252	242	96.0	(92.8, 98.1)	250	232	92.8	(88.9, 95.7)	3.2	(-0.8, 7.6)
7F	252	248	98.4	(96.0, 99.6)	250	232	92.8	(88.9, 95.7)	5.6	(1.9, 9.7)
19A	251	247	98.4	(96.0, 99.6)	250	232	92.8	(88.9, 95.7)	5.6	(1.9, 9.7)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
[d] Difference in proportions (13vPnC – PCV7 reference value) expressed as a percentage. For the additional serotypes, the reference value is serotype 6B from the PCV7 group.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC - PCV7 reference, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 76 (Table 9-4).

Data for the 6 additional pneumococcal serotypes: **post dose 3 IgG seroresponse rates ≥ 0.35 µg/mL**
Table 4 shows response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 3, because the PCV7 reference value (serotype 6B) used to calculate the difference in proportions was shown.

Table 4. Study 6096A1-004. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC				PCV7			
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7								
4	252	238	94.4	(90.9, 96.9)	251	246	98.0	(95.4, 99.4)
6B	252	220	87.3	(82.5, 91.1)	250	232	92.8	(88.9, 95.7)
9V	252	228	90.5	(86.2, 93.8)	252	248	98.4	(96.0, 99.6)
14	251	245	97.6	(94.9, 99.1)	252	245	97.2	(94.4, 98.9)
18C	252	244	96.8	(93.8, 98.6)	252	248	98.4	(96.0, 99.6)
19F	252	247	98.0	(95.4, 99.4)	251	245	97.6	(94.9, 99.1)
23F	252	228	90.5	(86.2, 93.8)	252	237	94.0	(90.4, 96.6)
Additional								
1	252	241	95.6	(92.3, 97.8)	248	4	1.6	(0.4, 4.1)
3	249	158	63.5	(57.1, 69.4)	241	11	4.6	(2.3, 8.0)
5	252	226	89.7	(85.2, 93.1)	197	61	31.0	(24.6, 37.9)
6A	252	242	96.0	(92.8, 98.1)	240	102	42.5	(36.2, 49.0)
7F	252	248	98.4	(96.0, 99.6)	248	7	2.8	(1.1, 5.7)
19A	251	247	98.4	(96.0, 99.6)	238	206	86.6	(81.6, 90.6)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 74 (Table 9-3).

Secondary immunogenicity analysis: post dose 3 pneumococcal IgG geometric mean concentrations *with comparisons to the lowest PCV7 GMC for the 6 additional serotypes*

With the exception of serotype 3, all serotypes met the 2-fold noninferiority criterion for this secondary endpoint. The lower limit of the 2-sided 95% CI for the GMC ratio was 0.30 for serotype 3.

Table 5. Study 6096A1-004. Pneumococcal IgG GMCs (µg/mL) After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC			PCV7				
Serotype	**n[a]**	**GMC[b]**	**(95% CI)[c]**	**n[a]**	**GMC[b]**	**(95% CI)[c]**	**Ratio[d]**	**(95% CI)[e]**
PCV7								
4	252	1.31	(1.19, 1.45)	251	1.93	(1.75, 2.13)	0.68	(0.59, 0.78)
6B	252	2.10	(1.77, 2.49)	250	3.14	(2.64, 3.74)	0.67	(0.52, 0.85)
9V	252	0.98	(0.89, 1.08)	252	1.40	(1.27, 1.55)	0.70	(0.61, 0.80)
14	251	4.74	(4.18, 5.39)	252	5.67	(5.02, 6.40)	0.84	(0.70, 1.00)
18C	252	1.37	(1.24, 1.52)	252	1.79	(1.63, 1.96)	0.77	(0.67, 0.88)
19F	252	1.85	(1.69, 2.04)	251	2.24	(2.01, 2.50)	0.83	(0.72, 0.96)
23F	252	1.33	(1.17, 1.51)	252	1.90	(1.68, 2.15)	0.70	(0.59, 0.84)
Additional								
1	252	2.03	(1.78, 2.32)	252	1.40	(1.27, 1.55)	1.45	(1.23, 1.71)
3	249	0.49	(0.43, 0.55)	252	1.40	(1.27, 1.55)	0.35	(**0.30**, 0.41)
5	252	1.33	(1.18, 1.50)	252	1.40	(1.27, 1.55)	0.95	(0.81, 1.11)
6A	252	2.19	(1.93, 2.48)	252	1.40	(1.27, 1.55)	1.56	(1.33, 1.83)
7F	252	2.57	(2.28, 2.89)	252	1.40	(1.27, 1.55)	1.83	(1.57, 2.13)
19A	251	2.07	(1.87, 2.30)	252	1.40	(1.27, 1.55)	1.48	(1.28, 1.71)

[a] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[b] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations.
[d] GMC ratio: 13vPnC to PCV7 reference. For the additional serotypes, the reference value is serotype 9V from the PCV7 group.
[e] Two-sided 95% CIs are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – PCV7 reference).

Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 84 (Table 9-7).

***Data for the 6 additional pneumococcal serotypes:* post dose 3 IgG GMCs**

Table 6 shows the GMCs for the 6 additional serotypes using GMCs among PCV7 recipients as the comparator. These data differ from those shown in Table 5, for which the PCV7 reference value (serotype 9V) used to calculate the difference in proportions was shown.

Table 6. Study 6096A1-004. Pneumococcal IgG GMCs (µg/mL) After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized					
	13vPnC			PCV7		
Serotype	**n[a]**	**GMC[b]**	**(95% CI)[c]**	**n[a]**	**GMC[b]**	**(95% CI)[c]**
PCV7						
4	252	1.31	(1.19, 1.45)	251	1.93	(1.75, 2.13)
6B	252	2.10	(1.77, 2.49)	250	3.14	(2.64, 3.74)
9V	252	0.98	(0.89, 1.08)	252	1.40	(1.27, 1.55)
14	251	4.74	(4.18, 5.39)	252	5.67	(5.02, 6.40)
18C	252	1.37	(1.24, 1.52)	252	1.79	(1.63, 1.96)
19F	252	1.85	(1.69, 2.04)	251	2.24	(2.01, 2.50)
23F	252	1.33	(1.17, 1.51)	252	1.90	(1.68, 2.15)
Additional						
1	252	2.03	(1.78, 2.32)	248	0.02	(0.02, 0.03)
3	249	0.49	(0.43, 0.55)	241	0.04	(0.03, 0.04)
5	252	1.33	(1.18, 1.50)	197	0.20	(0.16, 0.24)
6A	252	2.19	(1.93, 2.48)	240	0.25	(0.21, 0.29)
7F	252	2.57	(2.28, 2.89)	248	0.04	(0.03, 0.04)
19A	251	2.07	(1.87, 2.30)	238	0.89	(0.79, 0.99)

[a] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[b] Geometric mean concentrations were calculated using all subjects with available data for the specified blood draw.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 83 (Table 9-6).

Exploratory analysis: post-dose 3 OPA GMTs

A lower serotype 6B OPA GMT in the 13vPnC group is consistent with a lower serotype 6B post-dose 3 IgG GMC in the 13vPnC group. Comparisons of serotype 9V OPA GMTs after the third dose in PCV7 and 13vPnC vaccine recipients indicate similar functional antibody responses; the 95% CI for 9V OPA titers overlapped in the two study groups; this finding is not consistent with serotype 9V IgG GMCs in the two study groups.

Among the 6 new serotypes, a high serotype 6A OPA GMT in the PCV7 group is consistent with functional antibody production due to cross-reactivity with serotype 6B. A low serotype 19A OPA titer in the PCV7 group is consistent with cross-reactivity between 19F and 19A resulting in production of non-functional antibodies. Similar trends were observed when comparing post-dose 3 OPA and IgG seroresponse rates among PCV7 recipients (Tables 4 and 8).

Table 7. Study 6096A1-004. Comparison of Pneumococcal OPA GMTs After Dose 3 (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC			PCV7				
Serotype	**n[a]**	**GMT[b]**	**(95% CI)[c]**	**n[a]**	**GMT[b]**	**(95% CI)[c]**	**Ratio[d]**	**(95% CI)[e]**
PCV7								
4	92	359.32	(276.04, 467.72)	92	535.68	(421.13, 681.37)	0.67	(0.47, 0.96)
6B	94	1054.65	(817.34, 1360.87)	94	1513.66	(1206.64, 1898.81)	0.70	(0.50, 0.98)
9V	93	4035.4	(2932.68, 5552.75)	94	3259.01	(2288.43, 4641.25)	1.24	(0.77, 1.99)
14	94	1240.41	(934.93, 1645.69)	94	1480.55	(1133.40, 1934.02)	0.84	(0.57, 1.23)
18C	94	275.59	(210.33, 361.10)	94	375.64	(291.68, 483.75)	0.73	(0.51, 1.06)
19F	94	54.42	(40.20, 73.65)	94	44.92	(33.90, 59.52)	1.21	(0.80, 1.83)
23F	94	791.07	(604.96, 1034.44)	94	923.56	(708.59, 1203.74)	0.86	(0.59, 1.25)
Additional								
1	92	51.83	(38.84, 69.16)	92	4.41	(4.06, 4.80)	11.75	(8.72, 15.83)
3	94	120.67	(92.38, 157.62)	94	6.70	(5.27, 8.52)	18.00	(12.60, 25.72)
5	91	90.86	(67.10, 123.02)	93	4.15	(3.94, 4.38)	21.88	(16.17, 29.61)
6A	94	979.68	(783.04, 1225.71)	94	100.35	(66.22, 152.08)	9.76	(6.11, 15.61)
7F	94	9493.77	(7339.13, 12280.98)	89	128.00	(79.55, 205.97)	74.17	(43.68, 125.93)
19A	93	151.94	(105.16, 219.52)	92	6.53	(5.01, 8.50)	23.28	(14.83, 36.52)

[a] n = Number of subjects with a determinate antibody titer for the specified serotype.
[b] Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
[c] Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers.
[d] Ratio of GMTs; 13vPnC to PCV7 reference.
[e] CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – PCV7 reference).
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 105 (Table 9-17).

Exploratory analysis: post-dose 3 OPA seroresponse rates ≥ 1:8

Among the 6 new serotypes, a high OPA serotype 6A seroresponse rate (77.7%) in PCV7 recipients is consistent with functional antibody production due to cross-reactivity with serotype 6B. A low proportion of PCV7 recipients with serotype 19A OPA titers ≥ 1:8 (Table 8) and a higher than expected IgG seroresponse rate to serotype 19A (Table 4) in these same subjects is consistent with cross-reactivity between 19F and 19A, resulting in production of non-functional antibodies. A higher than expected percentage of PCV7 subjects (76.4%) achieved OPA titers ≥ 1:8 against serotype 7F. The reason for this high seroresponse rate is unclear.

Table 8. Study 6096A1-004. Comparison of Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ 1:8 after Dose 3 (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized									
	13vPnC				PCV7					
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**Difference[d]**	**(95% CI)[e]**
PCV7										
4	92	90	97.8	(92.4, 99.7)	92	91	98.9	(94.1,100.0)	-1.1	(-6.7, 3.9)
6B	94	93	98.9	(94.2,100.0)	94	94	100.0	(96.2,100.0)	-1.1	(-5.8, 2.8)
9V	93	93	100.0	(96.1,100.0)	94	93	98.9	(94.2,100.0)	1.1	(-2.9, 5.8)
14	94	94	100.0	(96.2,100.0)	94	94	100.0	(96.2,100.0)	0.0	(-3.9, 3.9)
18C	94	94	100.0	(96.2,100.0)	94	94	100.0	(96.2,100.0)	0.0	(-3.9, 3.9)
19F	94	85	90.4	(82.6, 95.5)	94	87	92.6	(85.3, 97.0)	-2.1	(-10.8, 6.3)
23F	94	93	98.9	(94.2,100.0)	94	93	98.9	(94.2,100.0)	0.0	(-4.8, 4.8)
Additional										
1	92	91	98.9	(94.1,100.0)	92	9	9.8	(4.6, 17.8)	89.1	(80.9, 94.7)
3	94	91	96.8	(91.0, 99.3)	94	20	21.3	(13.5, 30.9)	75.5	(65.3, 83.9)
5	91	84	92.3	(84.8, 96.9)	93	2	2.2	(0.3, 7.6)	90.2	(82.0, 95.4)
6A	94	94	100.0	(96.2,100.0)	94	73	77.7	(67.9, 85.6)	22.3	(14.4, 32.1)
7F	94	94	100.0	(96.2,100.0)	89	68	76.4	(66.2, 84.8)	23.6	(15.2, 33.8)
19A	93	85	91.4	(83.8, 96.2)	92	15	16.3	(9.4, 25.5)	75.1	(64.0, 83.7)

[a] N = number of subjects with a determinate postinfant series OPA antibody titer to the given serotype.
[b] n = Number of subjects with an antibody titer ≥1:8 for the given serotype.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7 reference, expressed as a percentage.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC – PCV7 reference, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 100 (Table 9-16).

Post-dose 3 IgG RCDC Curves: see Appendix I

- Serotype 6B: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 79 (Figure 9-1)
- Serotype 9V: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 80 (Figure 9-2)
- Serotype 3: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 81 (Figure 9-3)

Post-dose 3 OPA Titers - RCDC Curves: See Appendix I

- Serotype 6B: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 453 (Figure 16.26)
- Serotype 9V: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 455 (Figure 16.28)
- Serotype 3: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 451 (Figure 16.24)

Primary immunogenicity analysis: post dose 4 pneumococcal IgG geometric mean concentrations *with comparisons to the lowest PCV7 GMC for the 6 additional serotypes*

The criterion for demonstrating noninferiority based on post-dose 4 IgG GMCs was a lower limit of the 2-sided 95% CI for the GMC ratio (13vPnC / PCV7 reference) > 0.5 (2-fold criterion). The PCV7 reference value for the 6 additional serotypes is serotype 9V from the PCV7 group (the lowest response among the 7 serotypes contained in PCV7 achieved by subjects who received PCV7). With the exception of serotype 3, all serotypes met the 2-fold noninferiority criterion for this co-primary endpoint. The lower limit of the 2-sided 95% CI for the GMC ratio was 0.22 for serotype 3.

Table 9. Study 6096A1-004. Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 4 (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC			PCV7				
Serotype	**n[a]**	**GMC[b]**	**(95% CI)[c]**	**n[a]**	**GMC[b]**	**(95% CI)[c]**	**Ratio[d]**	**(95% CI)[e]**
PCV7								
4	235	3.73	(3.28, 4.24)	223	5.49	(4.91, 6.13)	0.68	(0.57, 0.80)
6B	234	11.53	(9.99, 13.30)	223	15.63	(13.80, 17.69)	0.74	(0.61, 0.89)
9V	234	2.62	(2.34, 2.94)	223	3.63	(3.25, 4.05)	0.72	(0.62, 0.85)
14	235	9.11	(7.95, 10.45)	223	12.72	(11.22, 14.41)	0.72	(0.60, 0.86)
18C	236	3.20	(2.82, 3.64)	223	4.70	(4.18, 5.28)	0.68	(0.57, 0.81)
19F	235	6.60	(5.85, 7.44)	223	5.60	(4.87, 6.43)	1.18	(0.98, 1.41)
23F	234	5.07	(4.41, 5.83)	222	7.84	(6.91, 8.90)	0.65	(0.54, 0.78)
Additional								
1	235	5.06	(4.43, 5.80)	223	3.63	(3.25, 4.05)	1.40	(1.17, 1.66)
3	232	0.94	(0.83, 1.05)	223	3.63	(3.25, 4.05)	0.26	(**0.22**, 0.30)
5	235	3.72	(3.31, 4.18)	223	3.63	(3.25, 4.05)	1.03	(0.87, 1.20)
6A	235	8.20	(7.30, 9.20)	223	3.63	(3.25, 4.05)	2.26	(1.93, 2.65)
7F	235	5.67	(5.01, 6.42)	223	3.63	(3.25, 4.05)	1.56	(1.32, 1.85)
19A	236	8.55	(7.64, 9.56)	223	3.63	(3.25, 4.05)	2.36	(2.01, 2.76)

[a] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[b] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC to PCV7 reference. For the additional serotypes, the reference value is serotype 9V from the PCV7 group.
[e] CIs are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – PCV7 reference).
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 94 (Table 9-13).

***Data for the 6 additional pneumococcal serotypes:* post dose 4 IgG GMCs**

Table 10 shows the response rates for the 6 additional serotypes among PCV7 recipients. These data differ from those shown in Table 9, for which the PCV7 reference value (serotype 9V) used to calculate the difference in proportions was shown.

Table 10. Study 6096A1-004. Pneumococcal IgG GMCs (µg/mL) After Dose 4 (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized					
	13vPnC			PCV7		
Serotype	**n[a]**	**GMC[b]**	**(95% CI)[c]**	**n[a]**	**GMC[b]**	**(95% CI)[c]**
PCV7						
4	235	3.73	(3.28, 4.24)	223	5.49	(4.91, 6.13)
6B	234	11.53	(9.99, 13.30)	223	15.63	(13.80, 17.69)
9V	234	2.62	(2.34, 2.94)	223	3.63	(3.25, 4.05)
14	235	9.11	(7.95, 10.45)	223	12.72	(11.22, 14.41)
18C	236	3.20	(2.82, 3.64)	223	4.70	(4.18, 5.28)
19F	235	6.60	(5.85, 7.44)	223	5.60	(4.87, 6.43)
23F	234	5.07	(4.41, 5.83)	222	7.84	(6.91, 8.90)
Additional						
1	235	5.06	(4.43, 5.80)	222	0.03	(0.03, 0.03)
3	232	0.94	(0.83, 1.05)	215	0.07	(0.05, 0.08)
5	235	3.72	(3.31, 4.18)	198	0.55	(0.47, 0.64)
6A	235	8.20	(7.30, 9.20)	221	1.87	(1.60, 2.19)
7F	235	5.67	(5.01, 6.42)	223	0.05	(0.04, 0.05)
19A	236	8.55	(7.64, 9.56)	211	3.54	(3.15, 3.98)

[a] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[b] GMCs were calculated using all subjects with available data for the specified blood draw.
[c] CIs are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 93 (Table 9-12).

Exploratory analysis: dose 4 OPA GMT

OPA GMTs post-dose 4 are consistent with post-dose 3 OPA GMT findings, with the exception of results for serotype 9V. A comparison between the two study groups with regards to serotype 9V OPA GMTs after dose 4 is consistent with the lower serotype 9V GMC after dose 3 (Table 5) in 13vPnC recipients compared to PCV7 recipients. The GMT ratio for serotype 9V, which was 1.24 (95% CI 0.77, 1.99) after dose 3, decreased to 0.66 (95% CI 0.45, 0.96) after dose 4.

Table 11. Study 6096A1-004. Comparison of Pneumococcal OPA GMTs After Dose 4 (Evaluable Toddler Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC			PCV7				
Serotype	**n[a]**	**GMT[b]**	**(95% CI)[c]**	**n[a]**	**GMT[b]**	**(95% CI)[c]**	**Ratio[d]**	**(95% CI)[e]**
4	88	1179.98	(847.34, 1643.20)	92	1492.46	(1114.40, 1998.78)	0.79	(0.51, 1.22)
6B	92	3099.51	(2337.02, 4110.79)	95	4066.22	(3243.42, 5097.76)	0.76	(0.53, 1.09)
9V	90	11856.03	(8809.85, 15955.49)	94	18032.33	(14124.99, 23020.53)	0.66	(0.45, 0.96)
14	92	2002.23	(1452.54, 2759.93)	96	2365.87	(1870.56, 2992.34)	0.85	(0.57, 1.25)
18C	91	993.27	(754.08, 1308.33)	96	1722.16	(1326.59, 2235.67)	0.58	(0.40, 0.84)
19F	92	199.65	(144.22, 276.38)	96	167.20	(121.35, 230.37)	1.19	(0.76, 1.88)
23F	90	2723.25	(1960.67, 3782.41)	92	4981.68	(3885.71, 6386.76)	0.55	(0.36, 0.82)
Additional								
1	89	164.23	(113.83, 236.93)	92	5.01	(4.22, 5.96)	32.75	(21.99, 48.78)
3	91	380.41	(300.19, 482.08)	96	11.81	(8.68, 16.08)	32.2	(21.82, 47.52)
5	91	300.41	(229.39, 393.40)	96	4.69	(3.99, 5.51)	64.07	(47.08, 87.20)
6A	92	2241.79	(1706.71, 2944.63)	96	538.54	(374.83, 773.75)	4.16	(2.65, 6.55)
7F	91	11629.44	(9053.62, 14938.11)	92	267.84	(164.49, 436.11)	43.42	(25.15, 74.97)
19A	91	1024.00	(774.12, 1354.54)	94	28.65	(18.58, 44.17)	35.74	(21.34, 59.85)

[a] Number of subjects with a determinate antibody titer for the specified serotype.
[b] Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
[c] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
[d] Ratio of GMTs; 13vPnC to PCV7 reference.
[e] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – PCV7 reference).

Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 112 (Table 9-19).

Exploratory analysis: dose 4 OPA seroresponse rates ≥1:8
Among the 6 additional serotypes, the OPA seroporesponse rate to serotype 6A increased from 77% (95% CI 67.9, 85.6) after dose 3 to 94.8% (95% CI 88.3, 98.3) after dose 4. The OPA seroresponse rate to serotype 19A increased from 16.3% (95%CI 9.4, 25.5) after dose 3 to 53.2% (95% CI 42.6, 63.6) after dose 4.

Table 12. Study 6096A1-004. Comparison of Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ 1:8 After Dose 4 (Evaluable Toddler Immunogenicity Population)

	Vaccine Group As Randomized									
	13vPnC				PCV7					
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**Difference[d]**	**(95% CI)[e]**
4	88	87	98.9	(93.8,100.0)	92	91	98.9	(94.1,100.0)	0.0	(-5.2, 4.9)
6B	92	91	98.9	(94.1,100.0)	95	95	100.0	(96.2,100.0)	-1.1	(-5.9, 2.8)
9V	90	89	98.9	(94.0,100.0)	94	94	100.0	(96.2,100.0)	-1.1	(-6.1, 2.9)
14	92	92	100.0	(96.1,100.0)	96	96	100.0	(96.2,100.0)	0.0	(-4.0, 3.8)
18C	91	90	98.9	(94.0,100.0)	96	96	100.0	(96.2,100.0)	-1.1	(-6.0, 2.8)
19F	92	89	96.7	(90.8, 99.3)	96	91	94.8	(88.3, 98.3)	1.9	(-4.6, 8.9)
23F	90	89	98.9	(94.0,100.0)	92	92	100.0	(96.1,100.0)	-1.1	(-6.1, 2.9)
Additional										
1	89	88	98.9	(93.9,100.0)	92	11	12.0	(6.1, 20.4)	86.9	(78.3, 93.1)
3	91	89	97.8	(92.3, 99.7)	96	42	43.8	(33.6, 54.3)	54.1	(43.2, 64.4)
5	91	90	98.9	(94.0,100.0)	96	5	5.2	(1.7, 11.7)	93.7	(86.8, 97.6)
6A	92	91	98.9	(94.1,100.0)	96	91	94.8	(88.3, 98.3)	4.1	(-1.4, 10.7)
7F	91	91	100.0	(96.0,100.0)	92	74	80.4	(70.9, 88.0)	19.6	(12.0, 29.1)
19A	91	89	97.8	(92.3, 99.7)	94	50	53.2	(42.6, 63.6)	44.6	(33.4, 55.6)

[a] Number of subjects with a determinate postinfant series OPA antibody titer to the given serotype.
[b] n = Number of subjects with an antibody titer ≥1:8 for the given serotype.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7 reference, expressed as a percentage.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC – PCV7 reference, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 107 (Table 9-18).

Post-dose 4 IgG RCDC Curves: See Appendix I

- Serotype 6B: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page442 (Figure 16.15)
- Serotype 9V: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 444 (Figure 16.17)
- Serotype 3: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 90 (Figure 9-4)

Post-dose 4 OPA Titers - RCDC Curves: See Appendix I

- Serotype 6B: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 463 (Figure 16.36)
- Serotype 9V: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 165 (Figure 16.38)
- Serotype 3: Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page 461 (Figure 16.34)

5.2 Study 6096A1-3005: lot consistency

Title: A phase 3, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 3 lots of 13-valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in the United States.

5.2.1 Study design

This trial was a randomized, active-controlled, double-blind, multi-center study.

Table 13. Study 6096A1-3005 Trial Design

Population n= 1400 (evaluable)	Vaccine	Dosing Schedule	Concomitant Vaccines
n=400	13vPnC pilot lot scale 1	2, 4, 6, and 12 mo	DTaP-HBV-IPV (Pediarix) at 2, 4, & 6 mo PRP-T (ActHIB) at 2, 4, and 6 mo MMRV (ProQuad) and HAV at 12 mo
n=400	13vPnC pilot lot scale 2		
n=400	13vPnC manuf. scale lot		
n=200	PCV7 (Prevnar)		

HBV (birth dose), RV (infant) and Hib (15-18 mo) vaccines permitted during the study period

5.2.2 Study objectives

Lot consistency primary objectives

1. To demonstrate that the IgG GMC ratio among 3 lots of 13vPnC (2 pilot, 1 manufacturing scale) are equivalent when measured 1 month after the 3rd dose.
2. To demonstrate that the immune response to antigens contained in DTaP-HBV-IPV [Pediarix] when co-administered with 13vPnC are noninferior to corresponding immune responses when Pediarix is co-administered with PCV7, when measured 1 month after the 3rd dose. Antibody responses to tetanus toxoid, poliovirus types 1, 2, and 3, and hepatitis B components of Pediarix were evaluated.

Other objectives

To demonstrate that immune responses induced by 3 lots of 13vPnC are equivalent when measured 1 month after the 4th dose.

Primary immunogenicity endpoints

- Post-dose 3 pneumococcal IgG GMC ratio
- Post-dose 3 % with anti-tetanus antibody level ≥ 0.1 IU/mL
- Post-dose 3 % with anti-polio antibody titer ≥ 1:8 for types 1 - 3
- Post-dose 3 % with anti-HBV antibody level ≥ 10.0 mIU/mL

Note: For concomitant vaccine antigen evaluation: subset N= 235 (13vPnC n=60 evaluable participants (pooled lots 1-3), n=175 evaluable participants)

Secondary immunogenicity endpoints

- Post-dose 3 % with pneumococcal IgG antibody concentration ≥ 0.35 and 1.0 µg/mL/mL
- Post-dose 4 % with pneumococcal serotype-specific IgG concentration ≥ 0.35 and 1.0 µg/mL
- Post-dose 4 pneumococcal serotype-specific GMC

5.2.3 Populations analyzed

The all available and evaluable infant immunogenicity analysis populations in study 3005 were identical to study 004. Immunogenicity analyses were performed according to subjects' randomized treatment assignment.

5.2.4 Lot consistency results

Primary immunogenicity analysis: post-dose 3 pair-wise comparisons of pneumococcal IgG geometric mean concentrations

The maximum difference in the log transformed geometric mean responses for each of the serotypes among the three 13vPnC lots was < 0.693 and > -0.693, and therefore each of the 13 serotypes met the equivalency criterion, that the ratio of GMCs for any 2 lots did not exceed 2-fold.

Table 14. Study 6096A1-3005. Equivalency Assessment of Pneumococcal IgG GMCs (µg/mL) After Dose 3 in the Three 13vPnC Lot Groups (Evaluable Infant Immunogenicity Population)

	13vPnC Lot Group As Randomized									Difference (95% CI) in Log-Transformed Geometric Means		
	Pilot Scale Lot 1			Pilot Scale Lot 2			Manufacturing Scale Lot					
Sero-type	n[a]	GMC	(95% CI)[b]	n[a]	GMC	(95% CI)[b]	n[a]	GMC	(95% CI)[b]	Lot 1 – Lot 2	Lot 1 – Mfr Lot	Lot 2 – Mfr Lot
PCV 7												
4	411	1.33	(1.24, 1.43)	404	1.34	(1.25, 1.44)	398	1.75	(1.63, 1.88)	-0.01 (-0.11, 0.09)	-0.27 (-0.38, -0.17)	-0.27 (-0.37, -0.16)
6B	409	2.89	(2.58, 3.23)	401	2.15	(1.91, 2.42)	396	2.54	(2.27, 2.85)	0.30 (0.13, 0.46)	0.13 (-0.04, 0.29)	-0.17 (-0.33, -0.01)
9V	411	1.05	(0.98, 1.12)	403	1.11	(1.04, 1.19)	396	1.11	(1.04, 1.19)	-0.06 (-0.16, 0.04)	-0.06 (-0.16, 0.04)	0.00 (-0.10, 0.10)
14	398	4.97	(4.59, 5.37)	387	5.13	(4.70, 5.59)	387	5.18	(4.72, 5.69)	-0.03 (-0.15, 0.09)	-0.04 (-0.16, 0.08)	-0.01 (-0.13, 0.11)
18C	413	1.30	(1.22, 1.38)	401	1.34	(1.24, 1.44)	398	1.48	(1.38, 1.58)	-0.03 (-0.13, 0.07)	-0.13 (-0.23, -0.03)	-0.10 (-0.20, 0.00)
19F	408	1.85	(1.71, 1.99)	399	2.07	(1.92, 2.24)	398	2.59	(2.40, 2.78)	-0.11 (-0.22, -0.01)	-0.34 (-0.44, -0.23)	-0.22 (-0.33, -0.11)
23F	411	1.24	(1.13, 1.36)	402	1.27	(1.15, 1.40)	399	1.03	(0.94, 1.14)	-0.03 (-0.16, 0.11)	0.18 (0.04, 0.31)	0.20 (0.07, 0.34)
Addit-ional												
1	411	1.62	(1.50, 1.76)	403	1.81	(1.66, 1.98)	395	1.91	(1.76, 2.07)	-0.11 (-0.23, 0.01)	-0.16 (-0.28, -0.04)	-0.05 (-0.17, 0.06)
3	406	0.52	(0.48, 0.55)	391	0.56	(0.52, 0.61)	393	0.61	(0.57, 0.66)	-0.09 (-0.19, 0.02)	-0.18 (-0.28, -0.07)	-0.09 (-0.19, 0.02)
5	412	1.35	(1.24, 1.47)	402	1.05	(0.96, 1.14)	393	1.35	(1.25, 1.47)	0.25 (0.13, 0.37)	0.00 (-0.12, 0.12)	-0.25 (-0.37, -0.13)
6A	413	2.40	(2.21, 2.61)	402	2.10	(1.92, 2.29)	398	2.12	(1.96, 2.30)	0.14 (0.02, 0.25)	0.12 (0.01, 0.24)	-0.01 (-0.13, 0.11)
7F	412	2.54	(2.37, 2.71)	401	2.52	(2.35, 2.70)	397	2.67	(2.50, 2.85)	0.01 (-0.09, 0.10)	-0.05 (-0.14, 0.04)	-0.06 (-0.15, 0.04)
19A	411	1.85	(1.71, 2.00)	403	2.00	(1.85, 2.16)	397	1.88	(1.74, 2.02)	-0.08 (-0.19, 0.03)	-0.02 (-0.12, 0.09)	0.06 (-0.05, 0.17)

GMCs were calculated using all subjects with available data for the specified blood draw.

[a] Number of subjects with a determinate antibody concentration for the specified serotype.

[b] Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations.

Source: 125324/0.3,m5.3.5.1, CSR-74251-report body.pdf, pages 62-63 (Table 9-4).

6.0 Safety

Table 15. Total numbers of randomized subjects

	13vPnC	PCV7	Total
U.S. Pivotal Studies 004 and 3005 (infants)	1908	701	2609
All infant studies	4730	2760	7490
Catch-up study 3002 (7 mo – 6 yrs)	354	0	354
All studies	5099	2775	7874

6.1 Pivotal studies

6.1.1 Safety monitoring

Safety monitoring was the same in pivotal studies 6096A1-004 and -3005. Study participants were monitored for immediate adverse reactions within a 30 minute time period. Solicited local reactions (erythema, induration, and tenderness) and systemic events (decreased appetite, irritability, increased sleep, decreased sleep, hives (urticaria), fever (rectal T $\geq$ 38.0^{o}C)) were recorded daily in an e-diary during the first 7 days after each vaccination. Day 1 corresponded to the day of vaccination. A solicited reaction still present on the 7th day after vaccination was followed until resolution. Unsolicited adverse events occurring within 30 days after each vaccination were recorded at the subsequent scheduled clinic visit. Newly diagnosed chronic medical conditions, hospitalizations, and serious adverse events (SAEs) that occurred 6 months after the last study dose were collected by scripted telephone interview. SAEs were reported throughout study period (visit 1 to 6 months after the last vaccination).

6.1.2 Populations analyzed

All available safety population

Safety analyses were based on the actual vaccine received and on the all available population, which consisted of all participants who received one dose of vaccine and for whom safety information was available. Immunogenicity analyses were performed according to the randomized treatment assignment.

6.1.3 Vaccine exposure and study completion

Table 16 Pivotal studies: Summary of vaccine exposure, safety population[1]

	6096A1-004		6096A1-3005		Total	
	Prevnar 13	Prevnar	Prevnar 13	Prevnar	Prevnar 13	Prevnar
	N	N	N	N	N	N
Dose 1	332	331	1455	244	1787	575
Doses 1, 2, and 3	294	290	1290	218	1584	508
Doses 1, 2, 3, and 4	264	252	N/A	N/A	264	252
Completed study	259	252	N/A	N/A	259	252
Completed 6-month follow-up	282	270	N/A	N/A	282	270

[1] The safety population included all subjects who received at least one dose of Prevnar 13 or Prevnar active control vaccine.
N/A indicates not applicable. These data were not ready for submission to the Prevnar 13 BLA.
Source: 125324/0.1,m5.3.5.1, CSR-69238-report body, pages 46 and 49 (Tables 8-2 and 8-5); 125324/0.3,m5.3.5.1, CSR-74251-report body, page 42 (Table 8-1).

6.1.4 Early study discontinuation due to an adverse event

Overall, nine 13vPnC subjects and 3 PCV7 participants in the two pivotal studies withdrew or discontinued test article administration due to an adverse event.

Table 17. Study 6096A1-004 and -3005 Study participants who withdrew due to an adverse event (AE)

AE #	Age (months)	Vaccine Group	Preferred Term	Dose #	Time to Onset after last dose (days)	Duration (days)	Outcome	SAE
	2.5		Convulsion	1	8	1	Resolved	
1	3	13vPnC	Convulsion	1	32	-	Persisted	Yes
2	12	13vPnC	Febrile convulsion	3	189	1	Resolved	Yes
3	4	13vPnC	Thrombocytopenia	2	22	100	Resolved	Yes
4	6	13vPnC	Near drowning	2	73	1	Resolved	Yes
5	4	13vPnC	Allergic reaction	2	1	8	Resolved	Yes
6	4	13vPnC	Urticaria	2	4	6	Resolved	No
7	5	13vPnC	Febrile convulsion	2	52	5	Resolved	Yes
8	4	13vPnC	Pyrexia	2	1	1	Resolved	No
9	4	13vPnC	Injection site reaction	2	1	2	Resolved	No
10	12	PCV7	Muscular weakness	1	54	-	Persisted	No
11	10	PCV7	Nephroblastoma	3	117	-	Persisted	Yes
12	12	PCV7	Varicella	3	159	15	Resolved	No

Source: 125324/0.1,m5.3.5.1, CSR69238-report-body.pdf, page s170-173 (Tables 10-20 – 10-25); 125324/0.3,m5.3.5.1, CSR74251-report-body.pdf, pages 136, 334-337 (Tables 15.89 - 15.92).

Pertinent case narratives

AE 2: febrile convulsion

A 12-month boy, 6 months after 13vPnC dose 3, was hospitalized for new onset complex febrile seizure. The generalized twitching (except for left arm) lasted for 10 minutes, and was associated with drooling and T102 F. Significant physical exam findings on hospital admission included T105.3 F and left arm paralysis. His head CT scan without contrast showed opacification in the mastoid air filled and middle ear cavity. Complete blood count, basic metabolic panel, magnesium and phosphate levels were within normal limits. EEG and EKG findings were within normal limits. Blood and urine cultures were negative. No subsequent seizure episode occurred during the 3 day observational hospital stay.

AE 3: recurrent thrombocytopenia

A 4-month old boy, 8 days after 13vPnC dose 2, was hospitalized for thrombocytopenia. He was noted by his parent to have bloody stool. A diffuse petechial rash was noted in the clinic, and in-office lab testing showed a platelet count of 6000/mL. Tests results for HIV, parvovirus, and toxoplasmosis testing were negative. The infant responded to intravenous immunoglobulin, which was administered for presumptive Idiopathic Thrombocytopenic Purpura (ITP). He went home after a 3-day hospital stay. Thrombocytopenia recurred 11 days after hospital discharge and lasted 3 months. After study withdrawal, the infant completed the 6-month safety follow-up.

AE 5: allergic reaction

A 4-month old boy, on the evening of 13vPnC (lot 2) dose 2, developed a diffuse, red, blanchable rash and T104°F. The infant's mother noted no respiratory symptoms. She gave the infant oral diphenhydramine, but the rash persisted the next day. The infant was then evaluated in a study clinic, and diagnosed an allergic reaction related to vaccination. Symptoms resolved following topical hydrocortisone (0.5%) treatment. The event was considered by the study investigator as "medically important," and therefore reported as an SAE. The parent withdrew the infant from study participation, and completed the 6-month safety follow-up.

AE 6: mild urticaria
A 4-month old boy, 4 days after 13vPnC dose 2 (lot 2), developed mild urticaria. The event was preceded by postviral cough about one week prior to the event. The subject was not hospitalized and the event was not considered a serious adverse event. Medical history is noncontributory. The investigator decided to withdraw the subject due to the adverse event. The subject continued the follow-up safety evaluation.

6.1.5 Serious adverse events

A total of 3 deaths (13vPnC n=2, PCV7 n=1) occurred in pivotal studies 6096A1-004 and -3005. Safety-related discontinuations are described separately.

13vPnC: SIDS
A 2-month old boy, 14 days after 13vPnC dose 1 (manufacturing scale lot), was found in the morning by his parent to be unresponsive, blue, and not breathing. He was in his crib. Emergency medical service arrived, started resuscitation, and transported the infant to the emergency room. Further resuscitative measures failed. An autopsy revealed that the subject died of undetermined causes. Medical history was pertinent for parental alcohol consumption and infant placement in a bed with multiple blankets the night prior to death.

13vPnC: SIDS
A 4-month previously healthy old girl, 3 days after 13vPnC dose 2 (lot 2), died due to SIDS. The infant was found to be unresponsive and cyanotic by the parent, who had been sleeping in bed with the infant. Parental co-sleeping was identified as a possible contributor to the event. Autopsy results describe no organic pathology, negative toxicology, and negative metabolic screenings.

PCV7: SIDS
A 2-month old boy, 13 days after PCV7 dose 1, was found supine, unresponsive, pulseless, blue, and not breathing in his crib by daycare workers to be. Cardiopulmonary resuscitation was initiated, and Emergency medical services (EMS) contacted. EMS arrived, continued the CPR, intubated and administered epinephrine to the baby. Resuscitative measured failed. An autopsy report concluded that the cause of death was SIDS.

6.1.6 Solicited local adverse events

There were no statistically significant differences between the two study groups in study 3005. Tenderness was the most frequently reported local adverse event followed by erythema and induration. Severe tenderness was reported more often by PCV7 recipients. Induration was reported more often by 13vPnC recipients after dose 2. Severe erythema (> 7.0cm) was not reported by either study group. There was one report of severe induration in a 13vPnC recipient.

Table 18. Study 6096A1-3005. Number (percentage) of subjects with solicited local adverse events, by severity, at the 13vPnC or PCV7 injection site within 7 days after each vaccination.

	Safety Populations by Dose					
	Dose 1		**Dose 2**		**Dose 3**	
Graded Local Reaction	**13vPnC N[a]=993-1229 %**	**PCV7 N[a]=164-212 %**	**13vPnC N[a]=733-1021 %**	**PCV7 N[a]=127-176 %**	**13vPnC N[a]=681-921 %**	**PCV7 N[a]=111-156 %**
Erythema[b]						
Any	22.5	22.8	33.4	30.1	37.7	39.4
0.5 - 2.0 cm	21.3	21.7	32.0	28.8	35.8	38.5
2.5 - 7.0 cm	1.7	1.2	2.8	3.1	5.1	7.8
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0
Induration[b]						
Any	18.5	18.2	25.3	17.7	26.5	30.5
0.5 - 2.0 cm	15.7	16.2	23.8	17.7	24.8	29.1
2.5 - 7.0 cm	4.8	3.6	3.5	3.9	4.0	7.0
> 7.0 cm	0.0	0.0	0.1	0.0	0.0	0.0
Tenderness						
Any	63.0	67.0	66.2	64.8	59.5	64.7
Interferes with limb movement	10.0	12.9	9.8	11.4	8.9	11.9

[a] Number of subjects reporting yes for at least 1 day or no for all days.
[b] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unite = 0.5 cm. Measurements were rounded up to the nearest whole number. Mild, $0.5 \leq x \leq 2.0$ cm; moderate, $2.5 \leq x \leq 7.0$ cm; and severe, >7.0 cm.
Source: 125324/0.16,m5.3.5.1.3, Study Report Body Additional Safety Information, Response to May 21, 2009 Questions, pages 5-7 (Tables 1-1 to 1-3).

In both study groups within study 004, the frequency and severity of local reactions increased with each subsequent dose. The incidence of local reactions after dose 4 was higher among PCV7 subjects compared to 13vPnC subjects. In both study groups, tenderness at the injection site was the most frequently reported local adverse event. Recipients of the 13vPnC vaccine reported severe tenderness (interfering with limb movement) more often after doses 1 and 4. After doses 1 and 2, more 13vPnC recipients than PCV7 recipients reported erythema. No subjects in either study group reported severe (> 7.0 cm) erythema or induration.

Table 19. Study 6096A1-004. Number (percentage) of subjects with solicited local adverse events, by severity, at the 13vPnC or PCV7 injection site within 7 days after each vaccination.

	Safety Populations by Dose							
	Dose 1		**Dose 2**		**Dose 3**		**Dose 4**	
Graded Local Reaction	**13vPnC N[a]=173-264 %**	**PCV7 N[a]=186-270 %**	**13vPnC N[a]=116-200 %**	**PCV7 N[a]=120-216 %**	**13vPnC N[a]=87-178 %**	**PCV7 N[a]=79-176 %**	**13vPnC N[a]=59-149 %**	**PCV7 N[a]=44-147 %**
Erythema[b]								
Any	35.6	32.3	45.2	37.8	48.9	50.0	54.4	65.5
0.5 - 2.0 cm	34.5	31.4	44.5	37.0	47.7	48.7	53.9	63.5
2.5 - 7.0 cm	4.5	2.6	1.7	3.2	5.5	5.0	8.1	14.0
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Induration[b]								
Any	27.4	23.6	31.2	29.5	37.9	36.9	44.0	50.7
0.5 - 2.0 cm	23.1	21.2	29.8	26.1	35.4	36.9	43.3	46.5
2.5 - 7.0 cm	6.8	5.2	5.1	7.1	6.6	6.1	14.7	14.3
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tenderness								
Any	72.7	72.2	77.0	75.9	78.7	80.9	81.2	84.4
Interferes with limb movement	13.7	9.2	10.6	11.5	8.8	9.3	15.4	12.2

[a] Number of subjects reporting yes for at least 1 day or no for all days.
[b] Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Mild, $0.5 \leq x \leq 2.0$ cm; moderate, $2.5 \leq x \leq 7.0$ cm; and severe, >7.0 cm.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, pages 130-132, and 135 (Tables 10-3 to 10-6).

6.1.7 Solicited systemic adverse events

In both study groups in study 3005, irritability was the most frequently reported solicited systemic adverse event. The highest incidence of moderate fever in the 13vPnC group was after dose 2 (3.4%), and this rate was statistically significantly higher than the rate in the PCV7 group. In the PCV7 group moderate fever was highest after dose 4 (6.2%). One 13vPnC subject reported fever > 40°C after each dose and one PCV7 subject reported fever > 40°C after dose 1 and 3. The occurrence of hives in the 13vPnC group ranged from 0.7% to 1.5%.

Table 20. Study 6096A1-3005. Number (percentage) of subjects with solicited system adverse events within 7 days after each vaccination.

	Safety Populations by Dose					
	Dose 1		**Dose 2**		**Dose 3**	
Graded Systemic Events	**13vPnC N[a]=978-1300 n (%)**	**PCV7 N[a]=160-226 n (%)**	**13vPnC N[a]=718-1123 n (%)**	**PCV7 N[a]=124-201 n (%)**	**13vPnC N[a]=674-1038 n (%)**	**PCV7 N[a]=111-186 n (%)**
Fever[b]						
38.0°C ≤ x ≤ 39.0°C	24.3	26.0	35.1	28.0	28.5	32.6
39°C < x ≤ 40.0°C	0.6	1.2	3.4	0.0*	3.9	6.2
> 40°C	0.1	0.6	0.1	0.0	0.1	0.9
Decreased appetite	48.9	49.0	48.5	49.4	48.2	50.0
Irritability	86.4	87.6	85.8	81.1	80.9	84.4
Increased sleep	71.2	72.6	66.8	63.3	58.0	51.4
Decreased sleep	44.4	46.4	47.5	48.4	47.1	56.5*
Hives (urticaria)	0.7	0.0	1.3	0.8	1.5	1.8

***** Statistically significant difference between the two study groups (Fisher exact test, 2-sided).

[a] Number of subjects reporting yes for at least 1 day or no for all days

[b] Fever gradings: mild (38.0°C ≤ x ≤ 39.0°C), moderate (39°C < x ≤ 40.0°C), and severe (> 40°C). No other systemic event other than fever was graded.

Source: 125324/0.16,m5.3.5.1.3, Study Report Body Additional Safety Information, Response to May 21, 2009 Questions, pages 41-43 (Tables 2-1 to 2-3).

In both study groups within study 004, irritability was the most frequently reported solicited systemic adverse event. Systemic adverse events occurred most often after dose 4. With the exception of fever, the incidence of each adverse event after dose 4 was higher among PCV7 subjects than 13vPnC subjects. Moderate fever, defined as > 39°C but ≤ 40°C, post-dose 1 was statistically significantly higher in the 13vPnC group (2.8%) than the PCV7 group (0%). The highest incidence of moderate fever in the 13vPnC group occurred after dose 3 (8.5%), whereas in the PCV7 group, moderate fever was highest after dose 4 (12.5%). One 13vPnC subject and one PCV7 subject reported fever > 40°C. The occurrence of hives in the 13vPnC group ranted from 1.7% to 4.8% and was more frequent in the 13vPnC group than the PCV7 group after the first three doses.

Table 21. Study 6096A1-004. Number (percentage) of subjects with solicited system adverse events within 7 days after each vaccination.

	Safety Populations by Dose[a]							
	Dose 1		**Dose 2**		**Dose 3**		**Dose 4**	
Graded Systemic Events	**13vPnC N[a]=174-289 n (%)**	**PCV7 N[a]=187-290 n (%)**	**13vPnC N[a]=116-236 n (%)**	**PCV7 N[a]=120-236 n (%)**	**13vPnC N[a]=87-216 n (%)**	**PCV7 N[a]=79-218 n (%)**	**13vPnC N[a]=60-199 n (%)**	**PCV7 N[a]=45-175 n (%)**
Fever[b]								
38.0°C ≤ x ≤ 39.0°C	47 (24.0)	43 (21.2)	63 (43.2)	61 (40.4)	49 (39.8)	40 (37.7)	53 (53.5)	39 (51.3)
39°C < x ≤ 40.0°C	5* (2.8)	0* (0.0)	3 (2.5)	6 (4.9)	8 (8.5)	2 (2.5)	4 (6.6)	6 (12.5)
> 40°C	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (1.3)	1 (1.7)	0 (0.0)
Decreased appetite	125 (54.8)	108 (45.4)	106 (59.9)	91 (52.3)	87 (59.2)	81 (59.6)	76 (65.5)	81 (73.6)
Irritability	259 (89.6)	249 (85.9)	212 (89.8)	216 (91.5)	191 (88.4)	201 (92.2)	183 (92.0)	163 (93.1)
Increased sleep	213 (79.5)	212 (78.5)	161 (79.3)	147 (73.5)	117 (71.3)	104 (69.8)	81 (70.4)	81 (74.3)
Decreased sleep	101 (45.7)	113 (47.9)	83 (49.1)	96 (55.8)	93 (60.4)	85 (63.4)	66 (58.4)	61 (64.2)
Hives (urticaria)	3 (1.7)	2 (1.1)	3 (2.5)	0 (0.0)	4[c] (4.5)	0[c] (0.0)	3 (4.8)	3 (6.4)

***** Statistically significant difference between the two study groups.
[a] Number of subjects reporting yes for at least 1 day or no for all days
[b] Fever gradings: mild (38.0°C ≤ x ≤ 39.0°C), moderate (39°C < x ≤ 40.0°C), and severe (> 40°C). No other systemic event other than fever was graded.
[c] One report of hives was recorded in error on the e-diary of subject 004-027-002402 in the 13vPnC group. The case of hives was actually in subject 004-027-002403 in the PCV7 group. These two subjects were a pair of twins enrolled in the study.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 137-139, and 142 (Tables 10-7 to 10-10).

6.1.8 Unsolicited adverse events

Study 6096A1-004:

Adverse events occurring in at least 1% (in favor of) 13vPnC subjects:

- Infant series safety population (n_{13vPnC}=332, n_{PCV7}=331): pneumonia (2.4%,1.5%), diarrhea (10.5%, 9.4%), otitis media (28.3%, 23.6%), bronchiolitis (16.9%, 16.3%), gastroenteritis rotavirus (1.2%, 0.3%).
- Toddler dose safety population (n_{13vPnC}=267, n_{PCV7}=258): diarrhea (3.4%, 3.1%), otitis media acute (1.9%, 1.2%).

Study 6096A1-3005:

Adverse events occurring in at least 1% (in favor of) 13vPnC subjects in the infant series population: otitis media acute (3.0%, 2.5%), wheezing (3.0%, 2.0%), pneumonia (2.1%, 1.6%)

6.2 Integrated safety analyses

6.2.1 Serious adverse events and other adverse events of interest

Table 22. Incidence of SAEs by Combined MedDRA Preferred Terms and Other Events of Interest, Integrated Analysis*

	Infant Series		Between Infant Series and Toddler Dose		Toddler Dose		6-month Follow-Up	
System Organ Class Preferred Term	**13vPnC N=4723 n (%)**	**PCV7 N=2754 n (%)**	**13vPnC N=2569 n (%)**	**PCV7 N=1800 n (%)**	**13vPnC N=2499 n (%)**	**PCV7 N=1482 n (%)**	**13vPnC N=1860 n (%)**	**PCV7 N=1356 n (%)**
Combined SAE Terms								
Wheezing	59 (1.3)	31 (1.1)	20 (0.8)	9 (0.5)	8 (0.2)	2 (0.1)	12 (0.6)	6 (0.4)
Pneumonia	32 (0.7)	7 (0.3)	17 (0.7)	5 (0.3)	0 (0.0)	1 (0.1)	8 (0.4)	4 (0.3)
Gastroenteritis	19 (0.4)	8 (0.3)	36 (1.4)	12 (0.7)	9 (0.4)	3 (0.2)	15 (0.8)	7 (0.5)
Convulsions	4 (0.1)	1 (0.0)	9 (0.4)	3 (0.2)	2 (0.1)	2 (0.1)	5 (0.3)	5 (0.4)
Meningitis	4 (0.1)	2 (0.1)	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic Reactions	4 (0.1)	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Croup	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breath holding	2 (0.0)	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Crying	2 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abscess	1 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Anaemia	1 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
GI Bleeding	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other important events:								
Kawasaki's disease	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cough	1 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SIDS	2 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes Mellitus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urosepsis	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Selective IgA Immunodeficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Otitis media	3 (0.1)	2 (0.1)	5 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Petechiae	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* The integrated safety analysis consists of data available for the 13vPnC clinical program as of 12-Oct-08. It includes pooled infant series safety data from thirteen 6096A1 protocols [003, 004, 006, 007, 008, 009, 011, 500, 501, 3000, 3005, 3007, and 3008], pooled safety post-infant series data from nine 6096A1 studies [003, 004, 006, 007, and 008], and pooled six-month follow-up data from 6 studies: 003, 004, 006, 009, 500, and 501.

Pneumonia combined terms: pneumonia, bronchopneumonia, pneumonia primary atypical, pneumonia viral, pneumonia respiratory syncitial viral, lobar pneumonia, pneumonia bacterial, and pneumonia aspiration.

Anaemia combined terms: anaemia, iron deficiency anaemia, microcytic anaemia, haemolytic anaemia

Otitis media combined terms: otitis media, otitis media acute, otitis media chronic, and otitis media viral.

Abscess combined terms: abscess, abscess neck, abscess oral, perianal abscess, perirectal abscess, rectal abscess.

Wheezing combined terms: asthma, bronchiolitis, bronchitis, wheezing, bronchial hyperreactivity, bronchospasm, status asthmaticus, allergic respiratory disease, and stridor
Convulsion combined terms: infantile spasms, convulsion, epilepsy, febrile convulsion, partial seizures, postictal paralysis,
Gastroenteritis combined terms: gastroenteritis, vomiting, diarrhea (nausea, abdominal pain, esophagitis, gastritis, infantile spitting up, regurgitation,
Croup combined terms: croup infectious, laryngotracheobronchitis (LLT or verbatim)
Allergic reactions combined terms: hives/urticaria, anaphylactic reaction, swelling face, bronchospasm, laryngospasm, and stridor
Breath holding combined terms: breath holding, apnoea, apnoeic episode, sleep apnoea syndrome, apnoeic attack
Meningitis combined terms: meningitis, meningitis aseptic, meningitis bacterial, meningitis enteroviral, meningitis meningococcal, meningitis pneumococcal, meningitis viral, meningococcal sepsis.
Source: 125324, m5.3.5.3.28, Integrated Summary of Safety, pages 48-75 (Table 8-7), pages 158-161 (Table 8-15)

Pertinent case narratives from non-pivotal studies:
A total of 4 deaths occurred in all 13vPnC studies. Three occurred in pivotal studies 004 and 3005 and were described in section 6.1.5. One death occurred in non-pivotal study 50 and is described below.

Study 501, 13vPnC: SIDS
A previously healthy 9 month old boy, 76 days after 13vPnC dose 3, was found dead in his crib without an obvious cause. The investigator diagnosed the event as probable sudden infant death syndrome (SIDS).

Study 008, PCV7: Meningitis
A 2-month-old boy, about 3 weeks after PCV7 dose 1, was hospitalized with a 2 day history of a febrile syndrome. The subject presented with impaired general health status, gray complexion, and moaning. Lab and microbiological tests suggested bacterial meningitis, although cultures were negative. The infant received intravenous antibiotics and an antipyretic. Transfontanellar ultrasonography results were normal. The infant was discharged after one week, and meningitis resolved after approximately three weeks. Repeat lumbar punctures were negative.

Study 501, PCV7: Pyrexia and fontanelle bulging
A 6 month old boy, 2 days after PCV7 dose 3, was hospitalized with high fever and tense fontanelle. The infant had been diagnosed with bronchiolitis 4 days prior to his 3rd PCV dose and was noted to have cough and respiratory symptoms on admission. Laboratory tests, including a metabolic profile and CBC were normal. Blood and urine cultures were negative. A lumbar puncture attempt but was unsuccessful. Treatment with antibiotics, an NSAID, and a bronchodilator was initiated. The tense fontanelle and bronchiolitis resolved on hospital day 2.

6.2.2 Early study discontinuation due to an adverse event

Table 23. Supportive studies. Early Withdrawal or Test Article Discontinuation Due to an Adverse Event

Study-AE#	Vaccine Group	Preferred Term	Dose #	Time to Onset (days)	Duration (days)	Outcome	SAE
003-1	13vPnC	Febrile convulsion	3	193	1	Resolved	Yes
007-1	13vPnC	Crying	Pediacel only	2	1	Resolved	No
008-1	13vPnC	Haemolytic anaemia	3	236	C	Persistent Resolved	Yes
008-2	13vPnC/13vPnC	Urticaria	3	3	8	Resolved	No
009-1	13vPnC+P80	Gastroesophageal reflux disease Pneumonia	1 1	32 32	21 21	Resolved Resolved	Yes Yes
009-2	13vPnC-P80	Bronchitis (treatment related AE)	3	2	6	Resolved	Yes
009-3	13vPnC-P80	Hypertonia	2	1	202	Resolved	No
009-4	13vPnC-P80	Meningococcal meningitis Meningococcal sepsis Hydrocephalus	2 2 2	8 8 62	37 37 10	Resolved Resolved Resolved	Yes Yes Yes
009-5	13vPnC-P80	Pneumonia	3	23	55	Resolved	Yes
009-6	13vPnC+P80	Breath holding	3	167	1	Resolved	Yes
009-7	13vPnC+P80	Leukocytosis	3	247	C	Persistent	Yes
011-1	13vPnC	Meningitis bacterial Convulsion	1 1	43 43	C 1	Persistent Resolved	Yes Yes
500-1	13vPnC	Kawasaki's disease	2	162	C	Persistent	Yes
501-1	13vPnC	Febrile convulsion	3	261	14	Resolved	Yes
003-2	PCV7	Pneumococcal meningitis (33F)	3	57	18	Persistent	Yes
006-1	PCV7	Gastroenteritis	1	77	C	Persistent	No
006-2	PCV7	Crying	1	1	1	Resolved	No
006-3	PCV7	Febrile convulsion	3	48	5	Resolved	Yes
007-2	PCV7	Congenital hemiplegia	3	107	C	Persistent	Yes
007-3	PCV7	Injection site erythema Injection site swelling High pitched crying Crying Wheezing Rash erythematous	2 2 2 2 2 2	1 1 1 1 1 1	1 1 1 1 1 1	Resolved Resolved Resolved Resolved Resolved Resolved	No No No No No No
007-4	PCV7	Somnolence Rash	1 1	1 1	1 1	Resolved Resolved	No No
500-2	PCV7	Hypokinesia	1	73	6	Resolved	Yes
500-3	PCV7	Pelizaeus-Merzbacher disease	2	175	C	Persistent	Yes
500-4	PCV7	Infantile spasms	2	38	C	Persistent	Yes
501-2	PCV7	Febrile convulsion	3	2	2	Resolved	Yes
501-3	PCV7	Febrile convulsion	3	113	1	Resolved	No
501-4	PCV7	Febrile convulsion	3	153	1	Resolved	Yes
3008-1	PCV7	Urticaria	3	2	1	Resolved	No

Source: 125324, CSR62926-report-body, CSR69237-report-body-infant, CSR69272-report-body-infant, CSR67343-report-body-infant, CSR71892-report-body-infant, CSR70616-report-body, CSR69239-report-body, CSR69273-report-body, CSR73720-report-body.

Pertinent narratives are summarized below:

008-2: Urticaria
A 4-month old boy, 2 days after 13vPnC dose 3, developed urticaria in the upper and lower extremities. The event resolved 9 days later. The subject also developed mild urticaria in the upper and lower extremities after the second study dose, which lasted approximately 17 days. He subject also had an insect sting 6 days after the second study dose and developed moderate urticaria which subsided the same day.

009-2: Bronchitis
A 6-month old girl, 1 day after 13vPnC-P80 dose 3, developed fever and cough. Three days after the third vaccination, the subject was hospitalized with acute bronchitis. The subject was afebrile and had wheezing and rhonchi on physical exam. Chest x-ray reported as "no changes". The subject was withdrawn because of the possible association between the event and vaccine administration.

009-4: Meningococcal meningitis, meningococcal sepsis, and hydrocephalus
A 3 month old boy, 2 days after 13vPnC-P80 dose 2, presented with a febrile illness (temp 39.3^{o}C). Two days later, the infant started on aminoglycoside therapy. On day 6, the subject presented to the emergency room with increased muscle tone, limb tremor, and eyeball rotation. The subject required intubation due to respiratory distress and was admitted to the intensive care unit. Blood cultures were positive for meningococcal serotype C. Repeat cranial ultrasonography revealed enlargement of the subdural spaces with increased fluid echogenicity, suggestive of a subdural effusion (possibly subdural empyema). After a complicated course, a diagnosis of acquired non-communicating post-inflammatory hydrocephalus was made and the subject was treated surgically with insertion of a ventriculo-peritoneal shunt. There were no post-operative complications and the subject was discharged home on day 70.

011-1: Meningitis bacterial and convulsion
A 3 month old girl, 43 days after 13vPnC dose 1, presented with one day of fever and rhinorrhea. She, was diagnosed with bronchiolitis and prescribed oral cephalexin and acetaminophen. The subject returned to the hospital the next day with a fever of 104.5^{o}F, tonic posturing, and irregular respiration. Intravenous cefotaxime and phenytoin were initiated. A diagnostic lumbar puncture on hospital day 2 was suggestive of acute pyogenic meningitis. The pyogenic meningitis and seizure events resolved with treatment. The subject remained asymptomatic, and oral phenytoin was discontinued at approximately 5 months of age.

500-1: Kawasaki disease
An 11-month old girl, 5 months after 13vPnC dose 2, presented and was hospitalized with 3 days of high fever and exanthema. The infant's fever was unresponsive to antipyretic medication. Signs consistent with Kawasaki disease were noted, and an echocardiogram was consistent with Kawasaki disease. The infant received treatment with intravenous immunoglobulin therapy and was discharged on hospital day 10. The subject was withdrawn from the study because of the SAE and the potential long-term cardiovascular risks associated with the disease. The status of the SAE is persisted and the subject continues to be monitored and evaluated.

003-2: Pneumococcal meningitis (33F)
An approximately 8 month old boy, 57 days after PCV7 dose 3, was seen at an outpatient clinic for 2 days of fever, irritability, lethargy, and vomiting. Blood and cerebrospinal fluid cultures both grew penicillin-susceptible *Streptococcus pneumoniae*. Serotyping, performed by CDC's ABCs serotyping laboratory, determined the isolate to be serotype 33F. The infant responded to IV antibiotic therapy and upon discharge, continued IV therapy as an outpatient. Two months after discharge, follow-up testing revealed profound sensorineural hearing loss in the right ear. The status of the adverse event is ongoing, due to the

persistent sequelae of sensorineural hearing loss. The child was withdrawn from the study, based on the invasive pneumococcal disease exclusion criterion.

006-1: Gastroenteritis
A 7.5 month old boy, 77 days after PCV7 dose 1, developed gastroenteritis which resolved after 84 days. The subject was withdrawn following this infection because a series of infections since the dose 2 causing continued delay of administration of further test articles.

501-2: Febrile convulsion
A 6-month old girl, 2 days after PCV7 dose 3, was hospitalized with a febrile seizure. The subject was treated with paracetamol for fever and was reported to be recovered; she was discharged on hospital day 2.

3008-1: Urticaria
A 5-month old boy, 2 days after PCV7 dose 3, developed urticaria which resolved the same day. The subject was not hospitalized and event was considered mild. The subject was discontinued because of the adverse event.

7.0 Concomitant Vaccine Evaluation

Study 6096A1-004: The first three study vaccine doses were administered concomitantly with DTaP-HBV-IPV and PRP-T vaccines. The fourth study vaccine dose was administered concomitantly with MMRV, PRP-OMP and HAV vaccines. Rotavirus vaccination was permitted during the study period.

Study *6096A1-3005:* The first three study vaccine doses were administered concomitantly with DTaP-HBV-IPV and PRP-T vaccines. The fourth study vaccine dose was concomitantly administered with MMRV and HAV vaccines. Rotavirus vaccination was permitted during the study period.

Concomitant vaccine results

7.1 PRP, diphtheria toxoid and pertussis

The criterion for demonstrating noninferior antibody responses to diphtheria toxoid, pertussis, and PRP antigens were defined as the lower limit of the 2-sided 95% CI for the difference in the proportion of subjects in each group achieving a pre-specified antibody concentration (13vPnC – PCV7). The primary objectives for PRP, diphtheria toxoid and pertussis vaccine antigens were met. Comparisons of GMC ratios for PRP, diphtheria and pertussis vaccine antigens were included as secondary objectives. These secondary objectives were met.

7.2 Measles, mumps, rubella, and varicella

The criterion for demonstrating noninferiority based on the proportion of subjects achieving a pre-specified antibody concentration for measles, mumps, and rubella antigens was a lower limit of a 2-sided 95% CI for the difference in two proportions (13vPnC – PCV7) > -0.05. The noninferiority criterion for varicella was met if the lower bound of the 2-sided 95% CI for the difference in two proportions was > -0.10.

These secondary objectives were met for each of the vaccine antigens contained in MMRV. Although the response rates to mumps (74-76%) and varicella (21-26%) antigens were similar in both study groups, they were lower than expected, particularly the responses to varicella. Results in the all-available infant immunogenicity population were similar, except the difference in proportions in subjects achieving an antibody level of 1.10 I.V. for mumps was 1.3% with a lower limit of the 95% CI of -6.6%, which did not meet noninferiority criterion of being at least within 5% difference.

7.3 Tetanus toxoid, polio types 1-3 and hepatitis B

The noninferiority criterion for tetanus toxoid, polio types 1-3, and hepatitis B was defined as a lower limit of the 95% CI for the difference in the proportion of subjects in each group achieving a pre-specified antibody concentration (13vPnC – PCV7) ≤ -10%. The primary objectives for tetanus toxoid, polio types 1-3 and hepatitis B vaccine antigens were met.

7.4 Safety: rotavirus vaccine

Study 004 permitted subjects to receive rotavirus vaccinations concomitantly with the study vaccines; study 3005 permitted rotavirus vaccination at any time throughout the study. The vast majority of subjects vaccinated with the rotavirus vaccine received the vaccine during the infant series. No subset safety analyses were provided by the sponsor for the subset of subjects who received rotavirus vaccinations. Events coded as gastroenteritis rotavirus were reported in 4 (1.2%) 13vPnC subjects and 1 (0.3%) PCV7 subject in study 004 and in 3 (0.2%) 13vPnC subjects in study 3005. Rotavirus infection was reported in 1 (0.3%) 13vPnC subject in study 004 and in 1 (0.1%) 13vPnC subject in study 3005.

Table 24. Rotavirus Vaccine Administration in pivotal studies 6096A1-004 and 6096A1-3005

	Study 004		Study 3005		Total	
	13vPnC	PCV7	13vPnC	PCV7	13vPnC	PCV7
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects who received rotavirus vaccine during the infant series	191 (57)	180 (54)	1195 (82)	206 (84)	1386 (77)	386 (67)

Source: 125324/0.1, m5.3.5.1, CSR69238-report body.pdf, page 233, Table 15.14; 125324/0.3,m5.3.5.1, CSR-74251-report body.pdf, page 184, Table 15.6.

8.0 Post Marketing Plans

The applicant has proposed a post marketing plan comprised of a pharmacovigilance component, to evaluate safety, and a vaccine effectiveness component, to evaluate the impact of 13vPnC vaccine on rates of IPD and OM caused by the 13 serotypes in the vaccine. Based on review of clinical data in the BLA to date, all proposed post marketing studies, whether for the purpose of pharmacovigilance or evaluation of vaccine effectiveness, are viewed by the Agency as voluntary post marketing commitments. To further clarify this point, the proposed studies to evaluate post-licensure vaccine effectiveness of 13vPnC vaccine are not considered "confirmatory studies," in a strict regulatory sense; such studies would be a condition of accelerated approval, which is not the situation for the 13vPnC infant development program. Nonetheless, the Agency recognized the importance of collecting and analyzing IPD surveillance data after U.S. licensure and introduction of the 13vPnC vaccine as a means to evaluate its impact on rates of IPD in the U.S. pediatric population, particularly for the six new serotypes (1, 3, 5, 6A, 7F and 19A).

The components of the post marketing plan, as described below, are a result of a dialogue between the Agency and the applicant to date, and were supported with cooperation from other parties, such as Northern California Kaiser Permanent (NCKP) and the CDC. This dialogue started before submission of the BLA and is expected to continue until finalization of the overall post marketing plan.

8.1 Pharmacovigilance

8.1.1 Summary of 13vPnC pre-licensure safety profile

A description of the vaccine's pre-licensure safety profile in infants and toddlers is provided below.

8.1.1.1 Preclinical safety data

No major safety concerns have been identified in review of the pre-clinical data to date.

8.1.1.2 Clinical safety data

Pre-licensure safety of 13vPnC vaccine is based on clinical data from 13 infant studies in which a total of 4730 subjects were randomly assigned to 13vPnC vaccine. Control groups (total N=2760) received Prevnar, the current standard of care in infants for immunization against pneumococcal disease. Data from an additional study, in which 354 older infants and young children 7 months to less than 6 years of age received 13vPnC vaccine, were also evaluated. In summary, the clinical safety database for 13vPnC vaccine demonstrated the following:

- The rates of solicited local reactions at the injection sites (swelling, tenderness and erythema) and solicited systemic reactions (fever, decreased appetite, irritability, increased sleep and decreased sleep) were similar in the 13vPnC and the Prevnar groups.
- Unsolicited AEs were reported in similar frequencies in both groups (13vPnC and Prevnar).
- 4 subjects died (three were vaccinated with 13vPnC vaccine and one was vaccinated with Prevnar). All deaths were classified as SIDS.
- Similar proportions of subjects did not complete the series (22% in the 13vPnC group and 17% in the Prevnar group).

From these data, no major risk associated with the administration of 13vPnC vaccine compared with that of Prevnar has been identified.

8.1.1.3 Postmarketing safety surveillance of Prevnar

Prior to licensure of Prevnar, Wyeth agreed, as a post marketing commitment, to evaluate less common adverse events in children who would receive Prevnar concomitantly with routinely recommended childhood vaccines. Wyeth fulfilled this commitment by conducting study 0887X-100494, titled "Postmarketing Evaluation of Prevnar Pneumococcal 7-Valent Conjugate Vaccine (CRM_{197} Protein Conjugate): Safety of Prevnar Administered Concurrently with Routine Infant Vaccinations at 2, 4, 6, and 12 to 15 Months of Age." In this observational database surveillance study, data were obtained from health care utilization databases (e.g., hospital, ER and clinic) and an immunization tracking database for the NCKP health system. Of note, the study was amended over the years to include additional cohorts as a result of discussions between Wyeth and the FDA. From FDA's perspective, for the primary analyses, 65,927 infants were followed for safety outcomes; however, secondary and additional analyses involved additional subjects from different cohorts.

FDA review of the data from post marketing safety study 0887X-100494 determined that the primary safety outcomes analyses did not demonstrate a consistently elevated risk of healthcare utilization for croup, gastroenteritis, allergic reaction, seizures, wheezing diagnoses or breath holding, across doses, health care settings, or multiple time windows. As in pre-licensure trials, fever was associated with Prevnar. In analyses of secondary safety outcomes, the adjusted relative risk of hospitalization for reactive airways disease was 1.23 (95% CI: 1.11, 1.35). Potential confounders, such as differences in concomitantly administered vaccines, yearly variation in respiratory infections, or secular trends in reactive airways disease incidence, could not be controlled. Extended follow-up of subjects originally enrolled in NCKP efficacy trial revealed no increased risk of reactive airways disease among Prevnar recipients. Kawasaki syndrome did not appear to be a risk after routine immunization with Prevnar. Autoimmune disease was a secondary outcome, and this study may not have had sufficient power to detect a small increase in the risk of Kawasaki. Based on limited information, Prevnar does not appear to be associated with an increased risk of neutropenia, which was a secondary outcome; however, this study may not have had sufficient power to detect a small increase in risk of neutropenia.

No new safety concerns have been identified for Prevnar through ongoing surveillance of the Vaccine Adverse Event Reporting System (VAERS) data/data mining.

8.1.2 Proposed pharmacovigilance plan (PVP) for Prevnar 13

The original draft pharmacovigilance plan for the 13vPnC infant/toddler indication was submitted to the applicant's active IND for infant/toddler development of 13vPnC vaccine in mid-December 2008. The PVP included a proposal for the basic design of a phase 4 safety study to be conducted at NCKP. Since then, there has been frequent communication between the FDA and the applicant, on the draft PVP and phase 4 safety study design. A final PVP and a final protocol for the phase 4 safety study are expected prior to the action due date for the BLA.

8.1.2.1 Routine pharmacovigilance for Prevnar 13

As routine pharmacovigilance, the applicant will submit 15-day "alert reports" for serious and unexpected adverse experiences and periodic adverse experience (AE) reports for other adverse experiences, in compliance with the requirements for post marketing reporting of adverse events per 21 CFR 600.80. With regard to the required periodic adverse experience reports, the sponsor agreed to submit a monthly line listing of all non-15 day adverse event reports to the FDA VAERS contractor for the first 3 years, as was done for Prevnar. The applicant agreed to present data in these reports in the manner requested by

the FDA and using MedDRA terminology. In addition, the sponsor will include dose distribution information in these reports.

The applicant agreed to analyze any specific safety concerns, identified as part of routine pharmacovigilance through VAERS, Wyeth post marketing surveillance, or other data sources, in the post-licensure safety study (Protocol number 6096A1-4002), (see section 9.1.2.2 below). The decision to further investigate any such identified safety concerns in the post-licensure safety study will be based on CBER and Wyeth's collaborative judgment.

8.1.2.2 Study 6096A1-4002: phase 4 safety study of Prevnar 13

This post-licensure observational safety study will be conducted at NCKP in a cohort of children who will receive 13vPnC vaccine as part of routine medical care. Approximately 43,000 infants who receive 3 doses of 13vPnC vaccine as part of the primary vaccination series at NCKP, will be enrolled and followed starting at 2 months of age. Additionally, children who receive at least 1 dose of 13vPnC vaccine at NCKP during the course of the study, will be enrolled and followed starting at 2 months of age. Older infants and toddlers enrolled with a history of at least one prior dose of Prevnar and who receive at least one dose of 13vPnC vaccine will be analyzed separately. All such children transitioning from Prevnar to Prevnar 13, regardless of Prevnar/13vPnC combination, will be analyzed in the same group. Safety data will be collected via electronic medical records databases maintained by the Kaiser Permanente Health System and based on ICD-9 codes. The estimated study duration is 4 years.

The study is designed to:

1. Rule out possible associations between 13vPnC vaccine and specific adverse events such as medically attended fever, rare adverse events, and other events evaluated in Prevnar post marketing safety study 0887X-100494 (see above). The events would include wheezing diagnoses, asthma, bronchiolitis, bronchitis (constrictive airway disease), pneumonia, upper respiratory infections, fever, seizure, gastroenteritis, and autoimmune diseases, including Kawasaki disease and diabetes mellitus.

2. Detect medical events to be further evaluated based on a heuristic statistical filter set at a p-value of 0.1 (2 -sided).

The rate of medically attended events will be compared to 2 self control windows, -30 to -5 days prior to vaccination and 31- 60 days post vaccination. This analysis will be conducted for each medical setting (clinic, ER and hospital) and for all settings combined. Similar comparisons will be performed for each dose (1^{st}, 2^{nd}, 3^{rd} dose) and for the infant series. A comparison will be done after the 4^{th} dose for those children who received this dose by the end of the study period.

Safety will be assessed in five phases:

1) comparison with self-control periods,
2) comparison with historical control cohort
3) further statistical analyses, including scan statistics
4) Medical chart review and,
5) Comprehensive assessment of available data.

Children who start immunization with PCV7 and later switch to 13vPnC vaccine to complete their pneumococcal vaccine series will be analyzed separately from infants who receive three 13vPnC vaccine

doses as part of the primary vaccination series. Tabulated updates will be provided for comparisons of adverse events between study groups by pre-existing conditions such as high risk groups, which will include infants with sickle cell anemia, HIV and airways constrictive diseases, as well as patients with steroids or other immunosuppressive medications. Also, listing of infants who die within 2 months of vaccination and causes of mortality will be provided. In addition, the applicant was requested to provide a listing of vaccinees who are hospitalized for invasive pneumococcal disease (IPD) due to any pneumococcal serotype.

As designed, the study will have > 80% power to detect a 2.5 fold increase over background rates of 1 per 10,000 vaccine doses of a medically attended adverse event for each setting (ER, hospital, outpatient clinic). The alpha value is defined as 0.05, 2-sided.

8.2 Vaccine effectiveness studies

The applicant plans to evaluate 13vPnC vaccine effectiveness against both IPD and OM, as summarized below. The VEP is still under discussion with the Agency, particularly the OM component. A final VEP is expected prior to licensure.

8.2.1 Invasive pneumococcal disease

Prior to submission of the 13vPnC BLA the Agency discussed with the applicant the need for post-licensure vaccine effectiveness data for IPD and how these data could be reasonably and reliably obtained. To date the applicant plans to provide IPD surveillance data, once available, to the BLA from two primary and complementary sources: the Active Bacterial Core Surveillance (ABCs) system, an active laboratory- and population-based surveillance system for invasive bacterial pathogens including *S. pneumonia,* and NCKP. The post-licensure IPD surveillance studies to be conducted within these systems are discussed in the subsections that follow. Again, to emphasize, neither of these studies will be conducted as postmarketing requirements.

In addition to the two primary post-licensure sources of IPD effectiveness data, limited data may be provided by the applicant from an open-label study with 13vPnC vaccine in the Yukon Kuskokwim (YK) Delta region of Alaska (protocol 6096A1-3010), which is currently being conducted under the applicant's IND for the 13vPnC vaccine. This study was designed to assess the impact of the vaccine on IPD in this population. Per the study protocol, the rate of IPD in this population is 5 times higher than in other Alaska Native children residing outside of this region. According to the study protocol rates of IPD caused by non-vaccine serotypes, specifically, 3, 6A, 7F and 19A, have substantially increased in recent years , despite an earlier decrease of 95% in rates of IPD caused by serotypes in Prevnar following introduction of Prevnar in the population. This study is not summarized below.

8.2.1.1 CDC ABCs IPD study

Early on in discussing the VEP with the applicant, the FDA concurred with the applicant's proposal to rely on IPD surveillance data from the CDC's ABCs, a collaborative effort between the CDC, state health departments and universities. Of note, IPD surveillance was conducted after licensure of Prevnar in 2000, by the Centers for Disease Control and Prevention (CDC) via the ABCs system. Data from this study suggested a substantial decline in rates of IPD in the U.S. populations after the introduction of Prevnar to the U.S. market.[22] FDA acknowledges the limitations in obtaining vaccine effectiveness data via such ecological studies. However, the Agency also acknowledges that likely this is the only feasible manner, in which to evaluate vaccine effectiveness of Prevnar 13 in preventing IPD, given the low rates of

pneumococcal disease in the U.S., since the introduction of Prevnar. The CDC expects this study to be initiated post-licensure immediately upon introduction of the 13vPnC vaccine.

This case-control study will measure the effectiveness of one or more doses of 13vPnC vaccine against IPD caused by 13vPnC vaccine serotypes among children using the ABC surveillance system. Secondary objectives include measurement of effectiveness of one or more doses of 13vPnC vaccine against overall IPD, measurement of IPD caused by the six additional serotypes included in the 13vPnC vaccine, but not in 7vPnC, as a group, and measurement of IPD caused by serotypes 19A, 7F and 3 (the most common serotypes included in the 13vPnC vaccine) among children recommended to receive 13vPnC vaccine as part of routine immunization. In addition, the study will measure the effectiveness of one or more doses of 13vPnC vaccine against IPD caused by vaccine serotypes separately in children with underlying conditions and in healthy children, will assess evidence of wide use of 13vPnC vaccine leading to high risk of IPD caused by non-vaccine serotypes, will measure the effectiveness of one or more doses of 13vPnC vaccine against IPD caused by pneumococci non-susceptible to antibiotics, will measure the effectiveness against vaccine type IPD in African-American and white children, and will assess known risk factors for IPD. IDP cases are defined as isolation of pneumococcus from normally sterile sites from residents of the catchment areas.

Cases of IPD will be identified through the ABCs and through enhanced surveillance conducted in Epidemiology Laboratory Capacity (ELC) sites. Four controls will be recruited for each eligible case. Children recommended to receive 13vPnC vaccine as part of routine immunization schedule living in an ABC area or ELC state on the culture date of the matching case child will be eligible for enrollment. Controls will be identified from birth certificates. Cases and controls will be matched by age and zip code. Parents or guardians will be contacted by phone for consent and interview. Health care providers will be contacted to obtain vaccination history and past medical history. Estimates of sample size will be driven largely by the six additional serotypes (1, 3, 5, 6A, 7F 19A), because so few cases of IPD are expected to be caused by Prevnar serotypes. Based on a true effectiveness of 70-90%, a coverage from 50-90%, with α=0.05, power of 80% and assuming 4 controls per case, the estimated number of cases needed to assess vaccine effectiveness of 80% is about 22.

The ABCs system is a population-based, national surveillance system for pneumococcal disease in 10 states. According to the 2007 census, about 900,000 children less than 2 years of age and 1.3 million 2-4 year olds reside in the ABCs sites. In 2007, 456 IPD cases were identified through the ABCs among children 3-59 months of age, 288 for those 3-23 months of age and 168 from 24-59 years of age. Of these 456 cases isolates were available for 87%. Of those, 251 (55%) were 13vPnC serotypes (108 cases were due to serotype 19A, 52 due to serotype 7F and 16 to serotype 3).

8.2.1.2 Study 6096A1-4005 – IPD surveillance study in the Northern California Kaiser Permanente population

The primary objective of this proposed, observational database study is to estimate the annual incidence of IPD in all NCKP members during each of the five years of the surveillance period (2010-2014). The study will compare these IPD incidence rates to those of IPD prior to Prevnar, during routine use of Prevnar, and following the introduction of 13vPnC vaccine. The study also will describe the serotype distribution of IPD cases, and describe the antibiotic susceptibility of vaccine serotype and non-vaccine serotype IPD observed over the five year period. Cases of IPD will be identified through a laboratory-based surveillance system within NCKP.

The annual birth cohort at NCKP is about 36,000 infants and the number of children under 5 years of age in the NCKP network is about 140,000 in any year. The expected number of IPD cases in a 5 year period is 12.5 for 7vPnC serotypes and 24 for 13vPnC vaccine serotypes, respectively.

An important benefit of conducting this study at NCKP is the availability of baseline incidence rates of serotype-specific IPD during the pre- and post-Prevnar era against which to compare incidence. Other HMOs may not routinely keep data on IPD or routinely do pneumococcal serotyping.

8.2.2 Otitis Media (OM)

At this time the applicant seeks an indication for prevention of OM caused by the serotypes in the vaccine and has proposed a plan to conduct post-licensure studies to evaluate vaccine effectiveness against OM. This presents a set of regulatory action options for the Agency to consider. Specifically, the Agency could 1) license the 13vPnC for an indication for the prevention of OM caused by all 13 serotypes in the vaccine; 2) license the 13vPnC for an indication for the prevention of OM caused by the seven common serotypes in Prevnar; or 3) not license the vaccine for an indication for prevention of OM at this time. A serological correlate or other endpoint for inference of efficacy against OM in lieu of conducting an OM efficacy study has not been established. In this regard, data from the 13vPnC pivotal immunogenicity study may not be used to infer efficacy against OM for the 13vPnC. Because efficacy against OM was demonstrated for Prevnar in two efficacy trials, it seems that these data should retain some value in support of an OM indication for the seven common serotypes in the 13vPnC vaccine. Scientifically, the pathophysiology of OM and IPD differ to the extent that the relevance of IgG antibodies for protection against OM has been questioned. Also, the relationship between NP colonization and OM may provide a useful link in understanding OM and for evaluating new preventive vaccines against OM. Given that OM is a leading cause of outpatient and ER visits in the U.S. and can result in significant morbidity, the pathway for approving OM indications for new pneumococcal vaccines warrants attention. It is possible that not including prevention of OM as an indication in the package insert for the 13vPnC could cause unnecessary confusion among practitioners and possibly have negative consequences, particularly for those children whose parents choose not to vaccinate them, because unlike Prevnar, the new vaccine is "not approved to prevent ear infections."

The applicant has proposed a post-licensure vaccine effectiveness plan for OM, comprised of two complementary studies: an observational study in which 13vPnC-immunized children presenting with AOM will undergo diagnostic tympanocentesis and an AOM surveillance study utilizing a national administrative database to track AOM-related medical visits. In addition, the sponsor is currently conducting a randomized, double-blind nasopharyngeal (NP) colonization study in Israel to evaluate differences in NP colonization between children immunized with Prevnar vs. 13vPnC vaccine. This study's role and pertinence in evaluating vaccine effectiveness against OM is not entirely clear. It is currently being discussed by the applicant and the Agency as a possible addition to the proposed post marketing effectiveness plan for OM. A link between NP colonization with *S. pneumoniae* and OM caused by *S. pneumoniae* has not been formally established, such that it can be used as the basis for clinical development plans to support regulatory decisions. All three studies are described in more detail below.

8.2.2.1 Study 6096A1-4010 – observational study of vaccine effectiveness in reducing AOM and NP colonization

This observational study, which would start soon after introduction and implementation of routine immunization with the 13vPnC vaccine, would be conducted by the applicant in collaboration with Michael Pichichero, MD, who would serve as the principal investigator. Dr. Pichichero's site, which is located in Rochester, NY, routinely collects tympanocentesis samples from all children with OM. The study is designed to demonstrate the effectiveness of 13vPnC vaccine in reducing AOM and nasopharyngeal colonization in young children caused by vaccine serotypes. Children presenting with AOM will undergo tympanocentesis. Children will be recruited prospectively beginning at 2 months of age and followed until 30 months of age. Nasopharyngeal (NP) and oropharyngeal (OP) samples will be obtained at 6, 9, 12, 15, 18, 24 and 30 months of age and middle ear fluid (MEF) will be obtained by tympanocentesis, using standard techniques, for every child presenting with a first and second episode of AOM and children who are identified as "otitis prone" and experience recurrent (AOM) with treatment failure throughout the study. The number of subjects to be enrolled is 350. All tympanocentesis samples will be tested by standard microbiologic techniques for presence of *S. pneumoniae* and *S. pneumoniae* isolates will be serotyped using standard methods. Effectiveness of the vaccine will be assessed by estimating the difference in rate of each serotype and overall to a pre-13vPnC baseline period. In addition, the effectiveness of the vaccine in reducing NP carriage will be assessed.

8.2.2.2 OM surveillance study

This ecologic study would assess trends in the diagnosis of OM in the U.S. over time as an indirect marker of effectiveness against OM based on the methods previously used by Carlos Grijalva et al[23], who compared national rates of outpatient visits for pneumonia and OM in children before and after Prevnar introduction. Grijalva analyzed data on outpatient visits to healthcare facilities obtained from the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Care Survey (NHAMCS). Both surveys obtain nationally representative visit data from physicians and other medical staff via randomly assigned surveys for a limited time period (i.e., 1 week for NAMCS and 4 weeks for NHAMCS). Data collected from both surveys include demographics, symptoms, procedures, diagnoses and prescribed medications, without any personal identifiers. In comparing 2002-2003 data to 1994-1999 data, Grijalva showed that OM visits declined by 20% in children < 2 years old.[23] The proposed study would include data from NAMCS and NHAMCS from the following three observation periods: pre-PCV7 (1994-1999), post-PCV7 (2000-2008) and post-13vPnC (approximately 2010-2012).

8.2.2.3 Study 6096A1-3006 - Israel NP colonization study

In collaboration with Ron Dagan, M.D.,from Soroka University Medical Center in Beer-Sheva, Israel, as the principal investigator, the applicant is currently conducting a study, entitled "A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Impact of a 13-valent Pneumococcal Conjugate Vaccine on Nasopharyngeal Colonization with Vaccine Serotypes of *Streptococcus pneumoniae* in Healthy Infants in Israel." This study is not being conducted under U.S. IND, but was recently brought to CBER's attention for consideration as a possible addition to the proposed post marketing plan for OM effectiveness. To date enrollment is completed with 1,864 infants who entered the study at 2 months of age across multiple sites. Subjects were randomized 1:1 to receive either Prevnar or 13vPnC vaccine. NP swabs will be collected from all subjects at 2, 4, 6, 7, 12, 13, 18, and 24 months of age and cultured for *S. pneumoniae* using standard practice. All *S. pneumoniae* isolates will be serotyped and tested for antimicrobial sensitivity. Sera collected at one month post dose 3 and one month post dose 4 will be shipped to the applicant for testing for serotype-specific IgG concentrations all 13 vaccine serotypes.

This study focuses on colonization with serotypes 6A and 19A, because among the six new serotypes these are considered frequent colonizers. Thus, the primary study objective is to demonstrate that 13vPnC vaccine reduces NP colonization with types 6A and 19A combined compared to Prevnar. Secondary and exploratory objectives are to demonstrate safety, reduction in colonization with the other serotypes and reduction in various serotype groupings at different ages. Also, the correlation between immune responses (IgG) to the 13 serotypes in the vaccine and the 13vPnC vaccine's impact on NP colonization will be explored. According to the applicant, the study is expected to be completed in late 2011.

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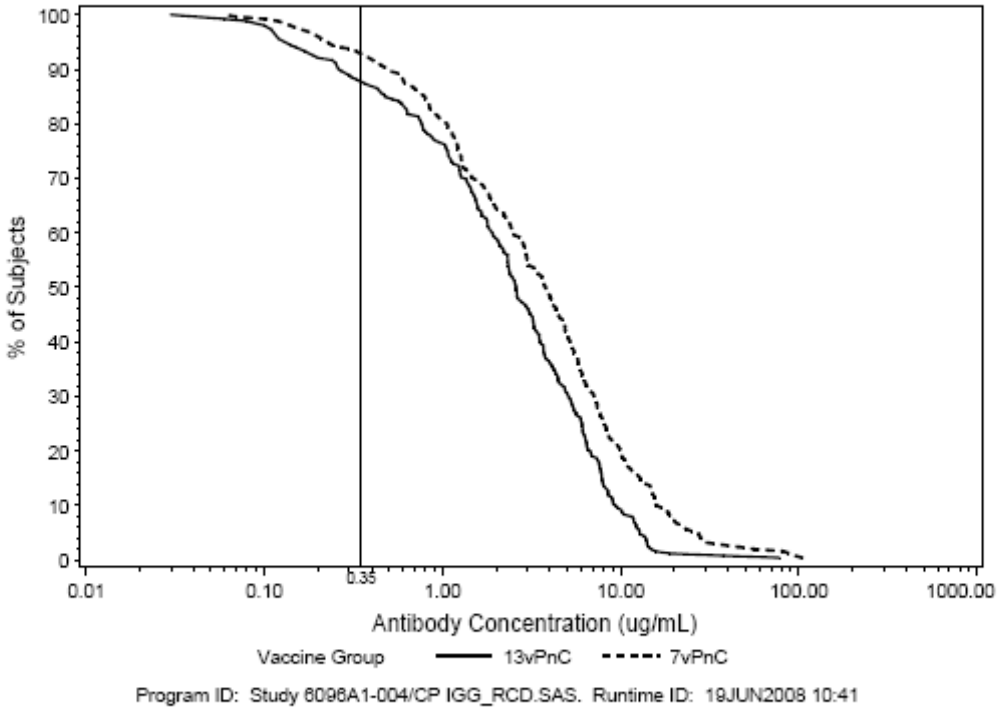
10.0 APPENDIX I: Study 6096A1-004 Reverse cumulative distribution curves
Post-dose 3 and 4: IgG Serotypes 6B, 9V, 3
Post-dose 3 and 4: OPA Serotypes 6B, 3, 9V
Source: CSR69238-report-body.pdf pages 79-81, 90, 442, 444, 451, 453, 455, 461, 463, and 465.

The figures below are reverse cumulative distribution curves (RCDC) showing the distribution of IgG and OPA antibody responses one month post-dose 3 and one month post-dose 4 in the 13vPnC and PCV7 vaccine groups for the serotypes that did not meet the primary endpoint noninferiority criterion (serotypes 6B, 9V, and 3).

Figure 9-1: Reverse Cumulative Distribution Curves, Pneumococcal Serotype 6B, IgG Antibody Concentrations in the Evaluable Infant Immunogenicity Population – After the Infant Series. The RCDCs are separated, with the 13vPnC vaccine curve being lower than the PCV7 curve at concentrations at or above the 0.35 µg/mL comparison level. The 2 curves approach one another at about the 1.0 µg/mL concentration, with the 13vPnC vaccine curve still lower than the PCV7 curve. The curves then separate and the PCV7 curve remains clearly higher compared to the 13vPnC vaccine curve at all remaining concentrations greater than 1.0 µg/mL. The 0.35 µg/mL comparison level is close to the top of both curves.

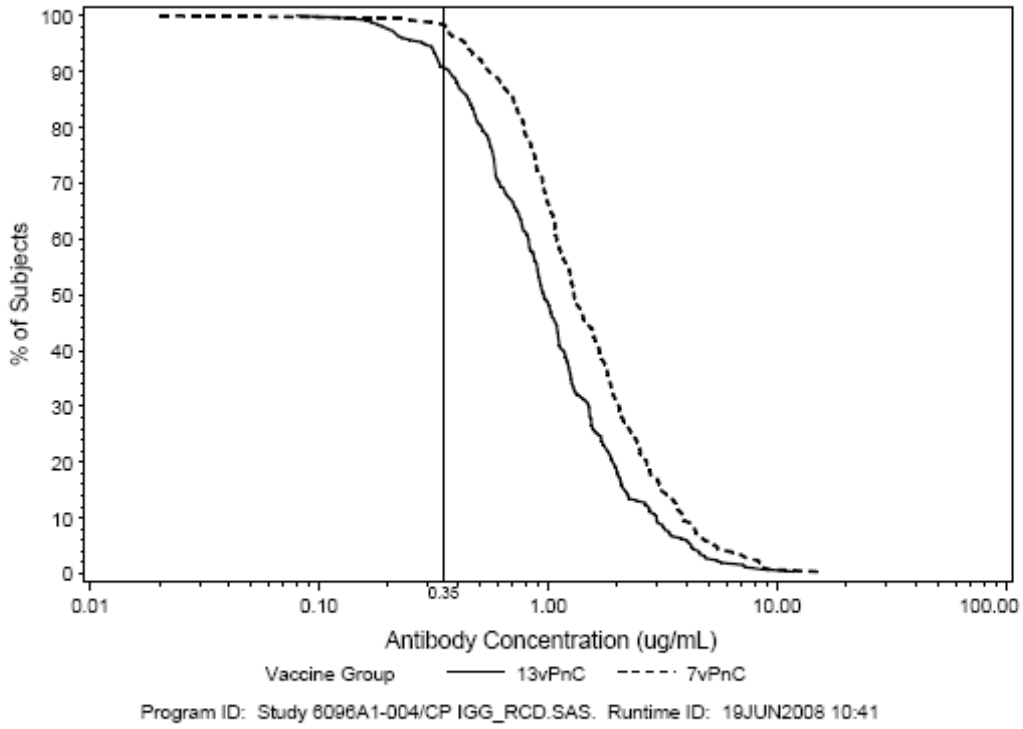
Figure 9-1: Reverse Cumulative Distribution Curves, Pneumococcal Serotype 6B, IgG Antibody Concentrations in the Evaluable Infant Immunogenicity Population – After the Infant Series



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/s6b_elisa_rcd_eval_i.cgm

Figure 9-2: Reverse Cumulative Distribution Curves, Pneumococcal Serotype 9V, IgG Antibody Concentrations in the Evaluable Infant Immunogenicity Population – After the Infant Series. The RCDCs are separated, with the 13vPnC vaccine curve being lower than the PCV7 curve at all concentrations at or above the 0.35 µg/mL comparison level. The 0.35 µg/mL comparison level is close to the top of both curves.

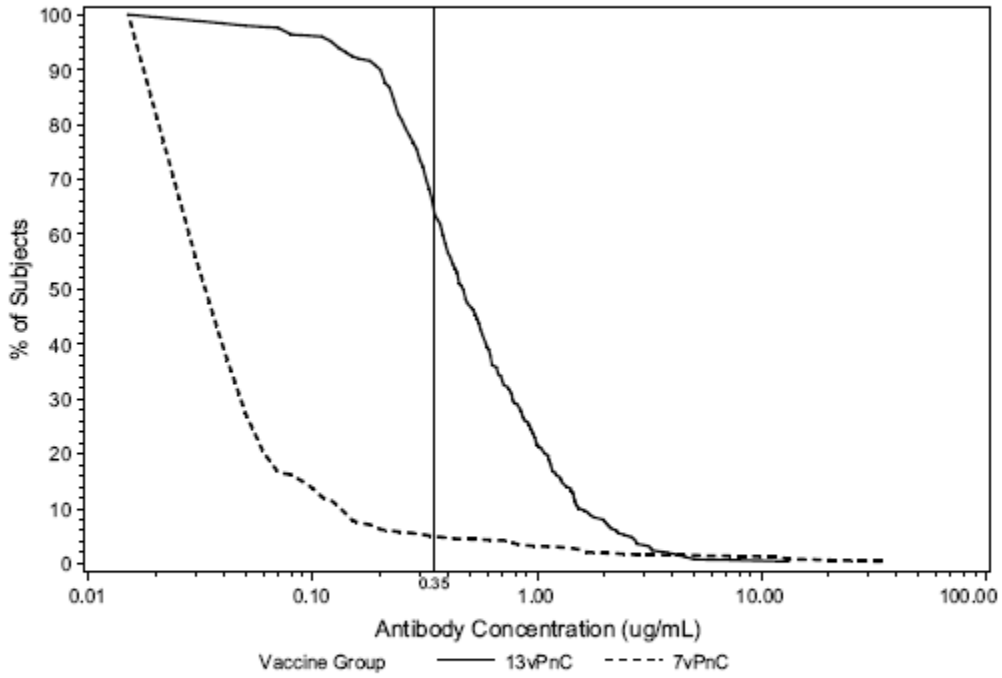
Figure 9-2: Reverse Cumulative Distribution Curves, Pneumococcal Serotype 9V, IgG Antibody Concentrations in the Evaluable Infant Immunogenicity Population – After the Infant Series



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/s9v_elisa_rcd_eval_i.cgm

Figure 9-3: Reverse Cumulative Distribution Curves, Pneumococcal Serotype 3, IgG Antibody Concentrations in the Evaluable Infant Immunogenicity Population – After the Infant Series. The RCDCs are separated to a large extent, with the 13vPnC vaccine curve lying much higher than the PCV7 curve. The 0.35 µg/mL comparison level is at about the middle of the 13vPnC vaccine curve and at the bottom of the PCV7 curve.

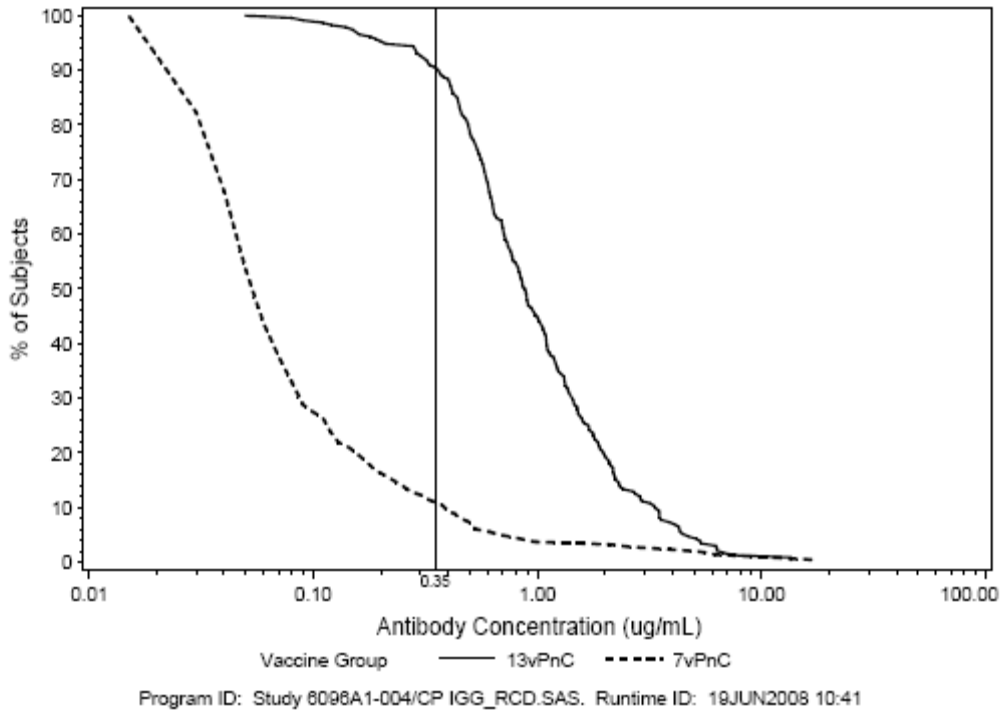
Figure 9-3: Reverse Cumulative Distribution Curves, Pneumococcal Serotype 3, IgG Antibody Concentrations in the Evaluable Infant Immunogenicity Population – After the Infant Series



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/s3_elisa_rcd_eval_i.cgm

Figure 9-4: Reverse Cumulative Distribution Curves, Pneumococcal Serotype 3, IgG Antibody Concentrations in the Evaluable Infant Immunogenicity Population – After the Toddler Dose. The RCDCs are separated to a large extent, with the 13vPnC vaccine lying much higher than the PCV7 curve.

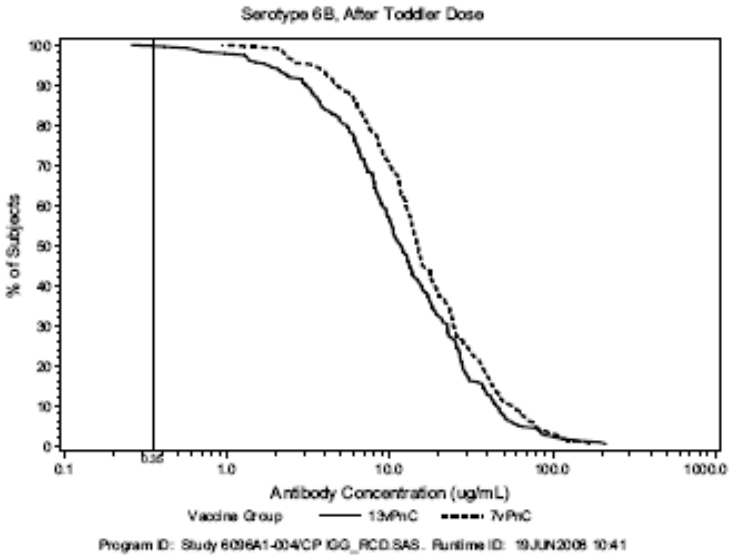
Figure 9-4: Reverse Cumulative Distribution Curves, Pneumococcal Serotype 3, IgG Antibody Concentrations in the Evaluable Infant Immunogenicity Population – After the Toddler Dose



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/s3_elisa_rcd_eval_t.cgm

Figure 16.15: Pneumococcal Serotype 6B, IgG Antibody Concentrations in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose. The RCDCs are separated, with the 13vPnC vaccine curve being lower than the PCV7 curve throughout the curve. The two curves approach one another at about the 25µg/mL comparison level; however the 13vPnC vaccine curve continues to remain lower than the PCV7 curve.

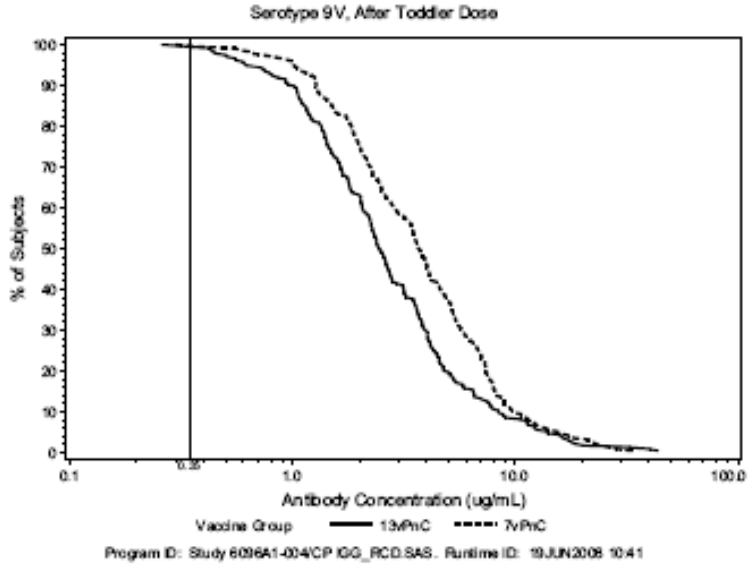
16.15 Pneumococcal Serotype 6B, IgG Antibody Concentrations in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/s6b_elisa_rcd_eval_t.cgm

Figure 16.17: Pneumococcal Serotype 9V, IgG Antibody Concentrations in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose. The RCDCs are separated with the 13vPnC vaccine curve being lower than the PCV7 curve at concentrations greater than 0.35 µg/mL. The two curves approach one another at approximately the 0.35 µg/mL and 10.0 µg/mL comparison levels.

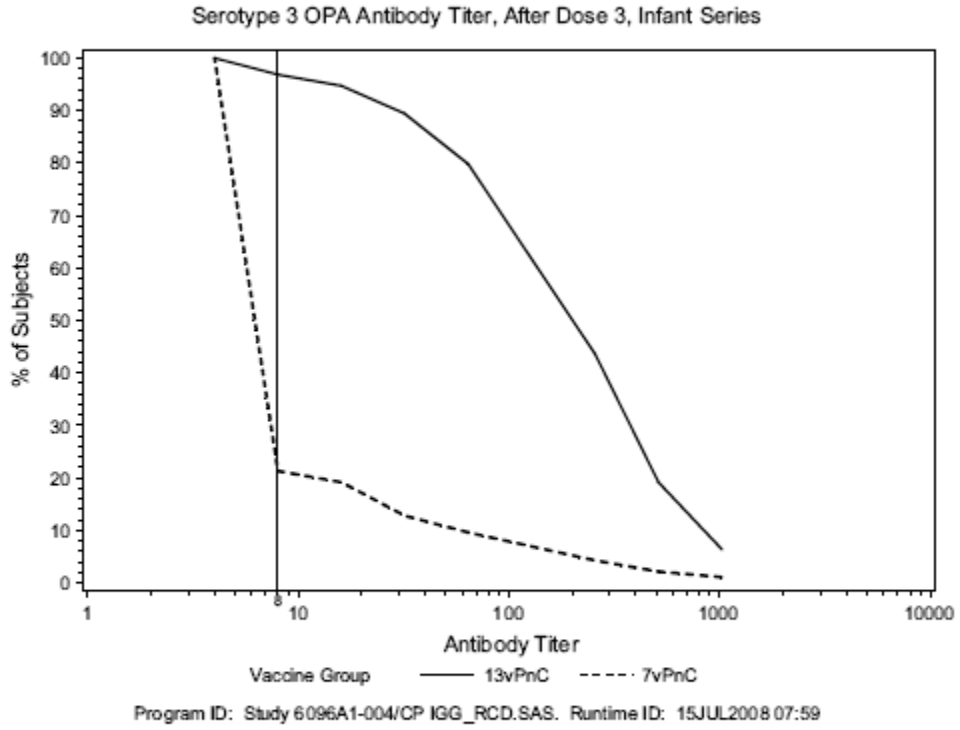
16.17 Pneumococcal Serotype 9V, IgG Antibody Concentrations in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/s9v_elisa_rcd_eval_t.cgm

Figure 16.24: Pneumococcal Serotype 3, OPA Titers in the Evaluable Infant Immunogenicity Population – After Infant Series. The RCDCs are separated to a large extent, with the 13vPnC vaccine curve lying much higher than the PCV7 curve along the entire curve.

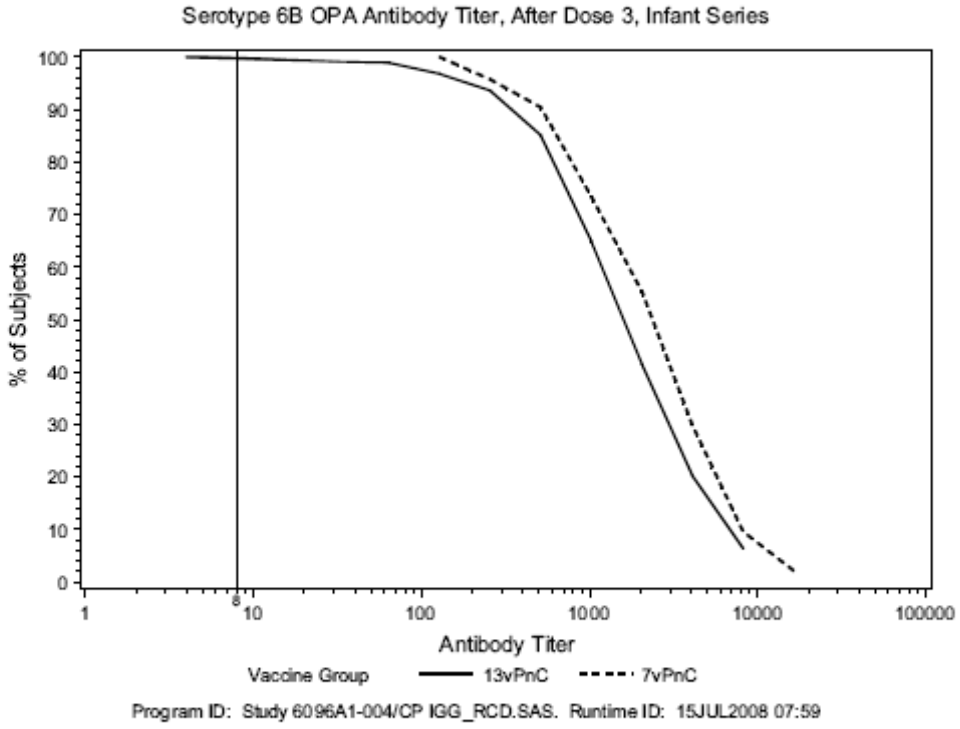
16.24 Pneumococcal Serotype 3, OPA Titers in the Evaluable Infant Immunogenicity Population – After Infant Series



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/6096-004 figs_immun_opa_conc.rtf

Figure 16.26: Pneumococcal Serotype 6B, OPA Titers in the Evaluable Infant Immunogenicity Population – After Infant Series. The RCDCs are separated with the 13vPnC vaccine curve being lower than the PCV7 curve.

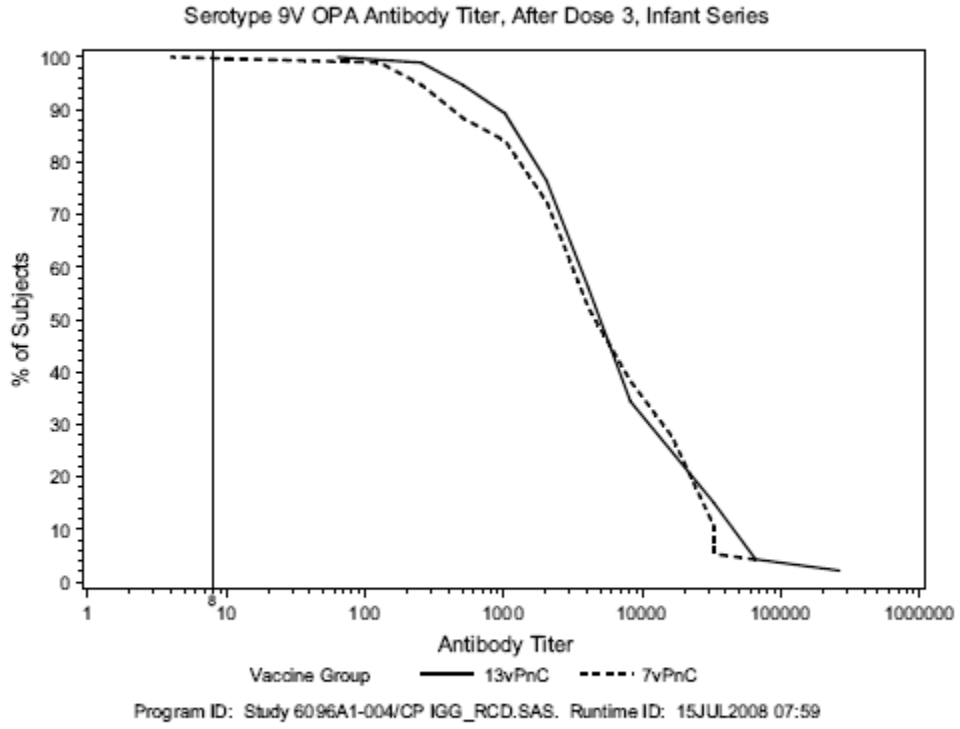
16.26 Pneumococcal Serotype 6B, OPA Titers in the Evaluable Infant Immunogenicity Population – After Infant Series



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/6096-004 figs_immun_opa_conc.rtf

Figure 16.28: Pneumococcal Serotype 9V, OPA Titers in the Evaluable Infant Immunogenicity Population – After Infant Series. The RCDCs are separated with the 13vPnC vaccine curve being higher than the PCV7 curve at antibody titers ≤ approximately 1:100. The curves lie close together along the downward slope of the curve.

16.28 Pneumococcal Serotype 9V, OPA Titers in the Evaluable Infant Immunogenicity Population – After Infant Series



Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Immunogenicity/6096-004 figs_immun_opa_conc.rtf

Figure 16.34: Pneumococcal Serotype 3, OPA Titers in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose. The RCDCs are separated, with the 13vPnC vaccine curve lying much higher than the PCV7 curve along the entire curve.

16.34 Pneumococcal Serotype 3, OPA Titers in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose

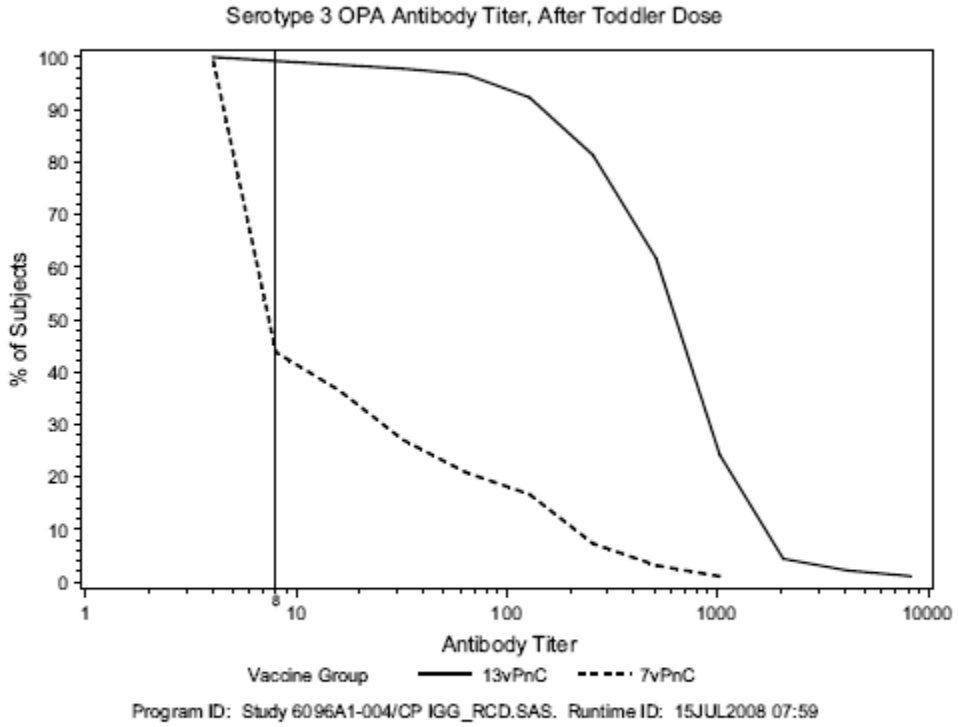


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Figure 16.36: Pneumococcal Serotype 6B, OPA Titers in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose. The RCDCs are separated at the top of the curve and along the mid-to lower slope of the curve. The curves lie close together at the upper portion of the slope of the curve.

16.36 Pneumococcal Serotype 6B, OPA Titers in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose

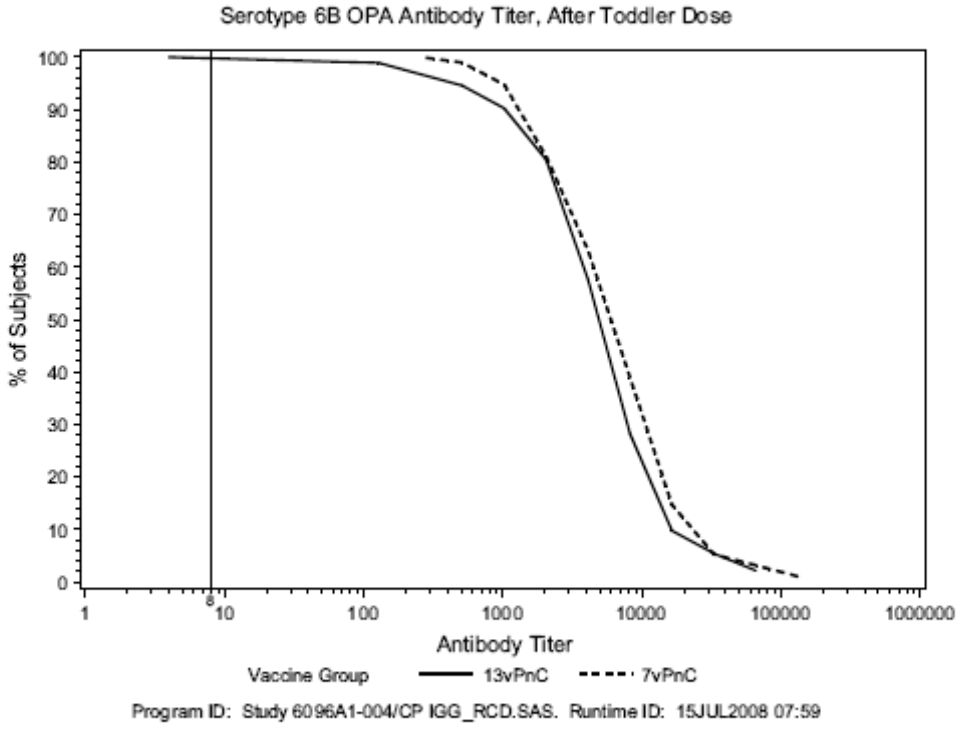

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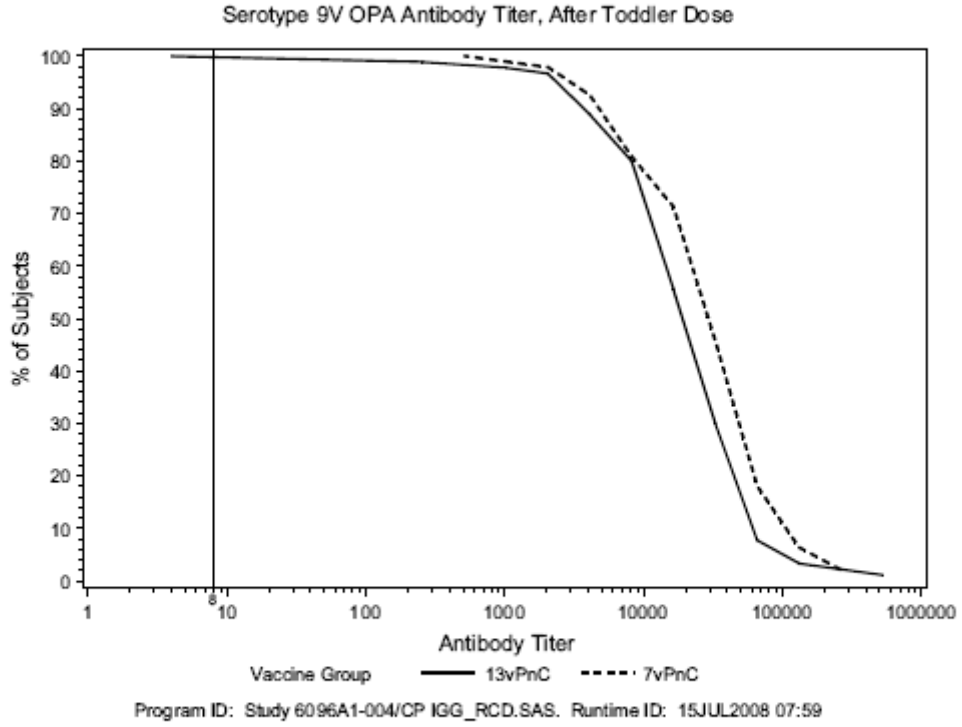
Figure 16.38: Pneumococcal Serotype 9V, OPA Titers in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose. The RCDCs lie close together at the top of the curve and are separated along the majority of the downward slope of the curve. The 13vPnC vaccine curve is lower than the PCV7 curve along the entire curve.

16.38 Pneumococcal Serotype 9V, OPA Titers in the Evaluable Toddler Immunogenicity Population – Posttoddler Dose



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