DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Office of Vaccines Research and Review (OVRR)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

TO: Biologics License Application Submission Tracking Number # 125324/0

SUBJECT: Clinical Review of Biologics License Application for Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein))

THROUGH: R. Douglas Pratt, M.D., M.P.H.
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APPLICANT: Wyeth Pharmaceuticals Inc.

1.0 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 Biologics License Application (BLA) Submission Tracking Number (STN) #: 125324

1.1.2 Submission received by CBER: March 31, 2009

1.1.3 Review completed: February 17, 2010

1.1.4 Material Reviewed

Amendments 1 – 3 comprised the rolling BLA submissions. Amendment 4 was the final rolling submission which completed the BLA filing on March 31, 2009.

The following general module sections of the BLA were reviewed:
m1.9 Pediatric Administrative Information
m1.14 Labeling
m2.5 Clinical Overview
m2.7 Clinical Summary
m5 Clinical Study Reports

A more detailed list of information in the BLA reviewed is provided below by amendment number:
Amendment 1: Date Submitted: 10/24/08
- m5.3.1.4 Bioanalytical and analytical methods for human studies
- m5.3.5.1 Study Reports of Controlled Clinical Studies: Studies 003, 004, 009, 3007
- m5.3.5.4 Other Study Reports: Study 002

Amendment 2: Date Submitted: 12/17/08
- m5.3.5.1 Study Reports of Controlled Clinical Studies: Studies 006, 500, 501, 3008
- m5.3.5.2 Study Reports of Uncontrolled Clinical Studies: Study 3002

Amendment 3: Portion 4, Date Submitted: 3/6/09
- m1.6.3 Correspondence Regarding Meetings
- m2.3.1 Quality Overall Summary Introduction
- m3.2.P.1 Description and Composition of the Drug Product
- m5.2 Tabular Listing of Clinical Studies
- m5.3.5.1 Study Reports of Controlled Clinical Studies: Studies 007, 008, 011, 3000, 3005
- 5.4 Literature References

Amendment 4: Date Submitted: 3/31/09
- m1.4.4 Cross Reference to Other Applications
- m1.14.1.2 Draft Labeling Text
- m1.14.1.3 Draft Labeling Text
- m1.16 Risk Management Plans
- m2.2 Common Technical Document Introduction
- m2.5 Clinical Overview
- m2.7 Clinical Summary
- m5.3.5.1 Study Reports of Controlled Clinical Studies: Study 004
- m5.3.5.3 Reports of Analysis of Data from More then One Study: Integrated Summary of Safety and Integrated Statistical Analysis Plan
- m5.4 Justification of Safety Labeling Decision (Apnoea) and Literature References

Amendment 11: Date Submitted: 5/14/09
- m1.9 Pediatric Administrative Information
- m1.11.3 Efficacy Information Amendment: Response to Agency Request – CBER Clinical Comments
- m5.3.5.1.3 Study Report Body (Word Version): Studies 003, 004, 009, 006, 008, 3005, 3002

Amendment 14: Date Submitted: 6/11/09
- m1.11.3 Efficacy Information Amendment: Response to Agency Request on Post-Marketing Protocols 6096A1-4002 and 6096A1-4010
- m5.3.5.2 Study 4010, Postmarketing study synopsis: Effectiveness of Prevnar 13 in reducing acute otitis media and nasopharyngeal colonization in young children
  Study 4002, Post-licensure Study: Safety of Prevnar 13 in routine use for infants and children
- m5.4 Literature Reference Grijalva, CG, 2006

Amendment 16: Date Submitted: 6/15/09
- m1.11.3 Efficacy Information Amendment: Response to May 21, 2009 Questions – Additional Safety Data
- m5.3.5.1.3 Study 3005 Study Report Body: Additional Safety Information

Amendment 18: Date Submitted: 6/18/09
- m2.5 Addendum to Clinical Overview – Response to 05-June-2009 Request for IPD Incidence Rates

Amendment 20: Date Submitted: 6/30/09
- m1.11.3 Efficacy Information Amendment: Response to Clinical Questions Regarding Pneumococcal IgG Antibody Comparison Studies

Amendment 24: Date Submitted: 7/31/09
- m1.14.1 Draft Labeling

Amendment 25: Date Submitted: 8/6/09
- m1.11.3 Efficacy Information Amendment: Clinical Information Response to Agency Request for Varicella Data from Study 6096A1-3005
- m5.3.1.4.1 Varicella Validation Report VR-ECD-10022: Validation of –b(4)------ Glycoprotein (gp) ELISA Assay for VZV Antibody Detection in Human Sera
  Varicella gpELISA Summary

Amendment 28: Date Submitted: 9/1/09
- m1.11.3 Efficacy Information Amendment: Response to Agency Request from 19-Aug-2009 Study 004 Mumps and Varicella Data

Amendment 39: Date Submitted: 10/9/09
- m1.11.3 Efficacy Information Amendment: Response to Agency Request – Study 6096A1-008 Additional Data and Study 6096A1-3005 Additional Data

Amendment 42: Date Submitted: 10/12/09
- m1.2 Response to Agency Request – Rationale for Age Range for High Risk Groups

Amendment 43: Date Submitted: 10/15/09
- m1.11.3 Efficacy Information Amendment: Response to Questions 03-Sep-2009 Mumps and Varicella
- m5.3.1.4.1 Legacy Study Report – Mumps ELISA
  Legacy Study Report – Mumps Validation Report VR-ECD-10026: Validation of Mumps --b(4)--- IgG ELISA

Amendment 49: Date Submitted: 11/6/09
- m1.11.3 Efficacy Information Amendment: Response to Agency Request on 21-Oct-09 for SAE Narratives Occurring Within 30 Days

Amendment 58: Date Submitted: 12/2/09
- m1.11.3 Efficacy Information Amendment: Response to Agency Comments 01-Dec-2009 on Safety Study 6096A1-3005: Toddler and 6-Month Follow-Up Safety Data
- m5.3.5.1 Analysis Datasets

Amendment 60: Date Submitted: 12/4/09
- m1.11.3 Efficacy Information Amendment: Response to Labeling Comments from Nov 23-24, 2009
- m1.14 Draft Labeling

Amendment 63: Date Submitted: 12/9/09
- m1.11.3 Efficacy Information Amendment: Response to Agency Request from 25-Nov-2009 with Clinical PMC Information and Synopsis
- m5.3.5.2.2 Synopsis of Study 4018: US National Trends in Otitis Media in Infants and Children Under 5 Years of Age Between 1997 and 2013

Synopsis of Study xxxx: Postmarketing Observational Study of the Effectiveness of Prevnar 13 in Reducing Oititis Media in Young Children Caused by Serotypes in the Vaccine

Amendment 66: Date Submitted: 12/14/09
m1.11.3 Response to Agency Request for Narratives from Study 3005
Amendment 67: Date Submitted: 12/16/09
m5.3.5.1 Study 3011 Study Report
Amendment 69: Date Submitted: 12/23/10
m1.14.1.3 Draft Labeling
Amendment 70: Date Submitted: 1/4/10
m1.11.3 Response to Agency Request from 22-Dec-2009 for Study 3005 Tables
Amendment 72: Date Submitted: 1/11/10
m1.11.3 Response to Clinical Information Request on 04-Jan-2010 for Safety Data
Amendment 74: Date Submitted: 1/20/10
m1.11.3 Response to Agency Request for Updated Integrated Safety Tables
Amendment 76: Date Submitted: 1/25/10
m1.14.1 Draft Labeling
Amendment 78: Date Submitted: 2/1/10
m1.14.1 Draft Labeling
Amendment 81: Date Submitted: 2/5/10
m1.14.1 Draft Labeling
Amendment 82: Date Submitted: 2/8/10
m1.11.3 Clarification Request Regarding SAE

1.1.5 Related Master File, INDs and BLAs

- Master File 14097: Type 5 Master File from CDC
- IND 11673: Wyeth's Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) Vaccine for use in children
- IND ----------b(4)----------
- BLA 103905: Wyeth's Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) Vaccine for use in children

1.2 Product name

1.2.1 Generic or proper name: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

1.2.2 Proposed trade name: Prevnar 13

1.2.3 Product formulation per 0.5 mL dose: 2.2 ug of each saccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4 ug of serotype 6B; approximately 32 ug of cross-reacting material 197 (CRM_{197}) carrier protein; and 5mM succinate buffer, 0.125 mg aluminum as AlPO4 adjuvant, and 0.02% polysorbate 80.

1.2.4 Abbreviations Used in This Review

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AOM	Acute Otitis Media
CI	Confidence Interval
CRM	Cross Reacting Material
ELISA	Enzyme Linked Immunosorbent Assay
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
IgG	Immunoglobulin
IPD	Invasive Pneumococcal Disease
NCKP	Northern California Kaiser Permanente
OM	Otitis Media
OPA	Opsonophagocytic Antibody
PCV7	Prevnar
PT	Preferred Term
SOC	System Organ Class
13vPnC	Prevnar 13

1.3 Applicant: Wyeth Pharmaceuticals Inc.

1.4 Pharmacologic Category: Vaccine

1.5 Proposed Indications: Active immunization of infants and toddlers for the prevention of invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; and active immunization of infants and toddlers for the prevention of otitis media caused by serotypes included in the vaccine

1.6 Proposed age range for use: Infants and children 6 weeks through 5 years of age.

1.7 Dosage Form and Route of Administration: 0.5 mL suspension for intramuscular injection, supplied in a single dose pre-filled syringe.

2.0 Table of Contents

3 Executive Summary

Wyeth Pharmaceuticals Inc. has submitted a Biologics License Application (BLA) for their Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein] (proposed proprietary name, Prevnar 13), which is a successor to Prevnar. Prevnar 13 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), each individually conjugated to non-toxic diphtheria CRM_{197} protein. The proposed indications for Prevnar 13 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.) in February 2000, was approved by the FDA for active immunization to prevent invasive pneumococcal disease (IPD). 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 conducted in Finland, which involved tympanocentesis and bacterial cultures of middle ear fluid, as well as information on health care utilization for otitis media within a large Health Maintenance Organization (Northern California Kaiser Permanente).

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 for pneumococcal disease. 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). According to the CDC, by 2007, rates of IPD caused by serotypes contained in Prevnar declined by 99% in children aged < 5 years. Although the 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 thirteen serotypes contained in Prevnar 13 were responsible for approximately 64% of IPD cases in children < 5 years of age in 2007. In this same age group, the six additional pneumococcal serotypes contained in Prevnar 13 were responsible for approximately 62% 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 for ethical reasons. 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 non-inferiority 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 effectiveness against IPD for the candidate vaccine. Of note, the committee did not provide conclusive advice about whether non-inferiority 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 effectiveness. Consequently, the clinical development for Prevnar 13 involved an approach in which vaccine effectiveness against IPD was to be inferred from immunologic parameters.

In a pivotal U.S. study, immunologic non-inferiority of Prevnar 13 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 efficacy against IPD for Prevnar or an investigational 9-valent CRM_{197} conjugate vaccine, also manufactured by Wyeth. For new serotypes not included in Prevnar, non-inferiority comparisons of Prevnar 13 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.

Ten of the 13 serotypes in Prevnar 13 met the non-inferiority criterion for both co-primary endpoints. For three vaccine serotypes, the non-inferiority 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 achieving ≥ 0.35 µg/mL(Prevnar 13 – Prevnar) exceeded CBER's agreed upon pre-specified non-inferiority margin of -10% and was -10.9%, -12.4%, and -36.2% for serotypes 6B, 9V, and 3 respectively. For serotype 3, the non-inferiority criterion was not met for the IgG GMC after the fourth dose; the lower limit of the 95% CI for the GMC ratio (Prevnar 13/Prevnar), 0.22, was less than CBER's agreed upon non-inferiority margin of 0.5. Although this study was not designed to demonstrate non-inferiority for secondary or exploratory endpoints, these additional immunogenicity endpoints were taken into account for serotypes 6B, 9V, and 3. Serotype 6B met the non-inferiority criteria for three out of four secondary endpoints. Serotype 9V met the non-inferiority criteria for two out of four secondary endpoints. Serotype 3 failed all four secondary endpoints. Exploratory analyses of pre-dose 4 GMCs showed that with the exception of serotype 3, all responses in the Prevnar 13 group met the non-inferiority criteria

Exploratory analyses of opsonophagocytic antibody (OPA) geometric mean titers (GMTs) showed that each serotype, including serotype 3, elicited some functional antibody response and that the OPA GMT one month post-dose 4 was higher than the OPA GMT at one month post-dose 3. Because protection against pneumococcal disease is thought to be via opsonophagocytosis, measurement of functional antibody activity may be more relevant than ELISA antibody levels. However, OPA data are considered exploratory, because the assay needs further development and because there is no concensus regarding criteria for assessing effectiveness of new pneumococcal vaccines based on OPA antibody levels.

Interpretation of the data for those serotypes that failed to meet at least one primary study endpoint in the pivotal non-inferiority study requires some caution, as the primary study endpoints (both based on IgG antibodies measured by ELISA) are not correlates of protection. In particular, it is not clear if the use of a single IgG antibody reference value of 0.35 µg/mL has the same clinical significance across all pneumococcal serotypes. Although the antibody responses to serotypes 6B and 9V did not meet the non-inferiority criteria for the post-dose 3 primary endpoint (the proportion of subjects achieving a pneumococcal antibody concentration of ≥ 0.35 µg/mL one month after dose 3), there is additional supportive data to suggest that these two serotypes may be effective. Both serotypes 6B and 9V met the non-inferiority criteria for the post-dose 3 GMC secondary endpoint and both serotypes elicited functional antibodies. Similar supportive data are more limited witth regards to serotype 3, which failed to meet each of the primary and secondary study endpoints, However, some functional anti-serotype 3 antibody response was elicitied after dose 3, and this response was higher after the fourth dose.

The safety data on Prevnar 13 reviewed by CBER raise no obvious safety concerns that would preclude licensure. Although the safety data on the use of Prevnar 13 in children up to 5 years of age are more limited, there are no data to suggest the presence of any new safety concerns with the use of Prevnar 13 in older children.

Across 14 studies, serious adverse events were evaluated in 5084 infants and young children who received Prevnar 13 and 2760 infants and young children who received Prevnar as the control vaccine. This includes integrated infant series data from 13 studies, integrated toddler dose data from 10 studies (8 studies with 4-dose schedules), and 6-month follow-up data from 6 studies. Toddler dose and 6-month follow-up safety data from study 3005 were submitted as an amendment to the BLA and were not included in the integrated summary of safety.

A total of 4 deaths occurred, three among Prevnar 13 recipients and 1 among Prevnar recipients; each death was suspected to be due to sudden infant death syndrome. Possible alternative contributing factors were identified in the deaths of two Prevnar 13 recipients. The two remaining deaths occurred 76 days after the third Prevnar 13 dose and 13 days after the first Prevnar dose. Using an age-specific background SIDS rate from California from the year 2000, the number of SIDS cases reported in Prevnar 13 clinical trials was not higher than what would be expected in the general population. The overall SIDS rate in the Prevnar 13 clinical trials was 0.063% among Prevnar 13 recipients and 0.036% among Prevnar recipients. The SIDS rate for infants 2 to < 3 months of age fom California from the year 2000 was 1.197 per 1000 live births or 0.12%.

Based on integrated safety data on serious adverse events occurring in all thirteen infant studies, from dose 1 through the post-infant series blood draw, 3.5-3.7% of subjects in both study groups experienced a serious adverse event; 2.7-3.5% of subjects experienced a serious adverse event from > 30 days after the 3rd dose to the 4th dose; 0.8 to 0.9% of subjects experienced a serious adverse event within 30 days after the toddler dose, and 2.5-2.8% of subjects experienced a serious adverse event from the post-toddler dose blood draw to the 6-month follow-up telephone contact [These rates include post-infant series safety data from study 3005, which were submitted to the BLA in December 2009].

Solicited local reactions and systemic events were monitored for 7 days after each vaccination in two phase 3 U.S. studies which included 1908 subjects who received at least one dose of Prevnar 13. Tenderness and irritability were the most frequently reported local and systemic solicited events respectively in both study groups. In the largest U.S. safety study (study 3005), moderate fever occurred at a statistically significantly higher rate in Prevnar 13 (3.4%) recipients compared to Prevnar (0%) recipients after the 2nd dose. This finding was not observed in study 004, a smaller phase 3 study.

CBER convened a Vaccines and Related Biological Products Advisory Committee (VRBPAC) on November 18, 2009, to seek input on the effectiveness and safety data submitted to the BLA. The committee voted that the safety and effectiveness data support the use of Prevnar 13 in infants and toddlers for the indications cited above.

Under the Pediatric Research Equity Act (PREA) (21 U.S. C. 355c), this application for a new active ingredient is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups, unless the requirement is waived, deferred, or inapplicable. The applicant indicates that studies for the pediatric subpopulation from 6 weeks through 5 years of age (prior to 6th birthday) have been completed. The applicant is therefore seeking an indication for the prevention of IPD and otitis media in this age group. The applicant requested a partial waiver from the requirements of PREA for children from birth up through 5 weeks of age (prior to 6 weeks of age) and a deferral for studies in children 6 through 16 years (prior to 17th birthday) of age. We are waiving the pediatric study requirement in infants from birth to < 6 weeks of age for the invasive pneumococcal disease and otitis media indications, because Prevnar 13 does not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age, and Prevnar 13 is not likely to be used in a substantial number of pediatric patients 0 to < 6 weeks of age. We are waiving the pediatric study requirement in children 6 through 16 years of age (prior to 17th birthday) for the otitis media indication, because Prevnar 13 does not represent a meaningful therapeutic benefit over existing antibiotic therapy in this age group, and Prevnar 13 is not likely to be used in a substantial number of pediatric patients 6 through 16 years of age. We are deferring submission of the pediatric study in children ages 6 to 16 years in this application for the invasive pneumococcal disease indication because this product is ready for approval for routine immunization in infants and children 6 weeks through 5 years of age, and the pediatric study in children 6

to 16 years of age has not been completed; waiting for results of such a study would unnecessarily delay approval of Prevnar 13 for children 6 weeks through 5 years of age. Enrollment in this study has been completed, and the projected date for the submission of this pediatric assessment is in 2010.

The applicant has committed to conduct a post-licensure observational safety study at Northern California Kaiser Permanente (NCKP) to further evaluate the safety of Prevnar 13 when administered as a four dose series to infants and toddlers. Approximately 43,000 infants will be enrolled and followed starting at 2 months of age; the estimated study duration is 4 years. In addition, the applicant has committed to conduct post-licensure IPD and OM effectiveness studies. IPD surveillance data will be submitted from the Active Bacterial Core Suveillance (ABCs) system, NCKP, and from an open-label study in the Yukon Kuskokwim (YK) Delta region of Alaska. OM surveillance data will be submitted from (1) an observational study in New York that evaluate the impact of Prevnar 13 on acute otitis media (AOM) caused by serotypes included in the vaccine, which will include typmanocentesis, bacterial cultures, and identification of middle ear fluid isolates, (2) an observational study utilizing a laboratory-based surveillance network of eight pediatric hospitals across the U.S. in which *S. pneumoaniae* isolates from identified AOM cases will be serotyped, and (3) an ecologic study evaluating national trends in health care visits for otitis media in children younger than 5 years of age using data from annual surveys conducted by the National Center for Health Statistics.

The available safety and immunogenicity data from Prevnar 13 clinical studies, combined with the pre-licensure efficacy studies with Prevnar and post-marketing safety experience with Prevnar, suggest that Prevnar 13 will be effective in preventing IPD caused by pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F when administered to infants as a 4 dose series at 2, 4, 6, and 12-15 months of age. Failure of serotype 3 to meet all pre-specified non-inferiority criteria lessens our confidence that a protective response will be elicited among a high proportion of vaccines for this serotype. However, its inclusion in Prevnar 13 may offer some benefit in eliciting some functional anti-serotype 3 antibody response in children who receive the vaccine.

With regards to the otitis media indication, the effectiveness of Prevnar 13 against otitis media was not assessed in pre-licensure clinical trials submitted to the BLA. This issue was presented and discussed at the November 18, 2009 VRBPAC meeting. Although the committee did not vote on this subject, the majority of the Committee agreed that an oitits media indication for Prevnar 13 is adequantely supported by Prevnar efficacy data (for the 7 common serotyeps) and the comparative immunogenicity data from Prevnar 13 clinical trials. However, the majority of Committee members expressed concern regarding the lack of any efficacy data for the 6 additional serotypes.

This reviewer concludes that the effectiveness of Prevnar 13 in preventing otitis media has not been demonstrated in the Prevnar 13 BLA. The 0.35 µg/mL reference value used for non-inferiority comparisons between Prevnar 13 and Prevnar applies only to IPD and not to otitis media or other non-invasive disease endpoints. It has been suggested that higher serum antibody concentrations are required to prevent otitis media and carriage compared to the concentrations required to prevent IPD. However, there is no consensus regarding the serologic criteria for assessing effectiveness of new pneumococcal conjugate vaccines against otitis media. The non-inferiority comparisons between Prevnar 13 and Prevnar using a higher antibody concentration of 1.0 µg/mL showed that 6 out of the 7 original Prevnar serotypes would have failed to meet the -10% non-inferiority criterion for the post-dose 3 endpoint. This data suggests that interference with Prevnar 13 is more pronounced at higher antibody concentrations, and that Prevnar 13 is inferior to Prevnar in eliciting higher antibody concentrations to the 7 common serotypes; these higher antibody concentrations are thought to be necessary to prevent otitis media. Therefore, there are insufficient data to support an otitis media indication for Prevnar 13 for the prevention of otitis media caused by serotypes contained in the vaccine. Data from post-marketing OM surveillance studies may be submitted when available in support of an otitis media efficacy supplement.

The available data submitted to BLA 125324 support the approval of Prevnar 13 for the prevention of invasive disease cause by *S. pneumoniae* serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

4 Introduction and Background

4.1 Epidemiology of pneumococcal infections in children

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.[1] Before U.S. licensure of Wyeth Lederle's 7-valent pneumococcal conjugate vaccine, Prevnar (PCV7) in 2000, the seven pneumococcal serotypes in the vaccine caused 80% of IPD cases among young children.[1] After U.S. licensure of PCV7, the incidence of invasive pneumococcal disease (IPD) caused by each of the 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 in children aged < 5 years of age 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. According to Rodgers et al, 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 Prevnar 13 include 1, 3, 6A, 7, and 19A.[6,8,9,10] Based on data from 5 hospitals that make up the U.S. Pediatric Multicenter Pneumococcal Surveillance Study Group (Pittsburgh, Houston, San Diego, Los Angeles, and Little Rock), 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 Prevnar 13.[6,8]

4.2 Currently Available Interventions and Rationale for Chosen Formulation

Two vaccines are currently available in the US to protect against pneumococcal disease. The 23-valent pneumococcal polysaccharide vaccine (23vPS) is licensed in the U.S. for use in persons ≥ 50 years of age and persons ≥ 2 years of age who are at increased risk of pneumococcal disease.[11] It is composed of purified capsular polysaccharides from 23 pneumococcal serotypes. Each 0.5mL dose contains 25 µg of each polysaccharide. These T-independent antigens stimulate mature B-lymphocytes but not T-lymphocytes and induce an immune response that is neither long-lasting nor anamnestic upon subsequent challenge. In addition, polysaccharide vaccines are not used in infants and children < 2 years of age, because these children respond poorly to T-independent antigens. Data suggest that the 23vPS vaccine protects adults and the elderly against IPD, however no consistent vaccine effect has been observed for prevention of pneumonia.[12]

Prevnar includes capsular polysaccharides from *S. pneumoniae* serotypes 4, 6B, 9V, 14, 19F, and 23F and oligosaccharide from serotype 18C each individually conjugated to a non-toxic variant of diphtheria toxin, CRM_{197} (CRM, cross reacting material). Each 0.5 mL dose contains 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, 4 µg of saccharide for serotype 6B, 20 µg of CRM_{197} carrier protein, and 0.125mg of aluminum as aluminum phosphate adjuvant. Conjugation of pneumococcal saccharides to the CRM_{197} protein creates saccharide-protein complex which is capable of inducing a T-dependent immune response; thus T-helper cells are stimulated leading to a substantial primary response in infants and a strong booster response at reexposure. In addition, this response has been reported to reduce carriage and result in population effects beyond direct protection.[11]

4.3 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.[13]

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[14] and (2) an acute otitis media efficacy trial that evaluated PCV7 in Finland and involved tympanocentesis.[15] 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.[15]

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.

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 non-inferiority 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 pneumococcal 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 reference concentration, determined in an ELISA, was derived from pooled vaccine efficacy estimates from three clinical studies conducted in NCKP [13] and in American Indians [16] using Prevnar, and in South Africa using an investigational 9-valent pneumococcal conjugate vaccine.[17] 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 at least 0.35 µg/mL).[18] The pneumococcal IgG antibody reference concentrations (and vaccine efficacy estimates) from each of the three pooled studies were 0.20 µg/mL (VE=97.4%) in the NCKP study, 0.99 µg/mL (VE=76.8%) in the American Indian study, and 0.68 µg/mL (VE=90%) in the South African study.[18] The ELISA assay used to establish the 0.35 ug/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.[19]

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.[18] 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.[18]

There is currently no consensus regarding the serologic criteria for assessing the effectiveness of pneumococcal conjugate vaccines in children beyond 12-15 months of age. However, because the 0.35µg/mL reference value is intended primarily for the evaluation of immune responses in infants aged 6 months, evaluation of GMCs are viewed as more meaningful information than seroresponse rates ≥ 0.35µg/mL in children beyond 7 months of age. In additional, functional OPA data are viewed as important supportive data for children in this age group.

Pneumococcal IgG antibody primary endpointsfor infant studies
The proportion of infants 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 non-inferiority 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 Prevnar 13 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.

CBER also requested an evaluation of the proportion of subjects achieving an anti-pneumococcal IgG antibody response ≥ 1.0 µg/mL, because of the limitations of the statistical modeling used to determine the 0.35 µg/mL reference value, which were described above. This additional analysis was assessed one month after the third and one month after the fourth dose as a secondary endpoint.

Pneumococcal opsonophagocytic antibody exploratory endpoint
Evaluation of functional antibodies, as measured in an opsonophagocytic antibody (OPA) assay may be considered a preferable outcome measure, because opsonophagocytosis is thought to be 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. The OPA assay assesses the ability of anti-pneumococcal functional antibody (present in a serially diluted human serum specimen) to bind to pneumococcal bacteria in the presence of functional baby rabbit complement and promote bacterial engulfment and death by a phagocytic human cell line (differentiated HL-60 cells). The OPA titer is the reciprocal of the highest serum dilution giving 50% reduction in the number of bacterial colonies compared to the bacteria-effector cell complement control, which does not contain human serum.

OPA geometric mean titers (GMTs) and the proportion of subjects achieving an OPA titer ≥ 1:8 were evaluated as exploratory endpoints in a subset of 100 subjects per study group.The titer cutoff of ≥ 1:8 was chosen because 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 was associated with an OPA titer of 1:8 for the 7 serotypes in Prevnar.[19] This OPA titer cutoff, however, is not known to correlate with effectiveness.

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 Prevnar 13 and PCV7 recipients were viewed as a more meaningful expression of the ability of Prevnar 13 to elicit opsonic activity.[20]

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.

4.4 Previous Human Experience with the Product
The data submitted in BLA 125324 describes the first human experience with Prevnar 13.

4.5 Chronology of regulatory milestones in the development of Prevnar 13

December 17, 2003	Pre-IND Meeting
May 11, 2006	End of Phase 2 Meeting
October 10, 2008	Clinical pre-BLA meeting
May 8, 2008	Fast Track Designation
September 15, 2008	Approval to submit BLA as rolling submission
September 22, 2008	First Rolling Submission
October 27, 2008	Second Rolling Submission
December 18, 2008	Third Rolling Submission
March 31, 2009	Final submission (PDUFA review clock started)
July 22, 2009	PeRC Meeting

August 10, 2009 Major Amendment Acknowledgement letter issued (re 7/23/09 CMC amendment)
November 18, 2009 VRBPAC Meeting

5 Significant Findings From Other Review Disciplines

5.1 Biostatistics

A CBER statistician reviewed the clinical effectiveness and safety data submitted to the BLA. The reviewer noted that for studies not conducted under U.S. IND, FDA/CBER did not review or concur with the study design before submission of the BLA. The reviewer also noted that the pivotal immunogenicity study (study 004) showed that serotypes 6B, 9V, and 3 failed to meet non-inferiority criterion of the primary objective. Since the study was designed without alpha adjustment, statistically non-inferiority is claimed only if all 13 serotypes meet the pre-specified criterion. Please refer to the CBER statistical review for more details.

5.2 Bioassay Statistical Review

A CBER statistician reviewed statistical issues in validation of bioassay. The reviewer concluded that no major bioassay-related statistical issues were noted that may prevent the submission from being approved by FDA. Assays reviewed included pneumococcal enzyme-linked immunosorbent assays, Hib ELISA, bordetella pertussis antigens ELISAs, -----b(4)----------ELISA.

5.3 Chemistry, Manufacturing, and Controls

A CBER product reviewer conducted a review of the manufacturing process. The reviewer recommends approval of Prevnar 13 on the basis of the information submitted to the BLA and post-marketing commitments that the applicant has agreed to conduct.

The reviewer noted that the drug formulation has changed from that of Prevnar. Polysorbate 80 was added to a final concentration of 0.02% and succinate buffer was added for ----b(4)----------

There were several concerns raised by the product reviewer in the course of the review concerning the manufacturing process, in-process specifications, and product lot release and stability testing. Issues identified by the product reviewer will be addressed by completion of a series of post-marketing commitments. Please refer to the CMC review of Prevnar 13 for more details.

5.4 Serology Methodology

CBER reviewers reviewed serology methodology used for the pneumococcal ELISA, pneumococcal OPA, *H. influenzae* type B ELISA, pertussis ELISA assays, polio neutralization assay, ---b(4)----------and meningococcal serum bactericidal assay. The reviewers concluded that the assays were appropriate for their intended use and that they were properly validated.

5.5 Bioresearch Monitoring (BIMO)

The BIMO data audit inspections focused on two phase 3 U.S. studies submitted to the BLA and the laboratory that performed pneumococcal assays. CBER's BIMO office issued high priority inspection assignments for the following 5 clinical investigator sites:

- Protocol 6096A1-3005, site 013 in Nampa, Idaho: Principle investigator: Richard Aguilar, M.D.
- Protocol 6096A1-3005, site 032 in Fayetteville, AR: Principle investigator: Terry S. Payton, M.D.
- Protocol 6096A1-3005, site 044 in Murray, Utah: Principle investigator: David C. Hurley, M.D.
- Protocol 6096A1-004, site 001 in Little Rock, Arkansas: Principle investigator: Anthony Johnson, M.D.

- Protocol 6096A1-004, site 021 in Park Ridge, Illinois: Principle investigator: Kristin Lundblad, M.D.

In addition, because approval hinges on immunogenicity assay data, an inspection assignment was issued for the applicant's laboratory that performed the pneumococcal IgG and OPA immunological assays in Pearl River, New York.

The BIMO reviewer concluded that the BIMO inspections did not reveal problems that impact the data submitted in the application.

5.6 Animal Pharmacology/Toxicology

A CBER toxicologist reviewed the data submitted from five toxicology studies evaluating Prevnar 13. The reviewer concluded that adequate nonclinical toxicology data were presented and that it is safe to approve Prevnar 13 from a toxicology stand point.

6. Clinical Data Sources, Review Strategy, and Data Integrity

6.1 Tables of Clinical Studies

The clinical section of the application contains study reports for 16 clinical studies.

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
Pivotal Infant and ToddlerStudies						
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
Final Formulation						
6096A1-009 (Poland)	13vPnC +/- Polysorbate 80	2,3,4,12	13vPnC without P80	Pentaxim[b], ActHIB (2,3,4) Engerix-B[b] (2), Priorix[b] (12)	500[a]	-
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
6096A1-3011 (US)	Safety and immunogenicity of 1 or 2 doses of 13vPnC in children < 5 yrs of age (cohort 1) with ≥ 3 prior PCV7 doses.[c]	Catch-up	None	N/A	307	-

Supporting Studies						
6096A1-002 (USA)	Phase 1 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[d]	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[d]	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[d]	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[d]	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] Safety results from cohort 2 and safety and immunogenicity results from children 5 to 17 yrs of age will be submitted as a supplement following licensure.
[d] For concomitant antigen and safety assessments only.

6.2 Good Clinical Practices (GCP) and Data Integrity

Results of facilities inspections and bioresearch monitoring data audit inspections of 5 clinical investigators and the laboratory that performed the pneumococcal IgG and OPA immunological assays did not reveal any problems that impact the quality or integrity of the data submitted in the BLA.

6.3 Financial Disclosures

On Form 3454, the applicant certified that the following statement is correct:

> *"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."*

7.0 Pivotal Clinical Studies

7.1. Clinical Study Protocol # 6096A1-004

Clinical trials.gov registry identifier: NCT00373958

CSR #69238: infant series, toddler dose, and 6-month follow-up analyses.

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

7.1.1 Objective/Rationale

The study was designed to meet the following objectives:

7.1.1.1 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 Pediarix given with 13vPnC are noninferior to the immune responses induced by Pediarix 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 [ActHIB] given with 13vPnC is noninferior to the immune response induced by PRP [ActHIB] given with PCV7 when measured 1 month after the 3rd dose.

7.1.1.2 Safety objective

To evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence of local injection site reactions, systemic events, and adverse events (AEs).

7.1.1.3 Secondary objectives

1. To demonstrate that, one month post-vaccination, the immune responses induced by ProQuad, when coadministered with 13vPnC, are noninferior to immune responses induced by ProQuad when given with PCV7. Responses to the following antigens in ProQuad were assessed: measles, mumps, rubella, and varicella.
2. 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.
3. To assess the immune response to PRP, at alternate cut off levels, after ActHIB when coadministered with 13vPnC, compared to the immune response induced by ActHIB given with PCV7 when measured 1 month after the infant series.
4. To assess the immune response to PRP, at alternate cut off levels, 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.

7.1.1.4 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).

Clinical Reviewer Note: Tetanus, Hepatitis B, and Polio virus types 1, 2, and 3 were evaluated in study 6096A1-3005.

7.1.2 Design Overview

This study was a phase 3, parallel-group, randomized, active-controlled, double-blind, multi-center trial.

Table 2. Study 6096A1-004 design

Population n= 640 (Planned enrollment)	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)			

Source: 125324/0.1,m5.3.5.1, CSR-69238-protocol-amend.pdf.

Clinical Reviewer Note: PedvaxHIB was used as the fourth Hib dose because ActHIB is only licensed for administration as a fourth dose at 15-18 months of age.

7.1.3 Protocol

7.1.3.1 Population

7.1.3.1.1 Study Period

The study period was September 18, 2006 to June 2, 2008.

7.1.3.1.2 Study sites and recruitment

Study 6096A1-004 was conducted at 38 sites in the United States.

7.1.3.1.3 Inclusion Criteria

1. Infants aged 2 months (42-98 days) at enrollment.
2. Available for entire study period and whose parent(s) / legal guardian(s) could be reached by telephone.
3. Healthy as determined by medical history, physical exam, and judgment of the investigator.
4. Parent / legal guardian must be able to complete all relevant study procedures during study participation.

7.1.3.1.4 Exclusion Criteria

1. Previous vaccination with licensed or investigational pneumococcal vaccine
2. Previous vaccination with Hib conjugate, diphtheria, tetanus, pertussis, polio, hepatitis A, measles, mump, rubella, or varicella vaccines
3. Previous anaphylactic reaction to any vaccine or vaccine-related component
4. Contraindication to vaccination with Hib conjugate, diphtheria, tetanus, pertussis, polio, hepatitis B, hepatitis A, measles, mumps, rubella, varicella, or pneumococcal vaccines
5. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection
6. Known or suspected immune deficiency or suppression
7. History of culture-proven invasive disease caused by *S. pneumoniae* or *H. influenzae* type b (Hib); or confirmed measles, mumps, rubella, or varicella infection
8. Known major congenital malformation or serious chronic disorder

9. Significant neurological disorder or history of seizure, including febrile seizure, or significant stable or evolving disorders, such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Did not include resolving syndromes due to birth trauma such as Erb palsy.
10. Receipt of blood or gamma-globulin products (including hepatitis B immunoglobulin and monoclonal antibodies). Topical and inhaled corticosteroids were permitted. Local anesthetic cream could be applied before blood draws.
11. Participation in another investigational trial. Participation in purely observational studies was acceptable.
12. Direct descendant (i.e. child, grandchild) of study site personnel

7.1.3.1.5 Criteria for Temporarily Delaying Vaccine Administration

1. A febrile illness (rectal temperature ≥ 38.0^{o}C) or other acute illness within 48 hours before study vaccine administration.
2. Receipt of non-live vaccine within prior 2 weeks or live vaccine within prior 4 weeks.
3. Subject is < 5 days into a course of antibiotic therapy for other acute illness.

7.1.3.1.6 Criteria for Withdrawal of a Subject From the Study

The criteria for withdrawal included, but were not limited to, the items listed below. Every effort was made to collect safety data for withdrawn subjects and to determine the reason why a subjects\ withdrew early or failed to return for study visits.

1. Request for withdrawal by parent / legal guardian
2. Failure to comply with study procedures
3. Loss to follow-up
4. Clinically significant AEs or AEs constituting contraindications, precautions, or exclusions to further vaccination

7.1.3.2 Concomitant medications

Antipyretic medications were permitted to prevent or treat symptoms related to study vaccination, and this information was collected on days 1 to 7 after vaccination. Data on the use of other concomitant medications, other than antipyretic medications, were not collected.

7.1.3.3 Vaccine administration

Children received the following study vaccines as per protocol.

13vPnC: Each 0.5ml dose contains 2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4ug saccharide for 6B individually conjugated to cross-reacting material 197 (CRM_{197}). The total concentration of CRM_{197} is 29ug. The final formulation contains 5mM succinate buffer and 0.125 mg aluminum as AlPO4. The vaccine is formulated as a liquid and appears as a homogeneous, white suspension after shaking. The vaccine was filled in containers that were identical to those containing PCV7. Route: intramuscular (IM), anterolateral left thigh. Lot number: 7-5093-003A.

PCV7 [Prevnar; WLVP]: Each 0.5 ml dose includes 2 ug of saccharide from pneumococcal serotypes 4, 9V, 14, 18C, 19F, 23F; 4 ug serotype 6B, 20ug CRM_{197} carrier protein, and 0.125mg of aluminum as $AlPO_4$ adjuvant. The vaccine is formulated as a white, liquid suspension, and packaged in single-dose vials. Route: IM, anterolateral left thigh. Lot number: 7-5092-005A.

DTaP-HBV-IPV [Pediarix; GSK]: The main components in each 0.5ml dose include diphtheria toxoid (30 international units (IU)), tetanus toxoid (40 IU), 3 pertussis antigens (PT 25 µg, FHA 25 µg, PRN (69-kDa outer membrane protein; 8 µg), HBsAg (recombinant) 10 µg, inactivated poliovirus type 1 (Mahoney; 40 D-antigen Units (DU)), type 2 (MEF-1; 8 DU), and type 3 (Saukett; 32 DU), 4.5 mg NaCl, and aluminum adjuvant (not more than 0.85 mg by assay). The diphtheria, tetanus, and pertussis antigens are individually adsorbed onto aluminum hydroxide; the hepatitis B component is adsorbed onto $AlPO_4$. Each dose also contains ≤ 100 µg residual formaldehyde and ≤ 100 µg polysorbate 80. Neomycin sulfate and polymyxin B may also be present at ≤ 0.05ng and ≤ 0.01 ng respectively per dose. The vaccine is formulated without preservatives. The vaccine appears as a turbid, white liquid suspension (after shaking

vigorously), and it is packaged in single-dose vials. Route: IM, upper anterolateral right thigh, at least 1.5 to 2 inches apart from ActHIB conjugate vaccine injection site. Lot numbers: AC21B065AA, UE764AA, UE767AA, UE784AA, UE785AA, UE836AA, UE840AA, and UE845AA.

PRP-T [ActHIB; Sanofi Pasteur SA]: Each 0.5ml dose contains 10ug purified capsular polysaccharide (PRP) conjugated to 24ug of inactivated tetanus toxoid and 8.5% sucrose. The vaccine is formulated as a lyophilized powder and packaged in a single dose vial. When reconstituted with saline, the vaccine is a clear, colorless liquid and contains to preservative. Route: IM, lower anterolateral right thigh, at least 1.5 to 2 inches apart from Pediarix injection site. Lot number: UE846AA, UE849AA, UE853AA, UE854AA, UE856AA, UE859AA, UE862AA, UE962AA, and UF052AA.

PRP-OMP [PedvaxHIB; Merck & Co., Inc.]: Each 0.5 mL dose contains 7.5 µg of *Haemophilus influenzae* type b PRP conjugated to 125 µg of *Neisseria meningitidis* OMPC (outer membrane protein complex) and 225 µg of aluminum as amorphous aluminum hydroxyphosphate sulfate in 0.9% sodium chloride. The vaccine appears as a liquid, slightly opaque, white suspension. Route: IM, lower anterolateral right thigh, at least 1.5 to 2 inches apart from VAQTA injection site. Lot number: 1275F.

MMRV [ProQuad; Merck & Co., Inc.]: This is a combined, attenuated, live-virus vaccine which contains no preservative. Each 0.5 mL dose contains the following active ingredients: measles virus (not < 3.00 $\log_{10}$ $TCID_{50}$ 1), mumps virus (not < 4.30 $\log_{10}$ $TCID_{50}$), rubella virus (not < 3.00 $\log_{10}$ $TCID_{50}$), and Oka/Merck varicella virus (a minimum of 3. 99 $\log_{10}$ plaque forming units (PFU). Each 0.5 mL dose contains no more than 21 mg sucrose, 11 mg hydrolyzed gelatin, 2.4 mg sodium chloride, 1.8 mg sorbitol, 0.40 mg monosodium L-glutamate, 0.34 mg sodium phosphate dibasic, 0.31 mg human albumin, 0.17 mg sodium bicarbonate, 72 µg potassium phosphate dibasic, residual components of MRC-5 cells, < 16 µg neomycin, 0.5 µg bovine calf serum, and other buffer and media ingredients. The lyophilized vaccine is a white to pale yellow compact crystalline plug. When reconstituted, the vaccine is a clear pale yellow to light pink liquid. Route: subcutaneously (SQ) into left or right deltoid. Lot number: 0616U and 3042U.

Hepatitis A [VAQTA; Merck & Co.]: Each 0.5ml dose of the Pediatric/Adolescent formulation contains 25 units of hepatitis A virus antigen, which is purified and formulated without a preservative and adsorbed onto about 0.225 µg or aluminum as amorphous aluminum hydroxyphosphate sulfate. The vaccine also contains 35 µg of sodium borate as a pH stabilizer in 0.9% sodium chloride. VAQTA is an inactivated whole virus vaccine derived from hepatitis A virus grown in cell culture in human MRC-5 diploid fibroblasts. It contains inactivated virus of a strain that was originally derived by further serial passage of a proven attenuated strain, and is a sterile suspension. Route: IM, upper anterolateral right thigh, at least 1.5 to 2 inches apart from PedvaxHIB injection site. Lot number: 0018U.

Permitted vaccines included the following: rotavirus vaccine; a second dose of a commercially available hepatitis A vaccine (6-12 months after the first dose); influenza vaccine beginning 10 days after dose 3 until 14 days before dose 4 and beginning 10 days after dose 4; IPV and DTaP after the blood draw at the 13-16 month visit; hepatitis B vaccine may be given from birth up to 14 days before the 1st study vaccine dose.

7.1.3.4 Endpoints

7.1.3.4.1 Primary Immunogenicity Endpoints

1. Proportion of subjects with pneumococcal serotype-specific IgG antibody concentrations ≥ 0.35 µg/mL 1 month post-dose 3
2. Pneumococcal serotype-specific IgG geometric mean concentration (GMC) measured 1 month after dose 4
3. Proportion of subjects with anti-diphtheria ELISA antibody concentrations ≥ 0.1 IU/mL 1 month after 3rd dose

1 $TCID_{50}$ = 50% tissue culture infectious dose

4. Proportion of Prevnar 13 recipients with anti-pertussis (PT, FHA, and PRN) antibody concentrations 1 month after the 3rd dose ≥ the observed anti-pertussis antibody concentration achieved by 95% of PCV7 recipients
5. Proportion of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL 1 month after 3rd dose

Clinical Reviewer Note: Historically, some inconsistent differences in responses to acellular pertussis antigens have been observed in prelicensure clinical trials in which Prevnar was administered concomitantly with a DTaP vaccine.[21,22,23] These inconsistencies and their clinical relevance have not yet been altogether resolved.[22,23,24] CBER's conventional approach for defining vaccine response to each pertussis antigen is based on a fold-rise in antibody level. Specific criteria are based on the prevaccination antibody level and the lower limit of quantitation (LLOQ) of the assay. Prevaccination antibody levels are needed to assess for potential nonresponders. The presence of maternal antibodies has been reported to inhibit vaccine antibody response (but not priming or boosting) for non-live vaccines such as pertussis.[25] The applicant chose not to revise the study design to include a pre-vaccination blood draw, as this could result in difficulty in enrolling a sufficient number of subjects.

The cutoff for evaluation of anti-pertussis antibody responses in the initial study protocol was ≥ 5 EU/mL. CBER requested that this be revised, because 5 EU/mL is below or too close to the LLOQ for the pertussis ELISA assays. The primary immunogenicity endpoint for pertussis antigens was modified by the applicant to replace a cutoff of 5 EU/mL with serum IgG concentration attained by 95% of the subjects in the PCV7 group (see section 7.1.3.7 Changes in the Study Protocol). The serum IgG concentration attained by 95% of subjects in the PCV7 group, and thus used for comparisons between 13vPnC and PCV7 subjects, were as follows:

- FHA: ≥ 40.5 EU/mL
- PT: ≥ 16.5 EU/mL
- PRN: ≥ 26 EU/mL

Despite being underpowered for the anlaysis, CBER requested a separate analysis of anti-pertussis GMCs using a non-inferiority criterion of an upper limit of the 95% CI for the GMC ratio (13vPnC/PCV7) > 0.67 (1.5 fold).

The above modified endpoints for pertussis antigen assessments were found to be acceptable by CBER (Please also refer to Dr. Drusilla Burns' review of the pertussis assays used for clinical serology studies).

7.1.3.4.2 Secondary Immunogenicity Endpoints

1. Proportion of subjects achieving pneumococcal serotype-specific IgG antibody concentrations ≥ 0.35 µg/mL at 1 month post-dose 4
2. Proportion of subjects achieving pneumococcal serotype-specific IgG antibody concentrations ≥ 1.0 µg/mL at 1 month post-dose 3 and 1 month post-dose 4
3. Pneumococcal serotype-specific IgG GMC at 1 month post-dose 3 and before dose 4
4. If any pneumococcal serotype failed non-inferiority at the 0.35µg/mL level post-dose 3, then an additional 0.15µg/mL level would be examined
5. Proportion of subjects achieving post-dose 4 anti-measles antibody concentrations ≥ 1.10 index value (I.V.) units
6. Proportion of subjects achieving post-dose 4 anti-mumps antibody concentrations ≥ 1.10 I.V. units
7. Proportion of subjects achieving post-dose 4 anti-rubella antibody concentrations ≥ 15.0 IU/mL
8. Proportion of subjects achieving post-dose 4 anti-varicella antibody concentrations ≥ 1.09 I.V. units by ELISA
9. For ActHIB, proportion of subjects achieving a post-dose 3 anti-PRP antibody alternative cutoff level ≥ 1.0 µg/mL
10. For PedvaxHIB, proportion of subjects achieving an anti-PRP antibody concentration ≥ 0.15 µg/mL and the proportion of subjects achieving an alternative anti-PRP concentration ≥ 1.0 µg/mL at one month post-dose 4

7.1.3.4.3 Safety Endpoint

The primary endpoints for safety comparisons include incidence rates of solicited local injection site reactions, solicited systemic events (including fever and use of antipyretic medications), and other unsolicited AEs occurring within 7 days after each vaccination.

Solicited local reactions collected included erythema, induration, and tenderness at the site of the pneumococcal vaccine injection. Solicited systemic events included fever (rectal temperature ≥ 38.0^{o}C and use of antipyretic medications to treat and to prevent symptoms, decreased appetite, irritability, increased sleep, decreased sleep and urticaria.

7.1.3.4.4 Exploratory Immunogenicity Endpoint

Proportion of subjects achieving a serotype-specific OPA antibody titer ≥ 1:8 measured 1 month after the 3rd dose and 1 month after the 4th dose, in a subset of 100 subjects per vaccine group.

Clinical Reviewer Note: OPA assays were performed on sera from a subset of subjects because of the laborious nature of the assay.

7.1.3.5 Surveillance

7.1.3.5.1 Immunogenicity Monitoring

Blood samples were obtained (~5 mL each) for immunogenicity analyses one month (28-42 days) after the third dose (~ 7 months of age), prior to the fourth dose (365-455 days of age; ~ 12-15 months of age), and one month (28-42 days) after the fourth dose for all subjects.

Table 3 summarizes the serological assays for pneumococcal and concomitant vaccine antigens. The pneumococcal ELISA assay employed -----b(4)---------- Pneumococcal assay values below the lower limit of quantification were adjusted to half the lower level of quantification for analysis. Indeterminate values were not assigned a numerical value. There was no imputation or estimation of missing values, which were excluded from analyses.

Table 3. Study 6096A1-004, Serological Assays for Pneumococcal and Concomitant Vaccine Antigens

Antigen	Assay	Units	Post-dose	Laboratory
13 pneumococcal serotypes	ELISA IgG Antibodies	µg/mL	3 & 4	EPP-CTAD[a], Wyeth, Pearl River, NY
	OPA	titers	3 & 4	EPP-CTAD[a], Wyeth, Pearl River, NY
Diphtheria toxoid	ELISA IgG antibodies	IU/mL	3	----b(4)----------
Pertussis (PT, FHA. PRN)	ELISA IgG antibodies	ELISA units/mL	3	----b(4)----------
Polyribosylribitol phosphate (PRP)	ELISA IgG antibodies	µg/mL	3 & 4	----b(4)----------
Measles, Mumps, & Varicella	Captia™ Measles IgG Captia™ Mumps IgG Captia™ VZV IgG[c]	I.V. units	4	----b(4)----------
Rubella	---b(4)---------- Rubella G assay[d]	IU/mL	4	----b(4)----------

[a] Early Phase Programs – Clinical Testing and Assay Development (EPP-CTAD)
[b] -----b(4)----------
[c] FDA approved ELISAs manufactured by Trinity Biotech USA (Jamestown, NY); automated ---b(4)----------.
[d] ----------b(4)----------

Source: 125324/0.1,m5.3.5.1, CSR-69238-report body, page 15 (Table 3-1); and m5.3.1.4.

7.1.3.5.2 Safety Surveillance / Monitoring

1. Immediate reactions: 30 minute observation

2. Solicited AE: local and systemic events monitored by parent(s)/legal guardian(s) and recorded in an e-diary on days 1-7 after each vaccination (day of vaccination = day 1). Reactions still present on the 7th day after vaccination (or the last recorded day of the e-diary) were followed until resolution (end-date capture).

    a. Local AE: erythema, induration, and tenderness at administration site of pneumococcal vaccine (left leg)
    Erythema and induration grading scale: 0: absent = none (0 caliper units); 1: mild = 0.5 - 2.4cm (1-4 caliper units); 2: moderate = 2.5 - 7.0cm (5-14 caliper units); 3: severe = > 7.0cm (> 14 caliper units). If a reaction is > 7.0cm, the parent/legal guardian was to contact study personnel for evaluation at an additional study visit. Measurements were of the largest diameter and were rounded up to the nearest whole number. One caliper unit = 0.5 cm.
    Tenderness grading scale: not present, present, present and interferes with limb movement.

    b. Systemic AE: decreased appetite, irritability, increased sleep, decreased sleep, hives (urticaria), fever (core (rectal) temperature > 38.0^{o}C), and use of antipyretic medication. Rectal temperature was measured at bedtime and any time a fever was suspected. The highest temperature for each day was recorded in the e-diary. If fever developed, temperature was measured daily until subject was afebrile for 24 hours.
    Temperature grading scale: absent: < 38.0^{o}C; mild: ≥ 38.0 to ≤ 39.0^{o}C; moderate: > 39.0 to ≤ 40.0^{o}C; severe: > 40.0^{o}C
    Rash categorization: Parents instructed to schedule a clinic visit if a rash is suspected. Clinical assessment of a rash will result in one of the following categorizations:
        - Rash no longer present and history not consistent with urticaria.
        - Rash no longer present but history is consistent with urticaria.
        - Rash present but clinical findings not consistent with urticaria. Alternative diagnosis should be specified as an adverse event.
        - Rash present and clinical findings consistent with urticaria.

    No grading scale for other solicited systemic AE.

3. Unsolicited AEs and nonstudy vaccinations: collected from signing of the consent form to the 7 month visit (visit 4), and from the 12-15 month visit (visit 5) to the 13-16 month visit (visit 6); from visit 4 to visit 5, only newly diagnosed chronic medical conditions, hospitalizations, and SAEs were captured via a telephone call.
    a. An AE was defined as any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observation (including clinically significant worsening of a pre-existing condition and AEs occurring from overdose, abuse, or discontinuation of a test article).
    b. Unsolicited AEs were collected based on clinical evaluation during a study visit, oral questioning during a study visit, and ancillary signs and symptoms recorded by parent(s)/legal guardian(s) on the e-diary as a memory aid.

4. SAEs: collected throughout study period (visit 1 to 6 months after last vaccination). An SAE was defined as an AE that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in a persistent or significant disability or incapacity, resulted in cancer, resulted in a congenital anomaly or birth defect, or other important medical events that, based on medical judgment, may have jeopardized the subject and required medical or surgical intervention to prevent any of the aforementioned outcomes.

5. A 6-month safety follow-up phone call was conducted to record any newly diagnosed chronic medical conditions, hospitalizations, and SAEs that occurred since the last study visit. An attempt was made to contact the parent(s)/legal guardians(s) of all subjects including those who had discontinued.

6. Mandatory unscheduled visits: for evaluation of large (>14 caliper units or 7cm) local reactions or evaluation of a rash (to assess for urticaria). Study staff will measure the subject's rectal temperature, the minimum and maximum diameter of erythema / induration and the degree of tenderness. Any reported rashes will also be assessed for presence of urticaria.

7. Electronic diaries (based on a personal digital assistant or equivalent technique):
    a. Allowed recording of subject AEs and use of antipyretic medication. Entries are only allowed within a fixed time-window. AEs reported on the e-diary will be transferred electronically to the e-diary vendor (a trusted 3rd party) and will be available for review by investigators at all times via an internet-based portal. This data is also periodically transferred electronically into Wyeth's database for analysis and reporting.
    b. Allows recording of signs and symptoms, thereby functioning as a memory aid from visit 1 through 6. Investigators will be required to review e-diary data on-line at frequent intervals and report relevant information from this review in the CRF.

8. Investigator was to follow-up on all AEs, SAEs and other reportable information until the event subsided, resolved or stabilized; in the event of permanent impairment, follow-up was required even if extended beyond the study closeout visit.

9. Any unanticipated risks must be promptly reported to the IRB.

10. SAEs, other reportable information that must be handled like an SAE, and medication errors must be reported within 1 business day by fax and phone or email confirmation of receipt.

Table 4. Study 6096A1-004 flowchart

Visit No.	1	2	3	4	5	6	7
Visit ID	2-Month Visit	4-Month Visit	6-Month Visit	7-Month Visit	12-15-Month Visit	13-16 Month Visit	18-21 Month Visit
Study Interval	Vaccine dose 1	Vaccine dose 2	Vaccine dose 3	Post-infant series	Vaccine dose 4	Post-toddler dose	6-Month Follow-up
Visit Window	42-98 days of age	42-70 days after visit 1	42-70 days after visit 2	28-42 days after visit 3	365-455 days of age	28-42 days after visit 5	165-210 days after last study vaccine
Informed consent	X						
Review inclusion/ exclusion/delay criteria	X						
Medical Hx/PE	X						
Core rectal temp	X	X	X		X		
Randomization	X						
Study vaccination & 30 minute observation	X	X	X		X		
Pediarix vaccination	X	X	X				
ActHIB vaccination	X	X	X				
ProQuad vaccination					X		
VAQTA vaccination					X		
PedvaxHIB vaccination					X		
Confirm continued eligibility		X	X	X	X	X	
AE collection	⟷ x ⟶				⟷ x ⟶		
SAE collection	⟷ x ⟶						
Obtain 5 mL blood sample				X	X (before 4th dose)	X	
E-diary, thermometer, calipers provided	X	X	X		X		
Assess acute reactions	Day 1 to 7*	Day 1 to 7	Day 1 to 7		Day 1 to 7		
Use of antipyretic medication	Day 1 to 7	Day 1 to 7	Day 1 to 7		Day 1 to 7		
Telephone call							X

*Day of vaccination is considered day 1.
Source: 125324/0.1,m5.3.5.1, CSR-69238-protocol-amend, pages 25-26 (Table 8-1)

7.1.3.6 Statistical considerations

Blinding:
This is a double blind study. The appearance of 13vPnC and PCV7 were identical. The database was to remain blinded until all data were collected, all data queries were resolved, and the 6-month follow-up data were received for all subjects. The analyses were performed by the study statistician who was provided with randomized vaccine information as well as actual vaccine packaging assignment information for the primary analysis. Results of unblinded assay data were not to be available to applicant personnel involved with the study except as necessary to perform the primary analysis. The database was unblinded for the final analysis of the 6-month follow-up data.

Randomization:
Eligible subjects were prospectively randomized in a 1:1 allocation into 1 of 2 treatment groups using Wyeth's Clinical Operations Randomization Environment II (CORE II), Interactive Voice Response System (IVRS) or equivalent system. Only subjects who withdrew before randomization could be replaced with additional subjects.

The random subset of 200 subjects for the OPA assays was selected once study enrollment was complete. Subjects were randomly ordered, and then the first 100 subjects in each vaccine group were selected. Additional subjects, if needed, were to be selected from the vaccine group of the subject they were replacing.

7.1.3.6.1 Sample Size/Statistical Power

Sample size estimation was based on the proportion of responders ≥ 0.35 µg/mL (measured by ELISA) for pneumococcal serotypes from study 6096A1-003 and GMC for pneumococcal serotypes from study D140-P001 for each vaccine group. Data from Wyeth studies 6096A1-003, D139-P500, and D140-P001 were used for Pediarix, ActHIB, and ProQuad concomitant vaccine antigens.

Overall a sample size of 250 evaluable subjects per group after the infant series and 240 evaluable subjects per group after the toddler dose will provide at least 85% overall power to declare non-inferiority for all 26 pneumococcal comparisons and 5 concomitant vaccine antigen comparisons (diphtheria, pertussis toxoid, filamentous hemagglutinin, pertactin, and PRP (Hib)) using a 2-sided, type I error of 0.05, and a non-inferiority criterion of – 0.10 for proportions and a 2-fold non-inferiority criterion for GMCs. Assuming a dropout rate of 15% to 25%, 320 subjects per group were to be enrolled.

Clinical Reviewer Note: This study was not powered to demonstrate lack of interference of immune responses when Prevnar 13 is concomitantly administered with routine childhood vaccines to prevent measles, mumps, rubella, or varicella. These concomitant vaccine antigens were assessed as secondary study objectives; the non-inferiority criteria was -5% for measles, mumps, and rubella and -10% for varicella.

7.1.3.6.2 Study Cohorts Analyzed

Four analysis populations were defined for the immunogenicity analyses: evaluable infant, all-available infant, evaluable toddler, and all-available toddler. The all-available infant population included all subjects who had at least 1 valid and determinate post-dose 3 assay result. The all available toddler population included all subjects who had at least 1 valid and determinate assay result before (excluding post-dose 3) or after the toddler dose. Immunogenicity analyses were based on subjects' randomized treatment assignment.

The evaluable infant immunogenicity population included subjects who:

1. Met study eligibility criteria
2. Were randomized to receive the treatment
3. Were ≥ 41 and ≤ 99 days of age on the day of first vaccination
4. When vaccinated, received the vaccine to which they were randomly assigned at all 3 doses
5. Received all 3 study vaccinations
6. When vaccinated, received all expected study concomitant vaccinations at all 3 doses
7. Had at least 1 valid and determinate assay result after the third vaccination, which contributed to a planned analysis
8. Had the blood draw after the third dose within the required time frame (27 to 56 days after the third vaccination).
9. Received no prohibited vaccines before the blood draw after the third dose.
10. Had no other protocol violations.

The evaluable toddler immunogenicity population included subjects who:

1. Met study eligibility criteria
2. Were randomized to receive the treatment
3. Were ≥ 41 and ≤ 99 days of age on the day of first vaccination
4. Were ≥ 364 and ≤ 456 days of age at the toddler dose
5. When vaccinated, received the vaccine to which they were randomly assigned at all 4 doses
6. Received all 4 study vaccinations
7. When vaccinated, received all expected study concomitant vaccinations at all 4 doses
8. Had at least 1 valid and determinate assay result after the toddler dose, which contributed to a planned analysis
9. Had the posttoddler blood draw within the required time frame (27 to 56 days after the 4^{th} dose).
10. Received no prohibited vaccines before the blood draw after the toddler dose.
11. Had no other protocol violations.

7.1.3.6.3 Statistical Analyses

7.1.3.6.3.1 Immunogenicity analyses

Primary hypotheses:

1. To demonstrate that the antibody response to each of the 7 common pneumococcal serotypes one month after the 3rd 13vPnC dose is non-inferior to the corresponding antibody response after the 3rd dose of PCV7. [antibody response: proportion of subjects achieving IgG antibody concentration ≥ 0.35 µg/mL]
   Criteria for non-inferiority (1 month after the 3rd vaccination): Lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC group – *p*PCV7 group) > -0.1; *p* is the percentage of subjects with pneumococcal serotype-specific IgG concentration ≥ 0.35 ug/mL

2. To demonstrate that the antibody response to each of the 6 additional pneumococcal serotypes one month after the 3rd 13vPnC dose is non-inferior to the lowest response among the 7 serotypes contained in PCV7. [antibody response: proportion of subjects achieving IgG antibody concentration ≥ 0.35 µg/mL]
   Criteria for non-inferiority (1 month after the 3rd vaccination): Lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC group – *p*lowest response in PCV7 group) > -0.1; *p* is the percentage of subjects with pneumococcal serotype-specific IgG concentration ≥ 0.35 ug/mL

3. To demonstrate that the antibody response to each of the 7 common pneumococcal serotypes one month after the 4th 13vPnC dose is non-inferior to the corresponding antibody response after the 4th PCV7 dose. [antibody response: log of geometric mean IgG antibody concentration]
   Criteria for non-inferiority(1 month after the 4th vaccination): Lower limit of the 2-sided 95% CI for the GMC ratio (13vPnC / PCV7) > 0.5 (2-fold criterion)

4. To demonstrate that the antibody response to each of the 6 additional pneumococcal serotypes one month after the 4th 13vPnC dose is non-inferior to the lowest response among the 7 serotypes contained in PCV7. [antibody response: log of geometric mean IgG antibody concentration]
   Criteria for non-inferiority (1 month after the 4th vaccination): Lower limit of the 2-sided 95% CI for the GMC ratio (13vPnC / lowest serotype in PCV7 group) > 0.5 (2-fold criterion)

5. To demonstrate that the antibody response to diphtheria and pertussis antigens contained in DTaP-HBV-IPV (Pediarix®), when co-administered with 13vPnC, is non-inferior to corresponding antibody responses when Pediarix® is administered concomitantly with PCV7.

   Diphtheria criteria for non-inferiority (1 month after the 3rd vaccination): Lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC group – *p*PCV7 group) > -0.1; *p* is the percentage of subjects with anti-diphtheria antibody ≥ 0.1 IU/mL.

   Pertussis criteria for non-inferiority: The lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC group – *p*PCV7 group) > -0.1; *p* is the seroresponse rate for each pertussis antigen (PT, FHA, and PRN). The antibody level achieved by 95% of subjects in the PCV7 group (in study 6096A1-004) will be the cutoff value for subjects in the 13vPnC group. For the PCV7 group, the seroresponse rate will be ~ 95% as defined by the pre-specified cut-off value.

6. To demonstrate that, following a 3-dose primary vaccination course, the immune response to PRP, when given with 13vPnC, is non-inferior to the immune response to PRP, when given with PCV7.
   Criteria for non-inferiority (1 month after the 3rd vaccination): Lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC group – *p*PCV7 group) is > -0.1, where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration > 0.15 µg/mL.

Secondary hypotheses:

1. To demonstrate that, one month post-vaccination, the immune responses induced by ProQuad, when coadministered with 13vPnC, are noninferior to immune responses induced by ProQuad when given with PCV7. Responses to the following antigens in ProQuad were assessed: measles, mumps, rubella, and varicella.
   Criteria for non-inferiority: lower limit of the 2-sided 95% CI for the difference in 2 proportions ((*p*13vPnC group – *p*PCV7 group) is > -0.05 for measles, mumps, and rubella and is > -0.10 for varicella; *p* is the proportion of subjects with the following: an anti-measles antibody concentration ≥ 1.10 index value (I.V.) units, an anti-mumps antibody concentration ≥ 1.10 I.V. units, an anti-rubella antibody concentration ≥ 15.0 IU/mL, or an anti-varicella antibody concentration ≥ 1.09 I.V. units.

2. 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.
   Criteria for non-inferiority: lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC group – *p*PCV7 group) is > -0.1, where *p* is the percentage of subjects with an anti-PRP antibody concentration ≥ 0.15 µg/mL.

3. To assess the immune response to PRP, at alternate cut off levels, after ActHIB when coadministered with 13vPnC, compared to the immune response induced by ActHIB given with PCV7 when measured 1 month after the infant series.
   Criteria for non-inferiority: lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC group – *p*PCV7 group) is > -0.1, where *p* is the percentage of subjects with an anti-PRP antibody concentration ≥ 1.0 µg/mL (alternative cutoff).

4. To assess the immune response to PRP, at alternate cut off levels, 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.
   Criteria for non-inferiority: lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC group – *p*PCV7 group) is > -0.1, where *p* is the percentage of subjects with an alternative anti-PRP antibody concentration ≥ 1.0 µg/mL.

For geometric means, each concentration or titer was logarithmically transformed for analysis. Two-sided 95% CIs were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the student t distribution.

Adjustment for multiplicity is not needed since non-inferiority for the study is demonstrated only if the lower bounds are > -0.1 for the 13 pneumococcal and 5 concomitant antigen proportion comparisons, and > 0.5 for all 13 pneumococcal geometric mean ratio comparisons. Empirical reverse cumulative distribution curves (RCDCs) will be presented graphically by treatment group for each of the serotype-specific pneumococcal IgG antibody concentrations and OPA titers and for each concomitant vaccine antigen. Post-dose 3 and post-dose 4 RCDCs will be presented separately.

7.1.3.6.3.2 Safety analyses:

Safety analysis was based on the actual study vaccine received. All participants who received at least 1 dose of study vaccine were included in the safety population. Subjects lacking safety data for a particular vaccination will be excluded from that analysis. Separate safety populations were defined for each vaccination. An additional infant series safety population, consisting of any subject in the dose 1, dose 2, or dose 3 safety population, was also created for the tabulation of AEs and SAEs. AEs were categorized according to MedDRA terminology.

Interim analyses:

A primary analysis was performed after all subjects completed their post-dose 4 visit, their assay data had become available, and the database was considered clean. All Type I error was to be spent for this analysis. A final analysis was performed at the 6 month follow-up after all data have been collected.

7.1.3.7 Changes in the Study Protocol (Protocol Amendments) and in the Planned Analyses

The four amendments to the original protocol (dated 20-Apr-06) are summarized below. Amendments 1 and 2 were issued before enrollment of any subjects.

- Amendment 1 (11-Jul-06): VAQTA added as a mandatory concomitant vaccine for 12 month old subjects. OPA testing added as an exploratory objective. Revisions were made that affected procedures for varicella testing and diphtheria ELISA.
- Amendment 2 (04-Aug-06): Period of collection of prompted symptoms increased from 4 to 7 days following each vaccination. Urticaria added to list of prompted systemic events. The non-inferiority margin for MMR was decreased from 10% to 5%. Assessment of MMR and varicella responses moved from a primary to a secondary objective.
- Amendment 3 (25-Jun-07): Concomitant Hib vaccine changed from ActHib to PedvaxHIB for toddler dose. Age range for toddler dose changed from 365-395 days to 365-455 days. Correction of a substantive typographic error to reflect an earlier change from tetanus toxoid to diphtheria toxoid.
- Amendment 4 (10-Apr-08): The analysis endpoint for the pertussis responses was modified to replace the cutoff of 5 EU/mL with a comparison based on the level of serum IgG attained by 95% of the subjects in the PCV7 group.

The statistical analysis plan (SAP) was submitted on 01-Jul-08. It contained changes to information described in the study protocol such as removal of the evaluation of the response to diphtheria at the 0.01 IU/mL cutoff, changes to the definition of the evaluable infant immunogenicity population, and changes to the measurements for grading erythema and induration. The SAP allowed for a 1-day deviation around age at the time of enrollment, age at toddler dose, and timing of blood draws for determination of evaluability, because the protocol did not provide investigators with directions on how to calculate age or timings. Blood draws 1 day before and 14 days after the protocol-specified time windows were permitted for determination of evaluability.

The SAP describes plans to include summaries of solicited events for the first 4 days in addition to summaries for the first 7 days in order to display data in a manner consistent with studies conducted outside of the U.S. where only 4 days of reactogenicity were collected.

Nonstudy vaccines received before enrollment were categorized according to the WHO drug dictionary and summarized according to the Anatomic Therapeutic Chemical (ATC) 4 class.

7.1.4 Results

7.1.4.1 Populations Enrolled/Analyzed

A total of 666 subjects were enrolled/randomized into this study; 334 subjects were randomized to the 13vPnC group and 332 subjects to the PCV7 group. Enrollment, by center, ranged from 2 to 51 subjects. There were 504 subjects in the evaluable infant immunogenicity population, 462 subjects in the evaluable toddler immunogenicity population, and 529 subjects in each of the infant and toddler all-available immunogenicity populations. The all-available infant series safety population included a total of 663 subjects who received at least one dose of a pneumococcal conjugate vaccine.

7.1.4.1.1 Subject Disposition and Follow-up

Table 5. Study 6096A1-004 Summary of Subject Disposition

	13vPnC N=334		PCV7 N=332		Total N=666	
	n	%	n	%	n	%
Subjects consented[a]	333	99.7	332	100.0	665	99.8
Subjects randomized	334[b]	100.0	332	100.0	666	100.0
Subjects vaccinated						
Dose 1	332[c]	99.4	331[d]	99.7	663	99.5
Dose 2	309	92.5	305[e]	91.9	614	92.2
Dose 3	298	89.2	300[f]	90.4	598	89.8
Dose 4	272[g]	81.4	265[h]	79.8	537	80.6
Completed infant series	294	88.0	290	87.3	584	87.7
Withdrawn during infant series	40	12.0	42	12.7	82	12.3
Reasons for withdrawal:						
Parent / legal guardian request	13	3.9	15	4.5	28	4.2
Failed to return	8	2.4	13	3.9	21	3.2
Lost to follow-up	6	1.8	5	1.5	11	1.7
Protocol violation[†]	3	0.9	7	2.1	10	1.5
Other[i]	6	1.8	0	0.0	6	0.9
Adverse event	3	0.9	1	0.3	4	0.6
Investigator request	1	0.3	1	0.3	2	0.3
Withdrawn after infant series	22	6.6	25	7.5	47	7.1
Reasons for withdrawal:						
Parent/legal guardian request	8	2.4	7	2.1	15	2.3
Failed to return	6	1.8	6	1.8	12	1.8
Lost to follow-up	4	1.2	6	1.8	10	1.5
Protocol violation	3	0.9	3	0.9	6	0.9
Adverse event	1	0.3	2	0.6	3	0.5
Investigator request	0	0.0	1	0.3	1	0.2
Withdrawn during toddler dose	8	2.4	13	3.9	21	3.2
Reason for withdrawal						
Lost to follow-up	5	1.5	8	2.4	13	2.0
Parent/legal guardian request	2	0.6	2	0.6	4	0.6
Failed to return	1	0.3	2	0.6	3	0.5
Protocol violation	0	0.0	1	0.3	1	0.2
Completed toddler dose	264	79.0	252	75.9	516	77.5
Withdrawn after toddler dose (lost to follow-up)	5	1.5	5	1.5	10	1.5
Completed study	259	77.5	247	74.4	506	76.0
Entered 6-month follow-up[j]	282	84.4	270	81.3	552	82.9
Completed 6-month follow-up[k]	272	81.4	262	78.9	534	80.2

[a] This does not include 4 subjects who were screened but not consented or randomized.
[b] Subject 004-034-003077 was pre-randomized to the 13vPnC group after verbal consent, however the consent form was never signed and the subject was not vaccinated.
[c] Two 13vPnC subjects did not receive study vaccines at dose 1. Subject 004-034-003077 was not vaccinated because consent was never signed. Subject 004-020-001881 was inadvertently given commercially available vaccine rather than test article.
[d] One PCV7 subject, subject 004-017-001657, did not receive PCV7 at dose 1. The subject's mother withdrew her child after concomitant vaccine administration and before PCV7 administration.
[e] Subject 004-010-001056, received all 3 vaccinations (PCV7, ActHIB, and Pediarix) at dose 2, but the Pediarix batch number was not entered into the database. Therefore, this subject was not counted among subjects who received Pediarix at dose 2 and was not included in either evaluable immunogenicity population due to an error.
[f] Includes subject 004-002-000078, who received 13vPnC rather than PCV7.

[g] Two subjects in the 13vPnC group (004-002-000077 and 004-024-002218) actually received PCV7 at the toddler dose. Subject 004-012-001204 in the 13vPnC group did not receive ProQuad as planned, and subject 004-020-001887 in the 13vPnC group did not receive VAQTA as planned.
[h] Subject 004-024-002193 was randomized to the PCV7 group but actually received 13vPnC at the toddler dose.
[i] Other reasons included loss of Kaiser coverage (4 subjects), child removed from home and put in protective custody (1 subject), subject never consented and so was randomized in error (1 subject).
j An attempt was made to contact all subjects 6-months after the last vaccination, regardless of whether they received all protocol-specified vaccinations.
[k] Completion of the 6-month follow up indicates subjects were reached by phone and provided the requested information.
Source: 125324/0.1,m5.3.5.1, CSR-69238-report body, page 46, 47, and 49 (Tables 8-2 and 8-5).

Table 6 summarizes the all-available and evaluable immunogenicity analysis populations, including a list of the major protocol violations that resulted in the exclusion of subjects from analysis. A major protocol violation was defined as a deviation from the protocol that was likely to materially affect the clinical observations or the immune response of the subject. Among subjects excluded from the analysis populations, most were excluded because no blood samples were obtained following the third dose.

Table 6. Study 6096A1-004 Summary of Immunogenicity Analysis Populations

	13vPnC N=334		PCV7 N=332		Total N=666	
	n	%	n	%	n	%
Randomized	334	100.0	332	100.0	666	100.0
All-available infant immunogenicity population	266	79.6	263	79.2	529	79.4
Subjects excluded from all-available infant immunogenicity population because no postinfant assay result for any pneumococcal serotype or concomitant antigen	68	20.4	69	20.8	137	20.6
Evaluable infant immunogenicity population	252	75.4	252	75.9	504	75.7
Subjects excluded from the evaluable infant immunogenicity population[a]	82	24.6	80	24.1	162	24.3
Not in all available infant immunogenicity population	68	20.4	69	20.8	137	20.6
Blood draw > 56 days after the infant series	6	1.8	6	1.8	12	1.8
Received prohibited vaccines	4	1.2	1	0.3	5	0.8
Forced randomization	2	0.6	1	0.3	3	0.5
No postinfant assay result for any concomitant antigen[c]	1	0.3	1	0.3	2	0.3
Not eligible for study	1	0.3	0	0.0	1	0.2
Received vaccine other than randomized[d]	0	0.0	1	0.3	1	0.2
Did not receive all pneumococcal study vaccinations	1	0.3	0	0.0	1	0.2
Did not receive all concomitant study vaccines	0	0.0	1[d]	0.3	1	0.2
Blood draw < 27 days after the infant series	1	0.3	0	0.0	1	0.2
Did not meet eligibility criteria	1	0.3	0	0.0	1	0.2
Exclusionary adverse event	0	0.0	1	0.3	1	0.2
All-available toddler immunogenicity population	268	80.2	261	78.6	529	79.4
Subjects excluded from all-available toddler immunogenicity population because no pre- or posttoddler pneumococcal serotype or concomitant antigen assay result	66	19.8	71	21.4	137	20.6
Evaluable toddler immunogenicity population	239	71.6	223	67.2	462	69.4
Subjects excluded from the evaluable toddler immunogenicity population[a]	95	28.4	109	32.8	204	30.6
Not in all-available toddler immunogenicity population	66	19.8	71	21.4	137	20.6
No posttoddler assay result for any concomitant antigen[c]	11	3.3	21	6.3	32	4.8
No posttoddler assay result for any pneumococcal serotype[c]	11	3.3	21	6.3	32	4.8
Blood draw >56 days after the toddler dose	8	2.4	11	3.3	19	2.9
Received prohibited vaccines	5	1.5	2	0.6	7	1.1
Received vaccine other than randomized[d]	2	0.6	2	0.6	4	0.6
Did not receive all concomitant study vaccinations[e]	2	0.6	1[e]	0.3	3	0.5
Forced randomization	2	0.6	1	0.3	3	0.5
Not eligible for the study	1	0.3	0	0.0	1	0.2
Age <364 days on the day of toddler dose	1	0.3	0	0.0	1	0.2
Age >456 days on the day of toddler dose	0	0.0	1	0.3	1	0.2
Did not receive all pneumococcal study vaccinations	1	0.3	0	0.0	1	0.2
Did not meet eligibility criteria	1	0.3	0	0.0	1	0.2
Exclusionary adverse event	0	0.0	1	0.3	1	0.2

[a] Subjects may have been excluded for more than 1 reason.
[b] Forced randomization refers to randomization of a subject based on available vaccine supply, such that site personnel administer vaccine without randomizing or assignment of a randomization number and the associated vaccine group is identical to that which the subject actually received.
[c] Does not include subjects already excluded because they were not in the all-available immunogenicity population.
[d] Two subjects randomly assigned to receive 13vPnC (004-002-000077 and 004-024-002218) actually received PCV7 at dose 4. Two subjects randomly assigned to receive PCV7 actually received 13vPnC (004-002-0000078 at dose 3 and 004-024-002193 at dose 4).
[e] Due to an error, subject 004-010-001056 was not counted among subjects who received Pediarix at dose 2. All but 1 subject in the 13vPnC group (004-012-001204) received ProQuad as planned, and all but 1 subject in the 13vPnC group (004-020-001887) received VAQTA as planned.
Source: 125324/0.1,m5.3.5.1, CSR-69238-report body, pages 49, 69-71, 126, 128, 277, and 278 (Tables 9-1 and 9-2).

Protocol violations during the infant series that did not result in exclusion from the evaluable infant immunogenicity population included the following: 7 subjects who received vaccinations with temperature deviations not large enough to jeopardize the quality of the test article; 2 subjects who received the correct study product but the wrong package number; 3 forced randomizations; 1 subject who had an AE resulting

in exclusion; 1 subject who did not meet study eligibility criteria [pg 53 and Table 15.5 on pg 213]. Protocol violations during the toddler dose that did not result in exclusion from the evaluable toddler immunogenicity population included 4 subjects who received vaccinations involving temperature deviations. Although these temperature deviations were outside of the protocol-specified range, they were described as not large enough to jeopardize the quality of the test article or impact immunogenicity results [Table 15.6, pg 214].

In addition, protocol violations involving vaccinations outside protocol-specified time windows did not result in subject exclusion from the evaluable immunogenicity population. Vaccinations outside of protocol-specified time windows occurred among 41/309 13vPnC subjects and 41/305 PCV7 subjects at dose 2; 40/298 13vPnC subjects and 57/300 PCV7 subjects at dose 3; and 1/272 13vPnC subjects and 1/265 PCV7 subjects at dose 4 [pg 46 & Table 8-3 and 8-6]. All subjects who were vaccinated at dose 1 did so during the protocol specified time window.

7.1.4.1.2 Subject Demographics

Table 7. Study 6096A1-004. Summary of Demographic Characteristics for All Subjects by Randomized Vaccine Group

	13vPnC N=334		PCV7 N=332		Total N=670	
	n	%	n	%	n	%
Gender						
Male	169	50.6	193	58.1	362	54.0
Female	165	49.4	139	41.9	304	45.4
Race						
White	228	68.3	235	70.8	463	69.1
Black	71	21.3	60	18.1	131	19.6
Other	25	7.5	28	8.4	53	7.9
Asian	8	2.4	8	2.4	16	2.4
Native Hawaiian or other Pacific Islander	2	0.6	1	0.3	3	0.4
Ethnicity						
Non-Hispanic and Non-Latino	279	83.5	271	81.6	550	82.1
Hispanic or Latino	55	16.5	61	18.4	116	17.3
Age at enrollment (months)						
Mean (SD)	2.1		2.1		2.1	
Min, Max	1.4, 3.3		1.4, 3.3		1.4, 3.3	
Weight at enrollment (lbs)						
Mean (SD)	11.6 (1.7)		11.7 (1.6))		11.7 (1.6)	
Min, Max	7.6, 16.5		7.3, 16.9		7.3, 16.9	

Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 63 (Table 8-14).

Clinical Reviewer Note: There was a higher proportion of males in the Prevnar group compared to the Prevnar 13 group. The applicant did not perform an analysis of gender effects on immunogenicity. Therefore, the impact of the observed male predominance in the Prevnar group on the non-inferiority assessments is not known. Future studies assessing gender effects on immunogenicity are warranted.

7.1.4.1.3 Nonstudy Concomitant Vaccinations

Table 8. Study 6096A1-004. Number of Subjects Who Received Permitted Non-Study Vaccinations

	13vPnC (N=334)		PCV7 (N=332)		Total (N=666)	
Permitted non-study vaccinations	**n**	**%**	**n**	**%**	**n**	**%**
Hepatitis B vaccine						
Before infant series	287	85.9	292	88.0	579	86.9
During infant series	1	0.3	0	0.0	1	0.2
Rotavirus vaccine						
Before infant series	1	0.3	1	0.3	2	0.3
During infant series	191	57.2	180	54.2	371	55.7
Before toddler dose	0	0.0	1	0.3	1	0.2
Influenza vaccine						
During infant series	6	1.8	1	0.3	7	1.1
Before toddler dose	2	0.6	5	1.5	7	1.1
During the toddler dose	11	3.3	7	2.1	18	2.7
Hepatitis A vaccine						
Before toddler dose	1	0.3	0	0.0	1	0.2
During toddler dose	1	0.3	1	0.3	2	0.3

Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 66-67.

7.1.4.2 Immunogenicity Endpoints/Outcomes

Unless otherwise specified, results from the corresponding all-available immunogenicity population were similar to the evaluable immunogenicity population.

7.1.4.2.1 Post-dose 3 Pneumococcal Serotype Immunogenicity Outcomes

Post-dose 3 IgG Seroresponse Rates ≥ 0.35µg/mL: Primary immunogenicity analysis

The criterion for demonstrating non-inferiority 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 non-inferiority 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 9. Study 6096A1-004. Comparison of Proportions 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)	‡				2.8	(-1.3, 7.2)
3	249	158	63.5	(57.1, 69.4)	‡				-29.3	(**-36.2**, -22.4)
5	252	226	89.7	(85.2, 93.1)	‡				-3.1	(-8.3, 1.9)
6A	252	242	96.0	(92.8, 98.1)	‡				3.2	(-0.8, 7.6)
7F	252	248	98.4	(96.0, 99.6)	‡				5.6	(1.9, 9.7)
19A	251	247	98.4	(96.0, 99.6)	‡				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.
[‡] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 6B [92.8% (95% CI 88.9, 95.7)].
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 ug/mL**

Table 10 shows the actual response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 9 because the PCV7 reference value (serotype 6B) was used to calculate the difference in proportions.

Table 10. Study 6096A1-004. Proportions 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]**
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).

Post dose 3 Pneumococcal IgG Geometric Mean Concentrations: Secondary immunogenicity analysis

With the exception of serotype 3, all serotypes met the 2-fold non-inferiority 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 11. Study 6096A1-004. Comparison of 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)	‡			1.45	(1.23, 1.71)
3	249	0.49	(0.43, 0.55)	‡			0.35	(**0.30**, 0.41)
5	252	1.33	(1.18, 1.50)	‡			0.95	(0.81, 1.11)
6A	252	2.19	(1.93, 2.48)	‡			1.56	(1.33, 1.83)
7F	252	2.57	(2.28, 2.89)	‡			1.83	(1.57, 2.13)
19A	251	2.07	(1.87, 2.30)	‡			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] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC to PCV7 reference. For 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).
[‡] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 9V [1.40 (95% CI 1.27, 1.55)].
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 12 shows the response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 11 because the PCV7 reference value (serotype 9V) was used to calculate the difference in proportions. The lowest GMC among Prevnar 13 recipients was in response to serotype 3. Although the serotype 3 GMC achieved by Prevnar 13 recipients was about 12 fold higher than the GMC achieved by subjects who received Prevnar (which does not contain serotype 3), the clinical relevance of this fold-rise is uncertain.

Table 12. 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 (GMCs) 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 concentrations.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 83 (Table 9-6).

Post-dose 3 OPA Results[2]

Among the 7 common serotypes, the lower limit of the 95% CI for the GMT ratio was < 0.5 for serotype 4 and the lower limit of the 95% CI for the difference in two proportions exceeded 10% for serotype 19F. Lower serotype 6B OPA titers in the 13vPnC group were consistent with a lower serotype 6B IgG GMC and IgG seroresponse in the 13vPnC group. Comparisons of serotype 9V OPA titers post-dose 3 indicate a similar functional antibody response among 13vPnC and PCV7 recipients; the 95% CI for 9V OPA titers overlapped in the two study groups. This finding is not consistent with IgG antibody response rates in the two study groups. A higher than expected percentage of PCV7 subjects (76.4%) achieved OPA titers ≥ 1:8 against serotype 7F. The reason for this high response rate is unclear, as PCV7 does not contain serotype 7F.

Among the 6 new serotypes, serotype 6A resulted in a high proportion of PCV7 subjects with an OPA titer ≥ 1:8 (77.7%), which is consistent with functional antibody production due to cross-reactivity with serotype 6B. Comparisons of 6A OPA GMTs show similar trends. A low proportion of PCV7 subjects with an OPA titer ≥ 1:8 to serotype 19A and a higher than expected proportion of PCV7 subjects with achieving an IgG concentration ≥ 0.35 µg/mL is consistent with cross-reactivity between 19F and 19A, resulting in production of non-functional antibodies.

[2] Because no standard exists against which OPA results can be normalized, comparisons of OPA titers across serotypes are not appropriate.

Table 13. Study 6096A1-004. Comparison of Pneumococcal OPA GMTs After Dose 3 of the Infant Series (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	4035.40	(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 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 105 (Table 9-17).

Table 14. Study 6096A1-004. Comparison of Proportions of Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ 1:8 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	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	(96.2,100.0)	-1.1	(-5.8, 2.8)
9V	93	93	100	(96.1,100.0)	94	93	98.9	(94.2,100.0)	1.1	(-2.9, 5.8)
14	94	94	100	(96.2,100.0)	94	94	100	(96.2,100.0)	0	(-3.9, 3.9)
18C	94	94	100	(96.2,100.0)	94	94	100	(96.2,100.0)	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	(-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	(96.2,100.0)	94	73	77.7	(67.9, 85.6)	22.3	(14.4, 32.1)
7F	94	94	100	(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 Seroresponse Rates ≥ 1.0 µg/mL

Evaluation of the proportion of subjects achieving an IgG antibody concentration ≥ 1.0 µg/mL provides additional data regarding how the two vaccines perform in eliciting higher antibody concentrations. When assessing the proportion of subjects achieving this higher antibody concentration, interference is more pronounced in the Prevnar 13 group. Among the 7 common serotypes, serotypes 4, 6B, 9V, 18C, 19F, and 23F exceeded the -10% non-inferiority criterion for this secondary endpoint.

Table 15. Study 6096A1-004. Comparison of Proportions of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 1.00 µg/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	170	67.5	(61.3, 73.2)	251	199	79.3	(73.7, 84.1)	-11.8	(-19.5, -4.1)
6B	252	192	76.2	(70.4, 81.3)	250	200	80.0	(74.5, 84.8)	-3.8	(-11.1, 3.5)
9V	252	121	48.0	(41.7, 54.4)	252	167	66.3	(60.1, 72.1)	-18.3	(-26.7, -9.6)
14	251	237	94.4	(90.8, 96.9)	252	237	94.0	(90.4, 96.6)	0.4	(-3.9, 4.7)
18C	252	167	66.3	(60.1, 72.1)	252	202	80.2	(74.7, 84.9)	-13.9	(-21.6, -6.2)
19F	252	203	80.6	(75.1, 85.3)	251	219	87.3	(82.5, 91.1)	-6.7	(-13.2, -0.3)
23F	252	164	65.1	(58.8, 71.0)	252	191	75.8	(70.0, 80.9)	-10.7	(-18.7, -2.7)
Additional					‡					
1	252	200	79.4	(73.8, 84.2)	‡				13.1	(5.3, 20.8)
3	249	54	21.7	(16.7, 27.3)	‡				-44.6	(-52.2, -36.5)
5	252	162	64.3	(58.0, 70.2)	‡				-2	(-10.4, 6.4)
6A	252	212	84.1	(79.0, 88.4)	‡				17.9	(10.4, 25.3)
7F	252	225	89.3	(84.8, 92.8)	‡				23	(15.9, 30.1)
19A	251	201	80.1	(74.6, 84.8)	‡				13.8	(6.1, 21.5)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥ 1.00 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 percentage. For the additional serotypes, the reference value is serotype 9V from the PCV7 group.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC - PCV7 reference, expressed as a percentage.
[‡] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 9V [66.3% (95% CI 60.1, 72.1)].
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 240 (Table 15.21).

Data for the 6 additional pneumococcal serotypes: **Post-dose 3 Seroresponse Rates ≥ 1.0 µg/mL**
Table 16 shows the actual response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 15 because the PCV7 reference value (serotype 9V) was used to calculate the difference in proportions.

Table 16. Study 6096A1-004. Comparison of Proportions of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 1.00 µg/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	170	67.5	(61.3, 73.2)	251	199	79.3	(73.7, 84.1)
6B	252	192	76.2	(70.4, 81.3)	250	200	80.0	(74.5, 84.8)
9V	252	121	48.0	(41.7, 54.4)	252	167	66.3	(60.1, 72.1)
14	251	237	94.4	(90.8, 96.9)	252	237	94.0	(90.4, 96.6)
18C	252	167	66.3	(60.1, 72.1)	252	202	80.2	(74.7, 84.9)
19F	252	203	80.6	(75.1, 85.3)	251	219	87.3	(82.5, 91.1)
23F	252	164	65.1	(58.8, 71.0)	252	191	75.8	(70.0, 80.9)
Additional								
1	252	200	79.4	(73.8, 84.2)	248	2	0.8	(0.1, 2.9)
3	249	54	21.7	(16.7, 27.3)	241	7	2.9	(1.2, 5.9)
5	252	162	64.3	(58.0, 70.2)	197	20	10.2	(6.3, 15.2)
6A	252	212	84.1	(79.0, 88.4)	240	33	13.8	(9.7, 18.8)
7F	252	225	89.3	(84.8, 92.8)	248	5	2.0	(0.7, 4.6)
19A	251	201	80.1	(74.6, 84.8)	238	107	45.0	(38.5, 51.5)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥ 1.00 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 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 241 (Table 15.20).

7.1.4.2.2 Dose 4 Pneumococcal Serotype Immunogenicity Outcomes

Pre-dose 4 Pneumococcal IgG Seroresponse Rates ≥ 0.35 µg/mL

Six months after the 3rd dose but prior to the 4th dose, seroresponse rates among 13vPnC recipients appear to wane substantially more than PCV7 subjects for most serotypes, especially for serotypes 3, 4, 5, 9V, 18C, and 23F. Less than 60% of Prevnar 13 recipients achieved an antibody concentration ≥ 0.35 µg/mL just before the fourth dose. A similar trend (with the exception of serotype 14) of lower pre-dose 4 GMCs in the Prevnar 13 group compared to the Prevnar group was observed (Table 19). These data support the need for a fourth dose to help increase antibody levels during the second year of life.

Table 17. Study 6096A1-004. Comparison of Proportions of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35 µg/mL Before Dose 4 (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	229	107	46.7	(40.1, 53.4)	208	139	66.8	(60.0, 73.2)	-20.1	(-29.1, -10.9)
6B	229	185	80.8	(75.1, 85.7)	205	178	86.8	(81.4, 91.1)	-6	(-13.0, 1.0)
9V	227	129	56.8	(50.1, 63.4)	206	147	71.4	(64.7, 77.4)	-14.5	(-23.4, -5.5)
14	228	212	93.0	(88.9, 95.9)	206	198	96.1	(92.5, 98.3)	-3.1	(-7.7, 1.2)
18C	229	105	45.9	(39.3, 52.5)	207	130	62.8	(55.8, 69.4)	-17	(-26.1, -7.6)
19F	229	181	79.0	(73.2, 84.1)	205	151	73.7	(67.1, 79.5)	5.4	(-2.8, 13.5)
23F	229	124	54.1	(47.5, 60.7)	207	127	61.4	(54.4, 68.0)	-7.2	(-16.5, 2.1)
Additional										
1	229	182	79.5	(73.7, 84.5)	‡				18.1	(9.5, 26.6)
3	224	36	16.1	(11.5, 21.5)	‡				-45.3	(-53.3, -36.7)
5	228	191	83.8	(78.3, 88.3)	‡				22.4	(14.0, 30.6)
6A	228	206	90.4	(85.8, 93.9)	‡				29	(21.2, 36.7)
7F	228	205	89.9	(85.2, 93.5)	‡				28.6	(20.7, 36.3)
19A	229	196	85.6	(80.4, 89.9)	‡				24.2	(16.0, 32.3)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥ 1.00 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 percentage. For the additional serotypes, the reference value is serotype 23F from the PCV7 group.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC - PCV7 reference, expressed as a percentage.
‡ Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 23F [61.4% (95% CI 54.4, 68.0)].
Source: 125324/0.20,m1.11.3, page 9 (Table 1-3).

Data for the 6 additional pneumococcal serotypes: **Pre-dose 4 Seroresponse Rates ≥ 0.35 µg/mL**
Table 18 shows the actual response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 17 because the PCV7 reference value (serotype 23F) was used to calculate the difference in proportions.

Table 18. Study 6096A1-004. Proportions of Subjects Achieving A Pneumococcal IgG Antibody Concentration ≥ 0.35 µg/mL Before Dose 4 (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	229	107	46.7	(40.1, 53.4)	208	139	66.8	(60.0, 73.2)
6B	229	185	80.8	(75.1, 85.7)	205	178	86.8	(81.4, 91.1)
9V	227	129	56.8	(50.1, 63.4)	206	147	71.4	(64.7, 77.4)
14	228	212	93.0	(88.9, 95.9)	206	198	96.1	(92.5, 98.3)
18C	229	105	45.9	(39.3, 52.5)	207	130	62.8	(55.8, 69.4)
19F	229	181	79.0	(73.2, 84.1)	205	151	73.7	(67.1, 79.5)
23F	229	124	54.1	(47.5, 60.7)	207	127	61.4	(54.4, 68.0)
Additional								
1	229	182	79.5	(73.7, 84.5)	205	6	2.9	(1.1, 6.3)
3	224	36	16.1	(11.5, 21.5)	198	13	6.6	(3.5, 11.0)
5	228	191	83.8	(78.3, 88.3)	188	112	59.6	(52.2, 66.7)
6A	228	206	90.4	(85.8, 93.9)	197	94	47.7	(40.6, 54.9)
7F	228	205	89.9	(85.2, 93.5)	204	11	5.4	(2.7, 9.4)
19A	229	196	85.6	(80.4, 89.9)	204	156	76.5	(70.0, 82.1)

[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: 125324/0.20,m1.11.3, page 10 (Table 1-4).

Pre-dose 4 Pneumococcal IgG GMCs

Table 19. Study 6096A1-004. Pneumococcal IgG Geometric Mean Concentrations (µg/mL) Before Toddler Dose (Evaluable Toddler 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	229	0.35	(0.31, 0.39)	208	0.51	(0.45, 0.57)
6B	229	0.78	(0.69, 0.89)	205	1.01	(0.88, 1.15)
9V	227	0.39	(0.35, 0.43)	206	0.53	(0.48, 0.59)
14	228	1.89	(1.64, 2.17)	206	2.49	(2.17, 2.85)
18C	229	0.34	(0.30, 0.37)	207	0.45	(0.41, 0.50)
19F	229	0.73	(0.65, 0.82)	205	0.65	(0.57, 0.74)
23F	229	0.38	(0.33, 0.44)	207	0.48	(0.42, 0.55)
Additional						
1	229	0.64	(0.57, 0.72)	205	0.03	(0.02, 0.03)
3	224	0.15	(0.13, 0.17)	198	0.05	(0.04, 0.06)
5	228	0.77	(0.69, 0.86)	188	0.44	(0.37, 0.51)
6A	228	0.83	(0.75, 0.92)	197	0.3	(0.26, 0.35)
7F	228	0.83	(0.75, 0.93)	204	0.04	(0.04, 0.05)
19A	229	0.92	(0.81, 1.05)	204	0.7	(0.61, 0.80)

[a] 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] Confidence intervals (CIs) are back transformations of a confidence interval 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 92 (Table 9-11).

Post-dose 4 Pneumococcal IgG Geometric Mean Concentrations: Primary immunogenicity analysis
The criterion for demonstrating non-inferiority 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 non-inferiority criterion for this co-primary endpoint. Serotype 3 did not meet the pre-specified non-inferiority criterion. The lower limit of the 2-sided 95% CI for the GMC ratio was less than 0.50 for serotype 3.

Table 20. Study 6096A1-004. Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 4 (Evaluable Toddler 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)	‡			1.40	(1.17, 1.66)
3	232	0.94	(0.83, 1.05)	‡			0.26	(0.22, 0.30)
5	235	3.72	(3.31, 4.18)	‡			1.03	(0.87, 1.20)
6A	235	8.20	(7.30, 9.20)	‡			2.26	(1.93, 2.65)
7F	235	5.67	(5.01, 6.42)	‡			1.56	(1.32, 1.85)
19A	236	8.55	(7.64, 9.56)	‡			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] Confidence intervals (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).
[‡] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 9V [3.63 95% CI 3.25, 4.05)].
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 21 shows the actual response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 20 because the PCV7 reference value (serotype 9V) was used to calculate the difference in proportions. The GMC for serotype 3 was 0.49 at one month post-dose 3, 0.15 µg/mL just prior to dose 4, and 0.94 µg/mL at one month post-dose 4 in the Prevnar 13 group. The GMC values for serotypes 6A and 19A among Prevnar recipients reflect cross reactive IgG antibodies induced by serotype 6B and 19F in Prevnar.

Table 21. Study 6096A1-004. Pneumococcal IgG GMCs (µg/mL) After Dose 4 (Evaluable Toddler 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] Geometric mean concentrations (GMCs) 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 concentrations.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 93 (Table 9-12).

Post-dose 4 Seroresponse rates ≥ 0.35 µg/mL: Secondary immunogenicity analysis
Serotype 3 exceeded the -10% non-inferiority criterion for this secondary endpoint; the lower limit of the 95% confidence interval for the difference in proportions was -12.8%.

Table 22. Study 6096A1-004. Comparison of Proportions of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL 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]
PCV7										
4	235	233	99.1	(97.0, 99.9)	223	223	100.0	(98.4,100.0)	-0.9	(-3.1, 0.8)
6B	234	233	99.6	(97.6,100.0)	223	223	100.0	(98.4,100.0)	-0.4	(-2.4, 1.3)
9V	234	232	99.1	(96.9, 99.9)	223	222	99.6	(97.5,100.0)	-0.4	(-2.6, 1.7)
14	235	232	98.7	(96.3, 99.7)	223	221	99.1	(96.8, 99.9)	-0.4	(-2.9, 2.1)
18C	236	233	98.7	(96.3, 99.7)	223	223	100.0	(98.4,100.0)	-1.3	(-3.7, 0.4)
19F	235	235	100.0	(98.4,100.0)	223	220	98.7	(96.1, 99.7)	1.3	(-0.3, 3.9)
23F	234	233	99.6	(97.6,100.0)	222	222	100.0	(98.4,100.0)	-0.4	(-2.4, 1.3)
Additional										
1	235	235		(98.4,100.0)	‡				1.3	(-0.3, 3.9)
3	232	210	90.5	(86.0, 94.0)	‡				-8.1	(-12.8, -4.0)
5	235	234	99.6	(97.7,100.0)	‡				0.9	(-1.2, 3.5)
6A	235	235	100.0	(98.4,100.0)	‡				1.3	(-0.3, 3.9)
7F	235	234	99.6	(97.7,100.0)	‡				0.9	(-1.2, 3.5)
19A	236	236	100.0	(98.4,100.0)	‡				1.3	(-0.3, 3.9)

[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, expressed as a percentage. For the additional serotypes, the reference value is serotype 19F from the PCV7 group.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC - PCV7 reference, expressed as a percentage.
‡ Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 19F [98.7% (95% CI 96.1, 99.7)].
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 87 (Table 9-9).

Clinical Reviewer Note: GMCs are the preferred endpoint for the post-dose 4 analysis of immune responses. The proportion of children achieving the 0.35 µg/mL antibody concentration after the fourth dose at 12-15 months of age is less useful in evaluating of immune responses at this timepoint, as it is a low bar for these comparisons. The proportion of subjects achieving the 0.35 µg/mL antibody concentration is high in both groups, which limits the ability to determine differences, if any, between the products.

Data for the 6 additional pneumococcal serotypes: **Post dose 4 IgG Seroresponse Rates ≥ 0.35 ug/mL**

Table 23 shows the response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 22 because the PCV7 reference value (serotype 19F) was used to calculate the difference in proportions.

Table 23. Study 6096A1-004. Proportions of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL 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]
PCV7								
4	235	233	99.1	(97.0, 99.9)	223	223	100.0	(98.4,100.0)
6B	234	233	99.6	(97.6,100.0)	223	223	100.0	(98.4,100.0)
9V	234	232	99.1	(96.9, 99.9)	223	222	99.6	(97.5,100.0)
14	235	232	98.7	(96.3, 99.7)	223	221	99.1	(96.8, 99.9)
18C	236	233	98.7	(96.3, 99.7)	223	223	100.0	(98.4,100.0)
19F	235	235	100.0	(98.4,100.0)	223	220	98.7	(96.1, 99.7)
23F	234	233	99.6	(97.6,100.0)	222	222	100.0	(98.4,100.0)
Additional								
1	235	235	100.0	(98.4,100.0)	222	7	3.2	(1.3, 6.4)
3	232	210	90.5	(86.0, 94.0)	215	23	10.7	(6.9, 15.6)
5	235	234	99.6	(97.7,100.0)	198	137	69.2	(62.3, 75.5)
6A	235	235	100.0	(98.4,100.0)	221	196	88.7	(83.8, 92.5)
7F	235	234	99.6	(97.7,100.0)	223	13	5.8	(3.1, 9.8)
19A	236	236	100.0	(98.4,100.0)	211	209	99.1	(96.6, 99.9)

[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, pages 85-86 (Table 9-8).

Dose 4 OPA Results

The proportion of subjects achieving OPA titers ≥ 1:8 post-dose 4 OPA and the post-dose 4 GMTs were higher compared to the corresponding post-dose 3 results. For the 7 common serotypes, the lower limit of the 95% CI for the post-dose 4 GMT ratios was less than 0.5 for serotypes 9V, 18C, and 23F. For the 6 additional serotypes, post-dose 4 trends were similar to the corresponding post-dose 3 OPA results.

Table 24. Study 6096A1-004. Comparison of Proportions 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]**
4	88	87	98.9	(93.8,100.0)	92	91	98.9	(94.1,100.0)
6B	92	91	98.9	(94.1,100.0)	95	95	100.0	(96.2,100.0)
9V	90	89	98.9	(94.0,100.0)	94	94	100.0	(96.2,100.0)
14	92	92	100.0	(96.1,100.0)	96	96	100.0	(96.2,100.0)
18C	91	90	98.9	(94.0,100.0)	96	96	100.0	(96.2,100.0)
19F	92	89	96.7	(90.8, 99.3)	96	91	94.8	(88.3, 98.3)
23F	90	89	98.9	(94.0,100.0)	92	92	100.0	(96.1,100.0)
Additional								
1	89	88	98.9	(93.9,100.0)	92	11	12	(6.1, 20.4)
3	91	89	97.8	(92.3, 99.7)	96	42	43.8	(33.6, 54.3)
5	91	90	98.9	(94.0,100.0)	96	5	5.2	(1.7, 11.7)
6A	92	91	98.9	(94.1,100.0)	96	91	94.8	(88.3, 98.3)
7F	91	91	100.0	(96.0,100.0)	92	74	80.4	(70.9, 88.0)
19A	91	89	97.8	(92.3, 99.7)	94	50	53.2	(42.6, 63.6)

[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 107 (Table 9-18).

Table 25. 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]**
4	88	1179.98	(847.34, 1643.20)	92	1492.46	(1114.40, 1998.78)
6B	92	3099.51	(2337.02, 4110.79)	95	4066.22	(3243.42, 5097.76)
9V	90	11856.03	(8809.85, 15955.49)	94	18032.33	(14124.99, 23020.53)
14	92	2002.23	(1452.54, 2759.93)	96	2365.87	(1870.56, 2992.34)
18C	91	993.27	(754.08, 1308.33)	96	1722.16	(1326.59, 2235.67)
19F	92	199.65	(144.22, 276.38)	96	167.2	(121.35, 230.37)
23F	90	2723.25	(1960.67, 3782.41)	92	4981.68	(3885.71, 6386.76)
Additional						
1	89	164.23	(113.83, 236.93)	92	5.01	(4.22, 5.96)
3	91	380.41	(300.19, 482.08)	96	11.81	(8.68, 16.08)
5	91	300.41	(229.39, 393.40)	96	4.69	(3.99, 5.51)
6A	92	2241.79	(1706.71, 2944.63)	96	538.54	(374.83, 773.75)
7F	91	11629.44	(9053.62, 14938.11)	92	267.84	(164.49, 436.11)
19A	91	1024.00	(774.12, 1354.54)	94	28.65	(18.58, 44.17)

[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 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).

7.1.4.2.3 Post-dose 3 Concomitant Vaccine Immunogenicity Results

Seroresponse rates
Each of the co-primary objectives for the concomitant vaccine antigens was met. Comparisons of PRP seroresponse rates at the alternative 1.0 µg/mL comparison level were included as a secondary objective. The difference in the two proportions for PRP responses at the 1.0 µg/mL level were within the -10% non-inferiority criterion.

Table 26. Study 6096A1-004. Comparison of Proportions of Subjects Achieving a Pre-specified antibody Concentration for Concomitant Vaccine Antigens After Dose 3 (Evaluable Infant Immunogenicity Population)

		Vaccine Group As Randomized									
		13vPnC				PCV7					
Concomitant Vaccine Antigen	Comparison level	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]	Difference[d]	(95% CI)[e]
Hib (PRP)	≥ 0.15 µg/mL	237	232	97.9	(95.1, 99.3)	230	225	97.8	(95.0, 99.3)	0.1	(-2.9, 3.1)
	≥ 1.0 µg/mL	237	184	77.6	(71.8, 82.8)	230	180	78.3	(72.4, 83.4)	-0.6	(-8.3, 7.0)
Diphtheria	≥ 0.1 IU/mL	233	223	95.7	(92.2, 97.9)	230	221	96.1	(92.7, 98.2)	-0.4	(-4.3, 3.5)
Pertussis											
FHA	≥ 40.5 EU/mL	239	231	96.7	(93.5, 98.5)	240	228	95	(91.4, 97.4)	1.7	(-2.1, 5.6)
PT	≥ 16.5 EU/mL	239	225	94.1	(90.4, 96.8)	240	228	95	(91.4, 97.4)	-0.9	(-5.2, 3.4)
PRN	≥ 26 EU/mL	239	224	93.7	(89.9, 96.4)	240	230	95.8	(92.5, 98.0)	-2.1	(-6.4, 2.0)

[a] N = number of subjects with a determinate postinfant series antibody concentration to the given concomitant antigen.
[b] n = Number of subjects with an antibody concentration ≥ prespecified level for the given concomitant antigen.
[c] Exact 2–sided confidence interval based upon the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[e] Exact 2–sided confidence interval for the difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[f] Comparison level = the level that 95% of the subjects in the PCV7 group achieve.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 116 (Table 9-20).

Geometric Mean Antibody Concentrations
Comparisons of post-dose 3 GMC ratios for Hib (PRP), diphtheria, and pertussis vaccine antigens were not included as study objectives/endpoints. The lower limits of the 95% confidence interval for the GMC ratios for PRP and diphtheria were greater than 0.5. The lower limit of the 95% CI for the GMC ratio for each of the pertussis antigens was > 0.67 (1.5 fold), which is the CBER preferred criterion for non-inferiority comparisons of pertussis antigen responses.

Table 27. Study 6096A1-004. Comparison of Concomitant Vaccine Antigen GMCs After Dose 3 (Evaluable Infant Immunogenicity Population)

		Vaccine Group As Randomized							
		13vPnC			PCV7				
Concomitant Vaccine Antigen	Units	N[a]	GMC[b]	(95% CI)[c]	N[a]	GMC[b]	(95% CI)[c]	Ratio[d]	(95% CI)[e]
Hib (PRP)	µg/mL	237	3.5	(2.92, 4.20)	230	2.89	(2.40, 3.47)	1.21	(0.94, 1.57)
Diphtheria	IU/mL	233	0.6	(0.53, 0.68)	230	0.65	(0.57, 0.75)	0.92	(0.77, 1.10)
Pertussis									
FHA	EU/mL	239	131.96	(121.25, 143.62)	240	136.66	(124.61, 149.88)	0.97	(0.85, 1.09)
PT	EU/mL	239	51.35	(47.02, 56.08)	240	54.61	(49.33, 60.45)	0.94	(0.82, 1.08)
PRN	EU/mL	239	116.15	(104.47, 129.14)	240	112.47	(100.70, 125.61)	1.03	(0.89, 1.20)

[a] n = Number of subjects with a determinate antibody concentration for the specified concomitant antigen.
[b] Geometric mean concentrations (GMCs) 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 concentrations.
[d] Ratio of GMCs; 13vPnC to PCV7.

[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).
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 119 (Table 9-22).

7.1.4.2.4 Post-dose 4 Concomitant Vaccine Immunogenicity Results

Comparisons of post-dose 4 seroresponse rates for PRP, measles, mumps, rubella, and varicella vaccine antigens were secondary study objectives/endpoints. The lower limits of the 95% CIs for difference in the response rates at the pre-specified levels were within the -10% non-inferiority criterion for varicella and within the -5% non-inferiority criterion for measles, mumps, and rubella. The -5% non-inferiority criterion was not met when rubella antibody responses were compared at the assay cut-off value, --b(4)-------. The percentage of subjects achieving a rubella antibody response ≥ 10 IU/mL was 94.3% in the 13vPnC group and 95.6% in the PCV7 group; the lower limit of the 95% CI for the difference in the two proportions was -5.9%.

Antibody responses to the varicella and mumps antigens were similar between the two study groups, but they were noted to be much lower than expected. Results in the all-available infant immunogenicity population were similar to the evaluable toddler population results, except the difference in the proportions of subjects achieving an antibody level of 1.10 l.V. for mumps was 1.3% with a lower limit of the 95% CI of -6.6%.

Table 28. Study 6096A1-004. Comparison of Proportions of Subjects Achieving a Pre-specified Level for Concomitant Vaccine Antigens After Dose 4 (Evaluable Toddler Immunogenicity Population)

		Vaccine Group As Randomized									
		13vPnC				PCV7					
Concomitant Antigen	Comparison level	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]	Difference[d]	(95% CI)[e]
Hib (PRP)	0.15 µg/mL	230	230	100.0	(98.4, 100.0)	214	214	100.0	(98.3, 100.0)	0	(-1.6, 1.7)
	1.0 µg/mL	230	208	90.4	(85.9, 93.9)	214	197	92.1	(87.6, 95.3)	-1.6	(-7.1, 3.8)
Measles	≥ 1.10 I.V.	221	213	96.4	(93.0, 98.4)	210	204	97.1	(93.9, 98.9)	-0.8	(-4.5, 2.9)
Mumps	≥ 1.10 I.V.	221	169	76.5	(70.3, 81.9)	210	153	72.9	(66.3, 78.7)	3.6	(-4.7, 11.9)
Rubella	≥ 15 IU/mL	209	192	91.9	(87.3, 95.2)	204	185	90.7	(85.8, 94.3)	1.2	(-4.4, 6.9)
Varicella	≥ 1.09 I.V.	221	59	26.7	(21.0, 33.0)	210	46	21.9	(16.5, 28.1)	4.8	(-3.4, 13.0)

[a] N = number of subjects with a determinate posttoddler dose antibody concentration to the given concomitant antigen.
[b] n = Number of subjects with an antibody concentration ≥ the prespecified level for the given concomitant antigen.
[c] Exact 2–sided confidence interval based upon the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[e] Exact 2–sided confidence interval for the difference in proportions, 13vPnC – PCV7, expressed as a percentage.
Non-inferiority criterion for Hib: -10% difference between two groups. Non-inferiority criterion for MMRV: -5% difference between two groups.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 117 (Table 9-21).

Table 29. Study 6096A1-004. Comparison of Proportions of Subjects Achieving a Pre-specified Level for Concomitant Vaccine Antigens After Dose 4 (All-Available Toddler Immunogenicity Population)

		Vaccine Group As Randomized									
		13vPnC				PCV7					
Concomitant Antigen	Comparison level	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]	Difference[d]	(95% CI)[e]
Hib (PRP)	0.15 µg/mL	248	248	100	(98.5, 100.0)	231	231	100	(98.4, 100.0)	0	(-1.5, 1.6)
	1.0 µg/mL	248	226	91.1	(86.9, 94.4)	231	212	91.8	(87.5, 95.0)	-0.6	(-5.8, 4.5)
Measles	≥ 1.10 I.V.	239	230	96.2	(93.0, 98.3)	227	221	97.4	(94.3, 99.0)	-1.1	(-4.7, 2.4)
Mumps	≥ 1.10 I.V.	239	181	75.7	(69.8, 81.0)	227	169	74.4	(68.3, 80.0)	1.3	(-6.6, 9.2)
Rubella	≥ 15 IU/mL	227	209	92.1	(87.8, 95.2)	221	202	91.4	(86.9, 94.7)	0.7	(-4.6, 6.0)
Varicella	≥ 1.09 I.V.	239	62	25.9	(20.5, 32.0)	227	47	20.7	(15.6, 26.6)	5.2	(-2.5, 13.0)

[a] N = number of subjects with a determinate posttoddler dose antibody concentration to the given concomitant antigen.
[b] n = Number of subjects with an antibody concentration ≥ the prespecified level for the given concomitant antigen.
[c] Exact 2–sided confidence interval based upon the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[e] Exact 2–sided confidence interval for the difference in proportions, 13vPnC – PCV7, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 274 (Table 15.54).

Comparisons of post-dose 4 geometric means for PRP, measles, mumps, rubella, and varicella vaccine antigens were not included as study objectives/endpoints. The lower limits of the 95% confidence interval for the geometric mean ratios for PRP, measles, mumps, rubella, and varicella antigens were greater than 0.5.

Table 30. Study 6096A1-004. Comparison of Concomitant Vaccine Antigen GMs After the Toddler Dose (Evaluable Toddler Immunogenicity Population)

		Vaccine Group As Randomized							
		13vPnC			PCV7				
Concomitant Antigen	Units	N[a]	GM[b]	(95% CI)[c]	N[a]	GM[b]	(95% CI)[c]	Ratio[d]	(95% CI)[e]
Hib (PRP)	µg/mL	230	6.57	(5.59, 7.72)	214	7.21	(6.11, 8.50)	0.91	(0.72, 1.15)
Measles	I.V.	221	1.98	(1.81, 2.16)	210	2.02	(1.86, 2.20)	0.98	(0.86, 1.11)
Mumps[f]	I.V.	221	1.33	(1.20, 1.47)	210	1.28	(1.16, 1.42)	1.03	(0.90, 1.19)
Rubella	IU/mL	209	75.24	(63.12, 89.68)	204	90.59	(75.71, 108.41)	0.83	(0.65, 1.07)
Varicella[g]	I.V.	221	0.74	(0.69, 0.80)	210	0.73	(0.69, 0.78)	1.01	(0.92, 1.11)

[a] n = Number of subjects with a determinate antibody concentration or index value for the specified concomitant antigen.
[b] Geometric means (GMs) 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 concentrations or index values.
[d] Ratio of GMs; 13vPnC to PCV7.
[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).
[f] Captia Varicella IgG ELISA
[g] Trinity Biotech Captia Mumps IgG ELISA
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 120 (Table 9-23).

Clinical Reviewer Note: Due to low varicella and mumps seroresponse rates achieved in both study group, other sera were tested by alternative assays. Sera from a study 3005 subset population were used for testing, because no additional sera were available from study 004. The subset included remaining sera obtained one month after the fourth dose for all subjects in the Prevnar group and for a randomly selected subset of equal number of subjects from the Prevnar 13 groups. Subejcts in study 3005 received Varivax.

The applicant noted that the low varicella and mumps seroresponse rates achieved in both study groups in study 004 are likely to be due to the low sensitivity of the commercial assays used. At the time study 004 was conducted, the applicant did not have access to the assays used for licensing mumps and varicella components of ProQuad [glycoprotein (gp)ELISA and Mumps ELISA], as they

were proprietary to Merck & Co., Inc. Mumps and varicella responses were therefore measured using the Trinity Biotech Captia varicella IgG ELISA and the Trinity Biotech Captia Mumps IgG ELISA. -------
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During the Prevnar 13 BLA review, Merck's proprietary varicella gpELISA and MMR assays became commercially available. The tables below show the results of the assays of the remaining sera from the study 3005 subset population, using Merck's more sensitive Mumps ELISA and varicella gpELISA assays. Results show that the varicella and mumps antibody responses are higher using the gpELISA and Mumps ELISA respectively. However, the -5% non-inferiority criterion is not met for mumps; the lower limit of the 95% conficence interval for the difference in the two proportions was -6.5%.

Table 31. Study 6096A1-3005. Comparison of Proportions of Subjects Achieving a Pre-specified Level for Concomitant Vaccine Antigens After Dose 4 (Evaluable Toddler Immunogenicity Population)

		Vaccine Group As Randomized									
		13vPnC				PCV7					
Concomitant Antigen	**Comparison level**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**Differ-ence[d]**	**(95% CI)[e]**
Varicella[f]	≥ 1.25 gpELISA µnits/mL	163	163	100.0	(97.8, 100.0)	173	173	100.0	(97.9, 100.0)	0.0	(-2.3, 2.2)
	≥ 5.0 gpELISA units/mL	163	163	98.8	(95.6, 99.9)	173	169	97.7	(94.2, 99.4)	1.1	(-2.3, 4.7)
Mumps[g]	≥ 10.0 Ab units	163	156	95.7	(91.4, 98.3)	167	163	97.6	(94.0, 99.3)	-1.9	(-6.5, 2.3)

[a] N = number of subjects with a determinate IgG antibody concentration to the given concomitant vaccine component.
[b] n = Number of subjects with an antibody concentration ≥ the prespecified level for the given concomitant vaccine component antigen.
[c] Exact 2–sided confidence interval based upon the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[e] Exact 2–sided confidence interval for the difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[f] Varicella gpELISA (Merck)
[g] Mumps ELISA (Merck)
Source: 125324/0.25,m1.11.3, efficacy-information-amendment.pdf, page 2 (Table 1-1) and 125324/0.43, m1.11, response-quality-information.pdf, page 6 (Table 1-1).

The difference between the two study groups in the mumps responses using the all-available population was -1.5% (95% CI -5.5, 2.2).

Table 32. Study 6096A1-3005. Comparison of Concomitant Vaccine Antigen GMs After the Toddler Dose (Evaluable Toddler Immunogenicity Population)

		Vaccine Group As Randomized							
		13vPnC			PCV7				
Concomitant Antigen	**Units**	**N[a]**	**GM[b]**	**(95% CI)[c]**	**N[a]**	**GM[b]**	**(95% CI)[c]**	**Ratio[d]**	**(95% CI)[e]**
Varicella[f]	gpELISA units/mL	163	15.38	(14.22, 16.64)	173	16.04	(14.61, 17.61)	0.96	(0.85, 1.08)
Mumps[g]	Ab units	163	58.55	(50.26, 68.21)	167	66.91	(58.27, 76.83)	0.88	(0.71, 1.07)

[a] n = Number of subjects with a determinate antibody concentration or index value for the specified concomitant vaccine component.
[b] Geometric means (GMs) 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 concentrations.
[d] Ratio of GMs; 13vPnC to PCV7.
[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).
[f] Varicella gpELISA (Merck)
[g] Mumps ELISA (Merck)
Source: 125324/0.25,m1.11.3, efficacy-information-amendment.pdf, page 3 (Table 1-2) and 125324/0.43, m1.11, response-quality-information.pdf, page 8 (Table 1-3).

CBER also requested analysis of Rubella data in study 004 subjects using a ---b(4)-------- comparison level, which is the accepted cut-off for the assay used in study 004. The -5% non-inferiority criterion was not met for rubella; the lower limit of the 95% CI for the difference in the two proportions was -5.9%.

Table 33. Study 6096A1-004. Comparison of Rubella Antigen GMs After the Toddler Dose (Evaluable Toddler Immunogenicity Population) using a 10 IU/mL cutoff.

		Vaccine Group As Randomized									
		13vPnC				PCV7					
Concomitant Antigen	**Comparison level**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**Differ-ence[d]**	**(95% CI)[e]**
Rubella	≥ 10 IU/mL	209	197	94.3	(90.2, 97.0)	204	195	95.6	(91.8, 98.0)	-1.3	(-5.9, 3.2)

[a] N = number of subjects with a determinate post-toddler dose antibody concentration to the given concomitant vaccine component.
[b] n = Number of subjects with an antibody concentration ≥ the prespecified level for the given concomitant vaccine component antigen.
[c] Exact 2–sided confidence interval based upon the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[e] Exact 2–sided confidence interval for the difference in proportions, 13vPnC – PCV7, expressed as a percentage.
Source: 125324/0.43, m1.11, response-quality-information.pdf, page 12-13 (Table 3-1 and 3-2).

The difference between the two study groups in the rubella responses using the all-available population was -1.7% (95% CI -6.0, 2.5).

7.1.4.3 Safety Outcomes

7.1.4.3.1 Immediate Reactions

Although immediate reactions were collected and reported along with other unsolicited adverse events, these events could not be identified from the data submitted to the BLA. The specific time-to-onset of symptoms was not recorded, therefore reactions that occurred within 30 minutes of vaccination could not be identified.

Clinical Reviewer Note: CBER requested data regarding immediate reactions, however, the applicant indicated in amendment 11 to the BLA, that the time of observation was not recorded in the case report

form. Therefore, the applicant could not identify those adverse events which occurred during the 30 minutes immediately following vaccination.

7.1.4.3.2 Solicited Local Reactions

In both study groups, 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 34. Study 6096A1-004. Proportions 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[a]							
	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).

7.1.4.3.3 Solicited Systemic Reactions

In both study groups, 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 two PCV7 subjects reported fever > 40°C. The

occurrence of hives in the 13vPnC group ranged from 1.7% to 4.8% and was more frequent in the 13vPnC group than the PCV7 group after the first three doses.

Table 35. Study 6096A1-004. Proportion 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[d] (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).

Antipyretic Use

The use of antipyretics/analgesics theoretically may affect the occurrence of some local or systemic AEs. There were no statistically significant differences between the two study groups in the use of antipyretics to treat or prevent symptoms related to vaccination within 7 days of vaccination.

Table 36. Study 6096A1-004. Number of subjects who received antipyretics to treat symptoms or to prevent symptoms within 7 days following each dose of 13vPnC or PCV7.

	Use of Antipyretics to Treat Symptoms		Use of Antipyretics to Prevent Symptoms	
Dose number	13vPnC n (%)	PCV7 n (%)	13vPnC n (%)	PCV7 n (%)
1	N[b]=257 202 (78.6)	N=266 191 (71.8)	N=272 204 (75.0)	N=274 205 (74.8)
2	N=221 182 (82.4)	N=221 181 (81.9)	N=233 202 (86.7)	N=231 193 (83.5)
3	N=203 167 (82.3)	N=187 160 (85.6)	N=202 164 (81.2)	N=189 159 (84.1)
4	N=162 136 (84.0)	N=138 121 (87.7)	N=164 145 (88.4)	N=162 147 (90.7)

[b] Number of subjects reporting yes for at least 1 day or no for all days
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 137-139, and 142 (Tables 10-7 to 10-10).

7.1.4.3.4 Unsolicited Adverse Events

Overall, a similar proportion of subjects in each study group reported unsolicited adverse events following any of doses 1-4. During the infant series (i.e. within 30 days following any of doses 1-3), unsolicited adverse events were reported by 83.1% (276/332) and 79.8% (264/331) of subjects in the 13vPnC and PCV7 groups respectively. During the 30 day period following the toddler dose, unsolicited adverse events were reported by 35.6% (95/267) and 39.1% (101/258) of subjects in the 13vPnC and PCV7 groups respectively. The most frequently reported adverse events during the infant series were upper respiratory tract infections (13vPnC: 39.5%, PCV7: 39.6%), otitis media (13vPnC: 28.3%, PCV7: 23.6%), and bronchiolitis (13vPnC: 16.9, PCV7: 16.3). Following the toddler dose, the most frequently reported adverse events were otitis media (13vPnC: 8.6, PCV7: 8.9) and upper respiratory tract infections (13vPnC: 7.9%, PCV7: 9.3%).

Unsolicited adverse events occurring in at least 1% of 13vPnC subjects and in more 13vPnC subjects compared to PCV7 subjects include the following:

- Across all infant series safety populations (n_{13vPnC}=332, n_{PCV7}=331): pneumonia (2.4%, 1.5%), eye discharge (1.2%, 0.3%), diarrhea (10.5%, 9.4%), otitis media (28.3%, 23.6%), bronchiolitis (16.9%, 16.3%), RSV bronchiolitis (2.1%, 1.8%), nasopharyngitis (6.6%, 5.4%), pharyngitis (2.1%, 1.8%), oral candidiasis (3.0%, 1.2%), sinusitis (3.6%, 1.8%), nasal congestion (10.8, 7.6%), dermatitis diaper (6.3%, 3.9%), gastroenteritis rotavirus (1.2%, 0.3%), skin candida (1.2%, 0.3%), candida diaper rash (2.1%, 1.5%).
- Toddler dose safety population (n_{13vPnC}=267, n_{PCV7}=258): diarrhea (3.4%, 3.1%), croup infections (2.6%, 2.3%), pharyngitis (2.2%, 1.6%), rhinorrhea (1.9%, 1.6%), otitis media acute (1.9%, 1.2%), teething (1.1%, 0.8%), viral infection (1.9%, 0.8%), nasopharyngitis (1.1%, 0.8%), and rhinitis allergic (1.1%, 0.8%).

After dose 2, a statistically significantly higher proportion of 13vPnC subjects compared to PCV7 subjects experienced pyrexia (5.5% vs. 2.0%; p=0.031) and candida diaper rash (2.0% vs 0.0%, p=0.030). These events occurred 8-30 days after vaccination. After dose 3, a statistically significantly higher proportion of 13vPnC subjects experienced nasal congestion (3.0%) compared to PCV7 subjects (0.3%)(p=0.011).

Table 37. Study 6096A1-004. Rates of other events of interest

	Post-dose 3		Post-dose 4	
MedDRA PT	13vPnC %	PCV7 %	13vPnC %	PCV7 %
Neutropenia	0.0	0.3	0.0	0.0
Convulsion	0.3	0.0	0.0	0.0
Febrile convulsion	0.3	0.0	0.0	0.4%
Wheezing	3.3	4.2	0.4%	1.2%
Bronchial hyperreactivity	1.8	2.7	0.0	1.2%

Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 146-152, and 157-161 (Tables 10-12 to 10-13).

7.1.4.3.5 Serious Adverse Events (SAEs)

SAEs reported in both groups were similar overall. No deaths were reported during the study. No subjects died during the course of the study.

Table 38. Study 6096A1-004. Incidence of select SAEs throughout the study period, by MedDRA system organ class and preferred term.

	Safety Populations by Dose											
	Infant Series: Doses 1-3			After Infant Series But Before Toddler Dose			Toddler Dose: Dose 4			6-month follow-up period		
System Organ Class Preferred Term	13vPnC N[a]=332 n (%)	PCV7 N[a]=331 n (%)	p-value[b]	13vPnC N[a]=332 n (%)	PCV7 N[a]=330 n (%)	p-value[b]	13vPnC N[a]=267 n (%)	PCV7 N[a]=258 n (%)	p-value[b]	13vPnC N[a]=330 n (%)	PCV7 N[a]=329 n (%)	p-value[b]
Any event	17 (5.1)	16 (4.8)	>.99	5 (1.5)	7 (2.1)	0.498	3 (1.1)	4 (1.6)	0.720	9 (2.7)	5 (1.5)	0.419
Infections and Infestations	9 (2.7)	13 (3.9)	0.396	1 (0.3)	5 (1.5)	N/A	0 (0.0)	1 (0.4)	0.491	7 (2.1)	3 (0.9)	0.340
Bronchiolitis	4 (1.2)	6 (1.8)	0.545	0 (0)	2 (0.6)	N/A	-	-	-	1 (0.3)	0 (0.0)	> 0.99
Bronchitis	-	-	-	-	-	-	-	-	-	1 (0.3)	0 (0.0)	> 0.99
Cellulitis	-	-	-	1 (0.3)	0 (0)	N/A	-	-	-	1 (0.3)	1 (0.3)	> 0.99
RSV bronchiolitis	3 (0.9)	2 (0.6)	>.99	-	-	-	-	-	-	1 (0.3)	1 (0.3)	> 0.99
RSV infection	0 (0)	2 (0.6)	0.249	-	-	-	-	-	-	1 (0.3)	0 (0.0)	> 0.99
Croup infectious	0 (0)	1 (0.3)	0.499	-	-	-	-	-	-	-	-	-
Mastoiditis	-	-	-	-	-	-	-	-	-	1 (0.3)	1 (0.3)	> 0.99
Nasopharyngitis	1 (0.3)	0 (0)	>.99	-	-	-	-	-	-	-	-	-
Otitis media	0 (0)	1 (0.3)	0.499	-	-	-	-	-	-	-	-	-
Pneumonia	1 (0.3)	0 (0)	>.99	0 (0)	1 (0.3)	N/A	-	-	-	1 (0.3)	1 (0.3)	> 0.99
Pneumonia RSV	0 (0)	1 (0.3)	0.499	-	-	-	-	-	-	-	-	-
Pneumonia viral	1 (0.3)	0 (0)	>.99	-	-	-	-	-	-	0 (0.0)	1 (0.3)	0.499
Rhinitis	-	-	-	-	-	-	-	-	-	1 (0.3)	0 (0.0)	> 0.99
Nervous System Disorders	2 (0.6)	0 (0.0)	0.499	-	-	-	1 (0.4)	1 (0.4)	> 0.99	1 (0.3)	0 (0.0)	> 0.99
Convulsion	1 (0.3)	0 (0)	>.99	-	-	-	-	-	-	1 (0.3)	0 (0.0)	> 0.99
Epilepsy	-	-	-	-	-	-	1 (0.47)	0 (0.0)	0.491	-	-	-
Febrile convulsion	1 (0.3)	0 (0)	>.99	1 (0.3)	0 (0.0)	N/A	0 (0.0)	1 (0.4)	0.491	-	-	-
Postictal paralysis	-	-	-	1 (0.3)	0 (0.0)	N/A	-	-	-	-	-	-
Respiratory, Thoracic and Mediastinal Disorders	2 (0.6)	2 (0.6)	>.99	-	-	-	1 (0.4)	2 (0.8)	0.618	1 (0.3)	3 (0.9)	0.373
Asthma	-	-	-	-	-	-	0 (0.0)	1 (0.4)	0.491	1 (0.3)	1 (0.3)	> 0.99
Bronchial hyperreactivity	-	-	-	-	-	-				0 (0.0)	1 (0.3)	0.499
Cough	1 (0.3)	1 (0.3)	>.99	-	-	-	0 (0.0)	1 (0.4)	0.491	-	-	-
Apnoea	0 (0)	1 (0.3)	0.499	-	-	-	-	-	-	-	-	-
Respiratory distress	1 (0.3)	0 (0)	>.99	-	-	-	-	-	-	-	-	-
Status asthmaticus	-	-	-	1 (0.3)	2 (0.6)	N/A	1 (0.4)	0 (0.0)	> 0.99	0 (0.0)	1 (0.3)	0.499

RSV: Respiratory Syncytial Virus;
[a] Number of subjects reporting yes for at least 1 day or no for all days. [b] p-values are not corrected for multiple comparisons.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, pages 165-169 (Tables 10-16 and 10-19).
Note: This table was created by CBER by adding up the numbers of subjects reporting each MedDRA PT. Because subjects may have more than 1 adverse event PT terms reported, some subjects may have been counted more than once when combining MedDRA PT terms. These numbers therefore provide an overestimate of the actual values.

Table 39. Study 6096A1-004. Subjects Who Experienced SAEs Within 30 Days After Any of Doses 1-3

Site-Subject Number	Vaccine Group	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Outcome
001-000013	13vPnC	1	Bronchiolitis	51	23	Resolved
004-000238	13vPnC	1	RSV bronchiolitis	7	11	Resolved
004-000267	13vPnC	1	Bronchiolitis	8	9	Resolved
006-000376	13vPnC	1	Cough	1	5	Resolved
006-000389	13vPnC	1	RSV bronchiolitis	13	14	Resolved
010-001058	13vPnC	1	Nasopharyngitis	11	5	Resolved
012-001215	13vPnC	1	Pyrexia	13	3	Resolved
016-001593	13vPnC	1	Bronchiolitis	25	16	Resolved
			Pneumonia viral	31	9	Resolved
018-001750	13vPnC	1	Bronchiolitis	43	14	Resolved
021-001978	13vPnC	2	Near drowning	73	1	Resolved
024-002212[a]	13vPnC	3	Constipation	30	6	Resolved
			Vomiting	30	2	Resolved
025-002269	13vPnC	2	Febrile convulsion	4	1	Resolved
			Pyrexia	4	5	Resolved
028-002486	13vPnC	2	RSV bronchiolitis	33	12	Resolved
029-002554	13vPnC	2	Thrombocytopenia	9	4	Resolved
			Thrombocytopenia	22	100	Resolved
029-002566[b]	13vPnC	1	Convulsion	8	1	Resolved
035-003155	13vPnC	2	Pneumonia	23	14	Resolved
035-003160	13vPnC	3	Respiratory distress	18	5	Resolved
			Respiratory distress	32	8	Resolved
001-000037	PCV7	1	Apnoea	52	93	Resolved
002-000088	PCV7	2	Bronchiolitis	3	14	Resolved
004-000246	PCV7	1	Bronchiolitis	27	19	Resolved
006-000377	PCV7	1	Cough	1	54	Resolved
006-000390	PCV7	1	Bronchiolitis	17	12	Resolved
006-000398	PCV7	3	Contusion	29	3	Resolved
009-000977	PCV7	2	Bronchiolitis	15	3	Resolved
010-001053[c]	PCV7	1	RSV bronchiolitis	48	5	Resolved
012-001205	PCV7	2	RSV infection	32	11	Resolved
018-001742	PCV7	2	Croup infectious	61	5	Resolved
018-001752	PCV7	1	Bronchiolitis	57	12	Resolved
027-002413	PCV7	1	Urinary tract infection	53	26	Resolved
027-002415	PCV7	1	Pneumonia RSV	36	22	Resolved
028-002489	PCV7	3	RSV bronchiolitis	13	4	Resolved
029-002553	PCV7	2	RSV infection	10	8	Resolved
207-000676	PCV7	1	Otitis media	37	8	Resolved
			Bronchiolitis	37	8	Resolved
			Varicella	37	8	Resolved

RSV: Respiratory Syncytial Virus
[a] Subject 024-002212 also experienced congenital megacolon 145 days after 4th dose of 13vPnC vaccine.
[b] Subject 029-002566 was withdrawn but safety data was collected at the 6-month follow-up. Following the 1st dose of 13vPnC, this subject experienced 3 additional convulsions on days 74, 109, and 152 and pneumonia on day 152.
[c] Subject 010-001053 also experienced asthma 33 days after the toddler dose
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf

Table 40. Study 6096A1-004. Subjects Who Experienced SAEs After the Infant Series And Before Dose 4

Site Subject Number	Vaccine Group	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Outcome
004-000261	13vPnC	3	Cellulitis	195	17	Resolved
006-000395	13vPnC	3	Skull fracture	136	87	Resolved
014-001428	13vPnC	3	Febrile convulsion Postictal paralysis	189 189	1 1	Resolved Resolved
033-002864	13vPnC	3	Femur fracture Tibia fracture	53 53	57 57	Resolved Resolved
106-000460[a]	13vPnC	3	Status asthmaticus Status asthmaticus	79 101	3 4	Resolved Resolved
001-000011	PCV7	3	Gastroenteritis viral	49	2	Resolved
003-000160	PCV7	3	Nephroblastoma	117	C	Persisted
006-000380[b]	PCV7	3	Bronchiolitis Pneumonia Status asthmaticus	73 73 73	33 33 33	Resolved Resolved Resolved
006-000388	PCV7	3	Rectal abscess	190	19	Resolved
009-000982	PCV7	3	Status asthmaticus	190	9	Resolved
014-001429	PCV7	3	Bronchiolitis	88	4	Resolved
028-002484	PCV7	3	Abscess neck	132	18	Resolved

[a] Subject 106-000460 also experienced status ashtmaticus 15 days after the toddler dose.
[b] Subject 006-000380 also experienced RSV bronchiolitis 108 days after the toddler dose.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf

Table 41. Study 6096A1-004. Subjects Who Experienced SAEs Within 30 Days After Dose 4

Site Subject Number	Vaccine Group	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Outcome
009-000983	13vPnC	4	Accidental overdose	37	2	Resolved
106-000460[a]	13vPnC	4	Status asthmaticus	15	2	Resolved
133-002937	13vPnC	4	Epilepsy	29	C	Persisted
010-001053[b]	PCV7	4	Asthma	33	4	Resolved
018-001738	PCV7	4	Dehydration Gastroenteritis	26 26	3 5	Resolved Resolved
030-002629	PCV7	4	Cough	17	24	Resolved
133-002940	PCV7	4	Febrile convulsion	44	2	Resolved

[a] Subject 106-000460 is also listed in the during infant series table.
[b] Subject 010-001053 is also listed in the after infant series table.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf

Table 42. Study 6096A1-004. Subjects Who Experienced SAEs During the 6-month Follow-up

Site Subject Number	Vaccine Group	Dose #	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Outcome
001-000004	13vPnC	4	Subcutaneous abscess Cellulitis	137 137	12 12	Resolved Resolved
006-000382	13vPnC	4	Asthma RSV infection	129 129	4 16	Resolved Resolved
009-000988	13vPnC	4	Selective IgA immunodeficiency Bronchitis Rhinitis	147 150 150	C 6 2	Persisted Resolved Resolved
018-001730	13vPnC	4	Mastoiditis	183	11	Resolved
024-002212[a]	13vPnC	4	Congenital megacolon	145	C	Persisted
025-002258	13vPnC	4	RSV bronchiolitis	113	12	Resolved
029-002566[b]	13vPnC	1	Convulsion Convulsion Pneumonia Convulsion	74 109 152 152	2 1 4 2	Resolved Resolved Resolved Resolved
035-003157	13vPnC	4	Bronchiolitis	47	9	Resolved
035-003162	13vPnC	4	Accidental exposure	81	1	Resolved
006-000380[c]	PCV7	4	RSV bronchiolitis	108	13	Resolved
006-000393	PCV7	4	Status asthmaticus Pneumonia viral	140 140	3 8	Resolved Resolved
006-000404	PCV7	4	Asthma	123	10	Resolved
024-002222	PCV7	4	Bronchial hyperreactivity	154	13	Resolved

RSV: Respiratory syncytial virus
[a] Subject 024-002212 is also in the dose 1-3 table)
[b] Subject 029-002566 is also in the dose 1-3 table. This subject was withdrawn after having had a convulsion after the first dose.
[c] Subject 000380 is also in the after infant series table.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf

7.1.4.3.6 Safety-Related Discontinuations

Overall, 7 subjects withdrew from the study or discontinued test article administration due to an AE.

- During the infant series (n=4): 13vPnC n=3 (0.9%), PCV7 n=1 (0.3%).
- After the infant series (n=3): 13vPnC n=1 (0.3%), PCV7 n=2 (0.6%).

Table 43. Study 6096A1-004. Study Withdrawal and Test Article Discontinuation Due to a AE

Subject number	Vaccine Group	Preferred Term	Vax #	Time to Onset (days)	Duration (days)	Severity[a]	Action[b]	Outcome	SAE
During infant series									
001978	13vPnC	Near drowning	2	73	1	Life	H, W	Resolved	Yes
002554	13vPnC	Thrombocytopenia	2	22	100	Severe	UT, D, W	Resolved	Yes
002566	13vPnC	Convulsion Convulsion	1 1	8 32	1 -	Severe Severe	H, ER, W, D C, ER, U, W, D	Resolved Persisted	Yes
000377	PCV7	Muscular weakness	1	54	-	Mild	W	Persisted	No
Post-dose 3 visit and before dose 4									
001428	13vPnC	Febrile convulsion	3	189	1	Severe	H, W, ER	Resolved	Yes
000160	PCV7	Nephroblastoma	3	117	-	Life	H, C, W, D	Persisted	Yes
002559	PCV7	Varicella	3	159	15	Moderate	C, U, W, D	Resolved	No

[a] Severity abbreviation: Life - life-threatening.
[b] Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page s170-173 (Tables 10-20 – 10-25.).

7.1.4.3.7 Clinical Case Narratives

Clinical case narratives are provided for subjects who had SAEs that were determined by the study investigator to possibly be related to the study vaccine or AEs resulting in study withdrawal.

Subject 6096A1-004-003-00160

Approximately 4 months after the 3rd PCV7 vaccination, this 10-month old white, male infant was diagnosed with bilateral Wilms tumor (nephroblastoma). A right renal mass was initially discovered during an evaluation (echocardiogram) for a heart murmur. A subsequent computed tomography (CT) scan revealed bilateral renal masses. Bilateral renal biopsies confirmed a nephroblastoma on the right side and a non-malignant nephrogenic rest on the left side. The subject developed a mild post-operative ileus following his first biopsy procedure. The infant was started on chemotherapy and underwent a complete right nephrectomy and partial left nephrectomy. Subsequent CT scan showed no residual malignancy. Medical history was significant for an undescended right testicle. The subject was withdrawn from the study because he met the serious chronic disorder exclusion criterion.

Subject 6096A1-004-006-000377

Fifty-four days after the 1st PCV7 vaccination, this 4-month old white, female infant was diagnosed with mild right arm weakness. The infant was withdrawn from the study because she met the significant neurologic disorder exclusion criterion. The subject completed safety follow-up at about 9.5 months of age (~ 7.5 months following the 1st vaccination), and the condition was reported as persistent at that time. Medical history is significant for permaturity, increased platelet count, lymphocyte count, and alkaline phosphatase, and decreased aspartate aminotransferase and alanine aminotransferase levels. Other significant AEs reported by this subject during the study include moderate coughing spells resulting in hospitalization (pertussis was ruled out) and mild torticollis (which persists).

Subject 6096A1-004-014-001428

Six months and one week after the 3rd 13vPnC vaccination, this 12-month old black, male infant with a noncontributory prior medical history experienced a fever of 102°F for several hours and a 10 minute episode of generalized twitching (except for left arm) associated with drooling. On admission, his fever measured 105.3°F and he was noted to have left arm paralysis. A head CT scan without contrast showed only opacification in the mastoid air filled and middle ear cavity. The subject's complete blood count, basic metabolic panel, magnesium, and phosphate levels were within normal limits. EEG and EKG findings were normal. Blood and urine cultures were also negative. The subject was diagnosed with a complex febrile seizure with Todd paralysis of the left arm and was admitted for observation. On the second day of hospitalization he was diagnosed with acute otitis media. On discharge, the subject was afebrile. The subject was withdrawn from the study because he met the significant neurologic disorder exclusion criterion. The event is considered resolved. This subject had other adverse events reported, described as consistent routine childhood illnesses; these other events included upper respiratory tract infection, pulmonary infiltrate, reactive airway disease, fever, and sinusitis.

Subject 6096A1-004-021-001978

About 2.5 months after the 2nd 13vPnC vaccination, this 6-month old black, male infant with a noncontributory prior medical history was admitted to the pediatric intensive care unit following a near drowning and resuscitation. The subject recovered without neurological sequelae. The investigator discontinued the subject from the study because the parent was overwhelmed by the event and did not feel that she could continue with study participation.

Subject 6096A1-004-025-002269

Four days after the 2nd 13vPnC vaccination, this 4-month old white, female infant with a noncontributory prior medical history experienced a fever of 104°F, decreased oral intake, cough, and diarrhea. She had seizure activity consisting of arching of the back and rolling of the eyes, lasting for 20 minutes, followed by generalized limpness for several minutes. Cerebrospinal fluid, blood, urine, and stool cultures were all negative. A CT scan of the head was reported as normal. Empirical treatment was begun until cultures proved negative; no antiseizure medication was given. The febrile seizure event was considered resolved on

the day of admission and the subject had no further seizure activity. Fever had resolved four days after admission, diarrhea had resolved 3 days after admission. The subject was diagnosed with gastroesophageal reflux disease on the day the 2nd 13vPnC vaccination was administered. The subject was withdrawn from the study at parent request on 11 Apr 2007 before the site was informed of these events. The subject would have met the significant neurological disorder exclusion criterion and would have been withdrawn because of the adverse event.

Subject 6096A1-004-029-002554
Eight days after the 2nd 13vPnC vaccination, this 4-month old male infant with a noncontributory prior medical history was noted by his parent to have blood in his stool. In the clinic, he was noted to have a diffuse petechial rash and his in-office lab testing showed a platelet count of 6000/mL. The infant was hospitalized with a diagnosis of thrombocytopenia. HIV, parvovirus, and toxoplasmosis testing were reportedly negative. Intravenous immunoglobulin was administered for presumptive Idiopathic Thrombocytopenic Purpura (ITP), and his platelet count rose to 137,000/mL. During the following month, serial platelet counts decreased to a range of 35,000 to 54,000/mL, but then steadily returned to normal range without further intervention. About four months after symptom onset, his platelet count was 149,000/mL, and it was determined that this condition had resolved. There were no medications taken before the adverse event. The child was withdrawn from the study because he met the bleeding diathesis or condition associated with prolonged bleeding time exclusion criterion. The subject completed safety follow-up at approximately 10 months of age.

Subject 6096A1-004-029-002559
Five months after the 3rd PCV7 vaccination, this 12-monh old white, male infant with a noncontributory prior medical history was diagnosed with varicella infection, which resolved after about 2 weeks. The infant was withdrawn from the study because he met the confirmed varcella infection exclusion criterion. He completed the 6 month safety follow-up. This subject had other adverse events reported, described as consistent with routine childhood illnesses; these other events were all non-serious and included upper respiratory infection, bilateral otitis media, eczema, bronchiolitis, early bilateral acute otitis media, viral upper respiratory infection, viral exanthema, and varicella infection. The subject completed safety follow-up at approximately 10 months of age.

Subject 6096A1-004—029-002566
Eight days after the 1st 13vPnC vaccination, this 2.5 month old white, female infant was admitted following a seizure lasting 8-10 minutes and a fever of 100.9° F. Medical history included gastroesophageal reflux disease, otitis media, and oral candidiasis, and candida diaper rash; prior medications included ranitidine, mycostatin, and amoxicillin. CSF, blood, and urine cultures were negative. A CT scan of the head and chest radiograph were normal. Two and half weeks after vaccination, the subject was diagnosed with another seizure and bronchiolitis. A subsequent EEG was normal. Another potential seizure was witnessed by the parent one month after vaccination; the subject was brought to the study clinic at which time the study team witnessed her having a generalized seizure. The subject was diagnosed with intermittent seizure disorder and was started on Keppra; the dose of Keppra was gradually increased over the next several months as additional seizures occurred 10.5 weeks, 15.5 weeks, and 5 months (life-threatening) following vaccination. Seizures lasted as long as 20 minutes and occurred mostly in the presence of febrile illness. The subject's seizure disorder remains persistent. The subject was withdrawn from the study one month following vaccination because she met the seizure disorder exclusion criterion. The subject completed safety follow-up through approximately 8 months of age. Other unsolicited AEs reported for this subject include: during first admission: rhinorrrhea, fever, diarrhea, heart murmur, rotavirus (coincident with seizure at 15.5 weeks following vaccination), pneumonia (coincident with seizure occurring 5 months after vaccination),

7.1.4.4 Summary and Conclusions

7.1.4.4.1 Safety
Prevnar 13 safety data from study 004 demonstrated no imbalance in the rates of serious adverse events compared to Prevnar recipients. Overall, rates of solicited local and systemic adverse events (other than fever) were similar to Prevnar. In addition, no consistent trends were identified. Tenderness was the most frequently reported local reaction. Irritability was the most frequently reported systemic adverse event.

Moderate fever (defined as > 39°C and ≤ 40.0°C) occurred in a statistically significantly higher percentage of Prevnar 13 recipients (2.8%) compared to Prevnar recipients (0%). Among Prevnar 13 recipients, mild fever (defined as ≥ 38.0°C and ≤ 39.0°C) was most common after dose 4 and moderate fever was most common after dose 3. No deaths occurred in this study.

7.1.4.4.2 Immunogenicity

This phase 3 study was the pivotal immunogenicity trial for inferring effectiveness of Prevnar 13 in infants and toddlers.

Based on pre-specified objectives in study 004, Prevnar 13 was non-inferior to Prevnar in inducing antibodies against 10 out of 13 serotypes contained in Prevnar 13. Serotypes 6B, 9V, and 3 did not meet the -10% non-inferiority criteria for the proportion of subjects achieving an antibody concentration ≥ 0.35 µg/mL one month after the third vaccination. Serotype 3 also did not meet the non-inferiority criteria for the post-dose 4 GMCs in comparisons to the lowest PCV7-vaccine serotype antibody concentration induced by Prevnar. Serotype 6B and 9V missed the post-dose 3 study endpoint by small margins. Serotype 3 missed both post-dose 3 and post-dose 4 endpoints by large margins.

Interpretation of the data for those serotypes that failed to meet at least one primary study endpoint in study 004 requires some caution, as the primary study endpoints (both based on IgG antibodies measured by ELISA) are not correlates of protection. Although the antibody responses to serotypes 6B and 9V did not meet the non-inferiority criteria for the post-dose 3 primary endpoint, it is noted that each serotype missed by a relatively small margin and both serotypes 6B and 9V met the non-inferiority criteria for the post-dose 3 GMC secondary endpoint. Serotype 9V also elicited higher functional antibody levels one month after the 3rd dose among Prevnar 13 recipients compared to Prevnar recipients.

Similar supportive data are more limited witth regards to serotype 3, which failed to meet the primary endpoints by a large margin and the secondary study endpoints. In addition, exploratory analyses of pre-dose 4 GMCs showed that with the exception of serotype 3, all responses in the Prevnar 13 group met the non-inferiority criteria. Some functional anti-serotype 3 antibody response was elicitied after dose 3, and this response was higher after the fourth dose compared to the third dose. However, there is no helpful comparator when assessing serotype 3 exploratory OPA data, because Prevnar lacks serotype 3.

When evaluating the proportion of subjects achieving an IgG antibody concentration ≥ 0.35 µg/mL just prior to the fourth study dose ,showed that, with the exception of serotype 19F, responses among Prevnar 13 recipients appeared to wane more by the time of the 4th study dose compared to Prevnar recipients. Less than 60% of Prevnar 13 recipients achieved an antibody concentration ≥ 0.35 µg/mL to serotypes 4, 9V, 18C, 23F, and 3 just before the 4th dose, indicating the need for a fourth dose to improve immune responses to these five serotypes in particular. A similar trend was seen with pre-dose 4 GMC levels, with the exception of serotype 14

Immune responses to concomitant vaccine antigens demonstrated no interference when Prevnar 13 is concomitantly administered with childhood vaccines to prevent diphtheria, pertussis, haemophiulus influenzae b, measles, and varicella. Based on limited data, responses to mumps and rubella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients.

7.2 Clinical Study Protocol # 6096A1-3005

Clinical trials.gov registry identifier: NCT00444457

CSR # 74251: Infant series analyses.

Protocol 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.

7.2.1 Objective/Rationale

The study was designed to meet the following objectives:

7.2.1.1 Primary objectives

1. To demonstrate that the immune responses induced by 3 lots of 13vPnC are equivalent when measured 1 month after the 3rd dose.
2. To demonstrate that the immune responses to antigens contained in DTaP-HBV-IPV [Pediarix] when co-administered with 13vPnC are noninferior to immune responses to the same antigens when Pediarix is given 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.

7.2.1.2 Safety objective

To evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence of local injection site reactions, systemic events, and adverse events (AEs).

7.2.1.3 Secondary objectives

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

7.2.2 Design Overview

Table 44. Study 3005 design: Parallel-group, randomized, active-controlled, double-blind, multi-center study

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 manufacturing scale lot		
n= 200	PCV7 (Prevnar)		

Source: 125324/0.3,m5.3.5.1, CSR-74251-protocol-amend.pdf

7.2.3 Protocol

7.2.3.1 Population

7.2.3.1.1 Study Period
The study period for the first three doses (the infant series) was August 15, 2007 to June 9, 2008.

7.2.3.1.2 Study sites and recruitment
Study 6096A1-3005 was conducted at 80 sites in the United States.

7.2.3.1.3 Inclusion Criteria
Study 3005 inclusion criteria were identical to study 004 inclusion criteria.

7.2.3.1.4 Exclusion Criteria
With one exception, study 3005 exclusion criteria were identical to study 004 exclusion criteria; study 3005 did not specify exclusion based on a history of culture-proven invasive disease caused *H. influenzae* type b (Hib) or confirmed measles, mumps, rubella, or varicella infection.

7.2.3.1.5 Criteria for Temporarily Delaying Vaccine Administration
The criteria for temporarily delaying vaccine administration were identical to those in study 004.

7.2.3.1.6 Criteria for Withdrawal of a Subject From the Study
The criteria for withdrawal of a subject from study 3005 were identical to those in study 004.
Every effort was made to collect safety data for withdrawn subjects as well as all data specified by the protocol, including post-vaccination blood draws.

7.2.3.2 Concomitant medications
Antipyretic medications were permitted to prevent or treat symptoms related to study vaccination, and this information was collected on days 1 to 7 after vaccination. Data on the use of other concomitant medications, other than antipyretic medications, were not collected.

7.2.3.3 Vaccine administration
Children received the following study vaccines as per protocol. Please see study-004 vaccine administration section (7.1.3.3) for Prevnar, Pediarix, ActHIB, and ProQuad vaccine composition.

13vPnC: Each 0.5ml dose contains 2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4ug saccharide for 6B individually conjugated to cross-reacting material 197 (CRM_{197}). The total concentration of CRM_{197} is 29ug. The final formulation contains 5mM succinate buffer, 0.02% polysorbate 80, and 0.125 mg aluminum as AlPO4. The vaccine is formulated as a liquid and appears as a homogeneous, white suspension after shaking. The vaccine was filled in containers that were identical to those containing PCV7. Route: intramuscular (IM), anterolateral left thigh. Lot numbers: 7-5095-003A (pilot lot 1); 7-5095-004 (pilot lot 2); 7-5095-005 (Mfg lot).

PCV7 [Prevnar; WLVP]: Route: IM, anterolateral left thigh. Lot number: 7-5092-009A.

DTaP-HBV-IPV [Pediarix; GSK]: Route: IM, upper anterolateral right thigh, apart from ActHIB conjugate vaccine injection site. Lot number: AC21B132BA.

PRP-T [ActHIB; Sanofi Pasteur SA]: Route: IM, lower anterolateral right thigh, apart from Pediarix injection site. Lot number: UF162AA.

MMRV [ProQuad; Merck & Co., Inc.]: Route: subcutaneously (SQ) into left or right deltoid. Lot number: will be provided in separate study report. If commercially available MMR-varicella vaccine supplies were limited due to anticipated shortages, commercially available MMR and varicella vaccines could be administered as separate subcutaneous injections (1 vaccine in each arm) at 12 months of age.

Hepatitis A: A commercially available hepatitis A vaccine was to be administered at 12 months of age. Route: IM, upper anterolateral right thigh, apart from injection site of any other vaccination. Lot number: will be provided in separate study report.

Permitted vaccines: The same as in study 004, except study 3005 permitted a booster dose of Hib vaccine at 15 to 18 months of age (provided by the applicant).

7.2.3.4 Endpoints

7.2.3.4.1 Primary Immunogenicity Endpoints

1. Pneumococcal serotype-specific geometric mean IgG concentrations one month after the 3rd dose
2. Proportion with anti-tetanus antibody level ≥ 0.1 IU/mL measured one month after the 3rd dose
3. Proportion with anti-polio antibody titer ≥ 1:8 for types 1 - 3 measured one month after the 3rd dose
4. Proportion with anti-HBV antibody level ≥ 10.0 mIU/mL measured one month after the 3rd dose

Note: For concomitant antigen analysis, a subset of approximately 60 evaluable subjects per 13vPnC lot group was compared to approximately 175 evaluable subjects in the PCV7 group.

7.2.3.4.2 Secondary Immunogenicity Endpoints

1. Proportion with post-dose 3 pneumococcal serotype-specific IgG concentration ≥ 0.35 and 1.0 ug/mL
2. Proportion with post-dose 4 pneumococcal serotype-specific IgG concentration ≥ 0.35 and 1.0 ug/mL
3. Post-dose 4 pneumococcal serotype-specific geometric mean IgG concentration

7.2.3.4.3 Safety Endpoint

Safety endpoints were the same as those of study 004.

7.2.3.5 Surveillance

7.2.3.5.1 Immunogenicity Monitoring

Blood samples (~ 5 mL each) were obtained for immunogenicity analyses one month (28-42 days) after the third dose (~ 7 months of age) and one month (28-42 days) after the fourth dose for all subjects.

Table 45 summarizes the serological assays for pneumococcal and concomitant vaccine antigens. The pneumococcal ELISA assay ----------(b)(4)----------. Missing assay results were not replaced or imputed; they were excluded from analyses.

Table 45. Study 6096A1-3005. Serological Assays for Pneumococcal and Concomitant Vaccine Antigens

Antigen	Assay	Units	Post-dose	Laboratory
13 pneumococcal serotypes	ELISA IgG Antibodies	µg/mL	3 & 4	EPP-CTAD[†], Wyeth, Pearl River, NY
Tetanus toxoid	ELISA IgG antibodies	IU/mL	3	----b(4)----------
Hepatitis B surface antigen	FDA approved in vitro diagnostic kit	mIU/mL	3	----------b(4)----------
Polio types 1, 2, and 3	--b(4)---------- neutralization assay	Neutralizing antibody titers	3	---b(4)----------

[†] Early Phase Programs – Clinical Testing and Assay Development (EPP-CTAD)
[‡] -----b(4)----------
Source: 125324/0.3,m5.3.5.1, CSR-74251-report body, page 12 (Table 3-1)

7.2.3.5.2 Safety Surveillance / Monitoring

Safety surveillance described in the protocol for study 3005 is identical to study 004 safety surveillance. Table 3 presents the study flowchart.

Table 46. Study 6096A1-3005 Flowchart

Visit No.	1	2	3	4	5	6	7
Visit ID	2-Month Visit	4-Month Visit	6-Month Visit	7-Month Visit	12-Month Visit	13 Month Visit	18 Month Visit
Study Interval	Vaccine dose 1	Vaccine dose 2	Vaccine dose 3	Post-infant series	Vaccine dose 4	Post-toddler dose	6-Month Follow-up
Visit Window	42-98 days of age	42-70 days after visit 1	42-70 days after visit 2 and ≥ 24 wks of age	28-42 days after visit 3	365-395 days of age	28-42 days after visit 5	165-210 days after last study vaccine
Informed consent	X						
Review inclusion/ exclusion/delay criteria	X						
Medical Hx/PE	X						
Core rectal temp	X	X	X		X		
Randomization	X						
Study vaccination & 30 minute observation	X	X	X		X		
Pediarix vaccination	X	X	X				
ActHIB vaccination	X	X	X				
MMRV vaccination					X		
Hepatitis A vaccination					X		
Confirm continued eligibility		X	X	X	X	X	
AE collection	← x →				← x →		
SAE collection	← x →						
Obtain 5 mL blood sample				X		X	
E-diary, thermometer, calipers provided	X	X	X		X		
Assess acute reactions	Day 1 to 7*	Day 1 to 7	Day 1 to 7		Day 1 to 7		
Use of antipyretic medication	Day 1 to 7	Day 1 to 7	Day 1 to 7		Day 1 to 7		
Telephone call							X

*Day of vaccination is considered day 1.
Source: 125324/0.3,m5.3.5.1, CSR-74251-protocol-amend, pages 21-22 (Table 8-1)

7.2.3.6 Statistical considerations

Blinding:
This is a double blind study. The appearance of the 3 lots of 13vPnC and PCV7 were identical. Before analysis was performed, a blinded statistical review of the database occurred to ensure that all data were as expected, that the planned analyses could be performed, and that no underlying statistical assumptions were violated.

The database remained blinded until all data were collected, but the statistician performing the primary analyses was provided with random treatment assignments as well as actual treatment packaging assignment information. Treatment codes were added to snapshots of the clinical database (data listings) and provided to applicant's staff involved in preparing the infant clinical study report for regulatory submission. Treatment codes were not added to the active clinical database, and data listings with unblinded information were placed in secure folders unavailable to applicant's staff involved in ongoing review of safety data.

Randomization:
Eligible subjects were randomized in a 2:2:2:1 ratio to four treatment groups using Wyeth's CORE II system, an interactive response system or equivalent system. Only subjects who withdrew before randomization could be replaced with additional subjects.

Assuming that the 3 lots of 13vPnC vaccine were considered equivalent, a subset of subjects receiving 13vPnC were randomly selected to be included in the concomitant vaccine analysis after all subjects had been enrolled. Subjects were randomly ordered within each of the three 13vPnC lot groups, and the first 76 subjects in each group were selected to ensure a total of about 180-200 evaluable subjects. Additional subjects, if needed, were to be selected from the vaccine group of the subject they were replacing.

7.2.3.6.1 Sample Size/Statistical Power

Sample size estimation was based on the proportion of responders in each treatment group and GMCs for the 13vPnC group for pneumococcal serotypes from study 6096A1-003 and 6096A1-009. Data from Wyeth studies D139-P500 and D140-P001 were used for the proportion of responders to the tetanus, polio, and hepatitis B concomitant vaccine antigens.

Overall, a sample size of 400 evaluable subjects per 13vPnC vaccine lot group and 200 evaluable subjects in the PCV7 group after the 3rd dose would provide at least 88% overall power to declare equivalence among responders for the 3 lots of 13vPnC for all 13 pneumococcal antigens and to declare non-inferiority for all 5 concomitant vaccine antigen comparisons, using a 2-sided, type I error of 0.05. Assuming a 15% drop out rate, 1645 subjects (470 subjects per 13vPnC group and 235 subjects in the PCV7 group) were to be enrolled.

- Concomitant vaccine antigen testing was performed for all PCV7 participants and a subset of 13vPnC participants. A sample size of 175 evaluable PCV7 subjects and 60 evaluable 13vPnC subjects per 13vPnC lot group would provide at least 90% power to declare non-inferiority of 13vPnC versus PCV7 with respect to concomitant vaccine antigens.
- For demonstrating lot consistency, a sample size of 400 evaluable subjects per 13vPnC lot group would provide at least 88% power to declare equivalence among responders for the 3 lots for all 13vPnC pneumococcal antigens. Assuming a 15% drop out rate, 1413 subjects were to be enrolled in the 13vPnC groups.

7.2.3.6.2 Study Cohorts Analyzed

The four analysis populations used in the immunogenicity analyses in study 3005 were identical to study 004, with one exception; the time window for receipt of the toddler dose was defined as 364 to 396 days inclusive in study 3005, whereas it was 364 to 456 days inclusive in study 004. In study 3005, a single all-available toddler immunogenicity analysis will be performed if there were no important differences between the evaluable toddler and all-available toddler immunogenicity populations. Immunogenicity analyses were based on subjects' randomized treatment assignment.

7.2.3.6.3 Statistical Analyses

7.2.3.6.3.1 Immunogenicity analyses

Primary hypotheses:

1. To demonstrate that the immune responses induced by 3 lots of 13vPnC are equivalent when measured 1 month after the 3rd dose. This hypothesis will be supported if the maximum difference between the log of the geometric mean IgG concentrations from subjects receiving any two lots is < 0.693 and > -0.693.

2. To demonstrate that the immune responses to selected antigens contained in DTaP-HBV-IPV [Pediarix], when co-administered with 13vPnC, are noninferior to immune responses to the same antigens when Pediarix is given with PCV7. Non-inferiority criteria: The lower limit of the 2-sided, 95% CI for the difference in two proportions (*p*13vPnC – *p*PCV7; where *p* = % of subjects achieving predetermined antibody levels) is >-10% for all of the following endpoints: % with anti-tetanus antibody level ≥ 0.1 IU/mL % with anti-polio antibody titer ≥ 1:8 for types 1-3, and % with anti-HBV antibody ≥ 10.0 mIU/mL. Hypothesis 1 must be met in order to proceed to hypothesis 2.

For geometric means, each concentration or titer was logarithmically transformed for analysis. Two-sided 95% CIs were constructed by back transformation of the CIs for the mean of the logarithmically

transformed assay results computed using the student t distribution. For the geometric mean ratio, the CIs were computed using the Student t distribution for the mean difference of the measures on the log scale. To evaluate equivalency among the 3 lots, the equivalence test of Wiens and Iglewicz was used [J Biopharm Stat. 1999;9(3):465-483].

Adjustment for multiplicity is not needed since non-inferiority for the study is demonstrated only if the lower bounds for the difference in proportions for all 5 concomitant vaccine comparisons are > -0.1. Empirical reverse cumulative distribution curves (RCDCs) were presented graphically by lot for each serotype. Post-dose 3 and post-dose 4 RCDCs will be presented separately.

7.2.3.6.3.2 Safety analyses

The safety analyses in study 3005 were identical to those described in study 004.

Interim analyses:

A primary analysis was performed after all assay results for the infant series were available. All Type I error was to be spent for this analysis. The primary analysis of the safety data collected during the infant series was planned for regulatory submission before the assay results were available. Data collected following the primary analysis are secondary and/or exploratory. A final analysis will be performed at the 6 month follow-up after all data have been collected.

7.2.3.7 Changes in the Study Protocol (Protocol Amendments) and in the Planned Analyses

The two amendments to the original protocol (dated 16-Jan-07) are summarized below.

- Amendment 1 (24-Aug-07):
  - Sample size increased from 1442 to 1645 to maintain a power of at least 88%. Per FDA request, changed primary endpoint from % of subjects with post-dose 3 serotype-specific IgG ≥ 0.35µg/mL to post-dose 3 serotype-specific geometric mean IgG concentrations.
  - Clarified that the analysis following completion of the 3 dose infant series was the primary analysis and that all subsequent analyses were secondary or exploratory.
  - Per FDA request, specified that data from each of the 3 groups of 13vPnC subjects would only be pooled for comparison to the PCV7 group if similar pneumococcal antibody responses were demonstrated among the 13vPnC groups (lot consistency).
  - Indicated that the final 13vPnC formulation (chosen based on data from study 6096A1-009) will contain polysorbate 80 and that the three 13vPnC lots would contain polysorbate 80.
  - Revised protocol to allow MMR vaccine and varicella vaccine to be administered as separate injections, due to anticipated shortages of Pro-Quad.
  - Clarified that parent/legal guardian should contact the study site by telephone if they suspected their child had hives to determine whether the rash was likely to be urticaria.
- Amendment 2 (11-Mar-08):
  - Acknowledged that the interim safety analysis would be performed following the infant phase of the study, and that analysis was planned for regulatory submission before the assay results would be available.
  - Removed the 12 month dose of ActHIB from the study vaccinations because the 4th dose of ActHIB is only licensed for administration at 15-18 months of age. The use of PedvaxHib, which is licensed for administration at 12-15 months of age as a fourth Hib vaccine dose, was also precluded because of a vaccine shortage.
  - Added rotavirus as a permitted nonstudy vaccination during anytime throughout the study.

The statistical analysis plan (SAP) was submitted on 24-Jun-08, approximately two weeks after the study had been completed. The SAP specified that the database was to remain blinded until all data queries were resolved and the 6-month follow-up data were received for all subjects. However, the applicant was actually unblinded at the time of the infant series analysis for the regulatory submission. The SAP also allowed for a 1-day deviation around age at the time of enrollment and age at toddler dose for determination of evaluability, because the protocol did not provide investigators with directions on how to calculate age or timings. Blood draws 1 day before and 14 days after the protocol-specified time windows were permitted for determination of evaluability.

Nonstudy vaccines received before enrollment were categorized according to the WHO drug dictionary and summarized according to the Anatomic Therapeutic Chemical (ATC) 4 class.

7.2.4 Results

7.2.4.1 Populations Enrolled/Analyzed

A total of 1712 subjects were enrolled/randomized into this study; 489, 488, and 489 subjects were randomized to 13vPnC pilot scale lot 1, pilot scale lot 2, and manufacturing scale lot groups respectively; 246 subjects were randomized to the PCV7 group.

7.2.4.1.1 Subject Disposition and Follow-up

Table 47. Study 6096A1-3005. Summary of Subject Disposition

	13vPnC Pilot Scale Lot 1 N=489		13vPnC Pilot Scale Lot 2 N=488		13vPnC Manufacturing Scale Lot N=489		PCV7 N=246		Total N=1712	
	n	%	n	%	n	%	n	%	n	%
Subjects consented[a]	489	100.0	486	99.6	488	99.8	246	100.0	1709	99.8
Subjects randomized	489	100.0	488	100.0	489	100.0	246	100.0	1712	100.0
Subjects vaccinated										
Dose 1	486	99.4	484	99.2	485	99.2	244	99.2	1699	99.2
Dose 2	455	93.0	447	91.6	455	93	228	92.7	1585	92.6
Dose 3	442	90.4	435	89.1	438	89.6	225	91.5	1540	90.0
Completed infant series	435	89.0	427	87.5	428	87.5	218	88.6	1508	88.1
Withdrawn during infant series	54	11.0	60	12.3	61	12.5	28	11.4	203	11.9
Unknown	0	0.0	1[b]	0.2	0	0.0	0	0.0	1	0.1
Reasons for withdrawal:										
Parent / legal guardian request	18	3.7	29	5.9	34	7	14	5.7	95	5.5
Lost to follow-up	10	2.0	11	2.3	7	1.4	6	2.4	34	2.0
Protocol violation[†]	16	3.3	8	1.6	6	1.2	3	1.2	33	1.9
Failed to return	5	1.0	4	0.8	4	0.8	2	0.8	15	0.9
Investigator request	4	0.8	3	0.6	3	0.6	2	0.8	12	0.7
Other[j]	0	0.0	2	0.4	4	0.8	0	0	6	0.4
Adverse Event	1	0.2	2	0.4	2	0.4	0	0	5	0.3
Death	0	0.0	1	0.2	1	0.2	1	0.4	3	0.2

[a] Subjects 3005-012-001101, 3005-013-001200, and 3005-081-007846 were prerandomized but not consented.
[b] Subject 3005-032-003041 had no completion or withdrawal data recorded.
Source: 125324/0.3,m5.3.5.1, CSR-74251-report body, page 42 (Table 8-1).

There were 1216 and 1243 subjects in the evaluable and all-available pneumococcal infant immunogenicity populations respectively. There were 385 and 393 subjects in the evaluable and all-available concomitant infant immunogenicity populations respectively. The all-available infant safety population included 1699 infants.

Table 48. Study 6096A1-3005. Summary of Analysis Populations

	13vPnC Pilot Scale Lot 1 N=489		13vPnC Pilot Scale Lot 2 N=488		13vPnC Manufacturing Scale Lot N=489		PCV7 N=246		Total N=1712	
	n	%	n	%	n	%	n	%	N	%
Randomized	489	100	488	100	489	100	246	100	1712	100
All-available concomitant infant immunogenicity population	67	13.7	64	13.1	64	13.1	198	80.5	393	23.0
All-available pneumococcal infant immunogenicity population[a]	425	86.9	409	83.8	409	83.6	N/A	N/A	1243	72.6
Subjects excluded from the all-available infant immunogenicity populations[b]	422	86.3	424	86.9	426	87.1	48	19.5	1320	77.1
No postinfant assay result for any concomitant antigen	422	86.3	424	86.9	425	86.9	48	19.5	1319	77.0
No postinfant assay result for any pneumococcal serotype[a]	64	13.1	79	16.2	80	16.4	N/A	N/A	223	13.0
Evaluable concomitant infant immunogenicity population	62	12.7	63	12.9	64	13.1	196	79.7	385	22.5
Evaluable pneumococcal infant immunogenicity population[a]	413	84.5	404	82.8	399	81.6	N/A	N/A	1216	71.0
Subjects excluded from the evaluable infant immunogenicity populations[b]	427	87.3	425	87.1	426	87.1	50	20.3	1328	77.6
Not in all-available concomitant infant immunogenicity population	422	86.3	424	86.9	425	86.9	48	19.5	1319	77.0
Not in all-available pneumococcal infant immunogenicity population[a]	64	13.1	79	16.2	80	16.4	N/A	N/A	223	13.0
Blood draw > 56 days after the infant series	7	1.4	2	0.4	5	1.0	2	0.8	16	0.9
Received vaccine other than randomized[d]	3	0.6	1	0.2	4	0.8	0	0.0	8	0.5
Subject vaccinated with another package number	2	0.4	0	0.0	4	0.8	0	0.0	6	0.4
Blood draw < 27 days after the infant series	1	0.2	2	0.4	1	0.2	0	0.0	4	0.2
Not eligible for study	0	0.0	2	0.4	1	0.2	0	0.0	3	0.2
Did not receive all pneumococcal study vaccinations	0	0.0	2	0.4	1	0.2	0	0.0	3	0.2
Subject assigned and vaccinated with incorrect package number (wrong subject # entered)	2	0.4	0	0.0	0	0	0	0	2	0.1

[a] Only applies to 13vPnC groups.
[b] Subjects may have been excluded for more than 1 reason.
Source: 125324/0.3,m5.3.5.1, CSR-74251-report body, pages 55, 56, 76, 206, and 208 (Table 9-1, 10-1, 15.13, and 15.14).

7.2.4.1.2 Subject Demographics

There was a higher proportion of males than females in all study groups; and there was a higher proportion of Black subjects in each of the 13vPnC groups compared to the PCV7 group. The all-available and evaluable concomitant infant immunogenicity populations had a more equal gender distribution and a slightly lower proportion of Hispanic or Latino subjects in the 13vPnC pilot scale lot 1 group and a higher proportion of males (63-64%) in the 13vPnC pilot scale lot 2 group compared to demographics for all subjects shown in Table 6.

Table 49. Study 6096A1-3005. Summary of Demographic Characteristics for All Subjects by Randomized Vaccine Group

	13vPnC Pilot Scale Lot 1 N=489		13vPnC Pilot Scale Lot 2 N=488		13vPnC Manufacturing Scale Lot N=489		PCV7 N=246		Total N=1712	
	n	%	n	%	n	%	n	%	n	%
Gender										
Male	259	53.0	260	53.3	275	56.2	131	53.3	925	54.0
Female	230	47.0	226	46.3	213	43.6	115	46.7	784	45.8
Unknown	0	0.0	2	0.4	1	0.2	0	0.0	3	0.2
Race										
White	394	80.6	405	83.0	389	79.6	211	85.8	1399	81.7
Black	60	12.3	49	10.0	58	11.9	21	8.5	188	11.0
Other	23	4.7	27	5.5	26	5.3	10	4.1	86	5.0
Asian	9	1.8	4	0.8	10	2.0	3	1.2	26	1.5
Native Hawaiian or other Pacific Islander	0	0.0	2	0.4	1	0.2	0	0.0	3	0.2
Unknown	2	0.4	1	0.2	3	0.6	0	0	6	0.35
American Indian or Alaska Native	1	0.2	0	0.0	2	0.4	1	0.4	4	0.2
Ethnicity										
Non-Hispanic and Non-Latino	414	84.7	406	83.2	416	85.1	202	82.1	1438	84.0
Hispanic or Latino	75	15.3	80	16.4	72	14.7	44	17.9	271	15.8
Unknown	0	0.0	2	0.4	1	0.2	0	0.0	3	0.2
Age at enrollment (months)										
Mean (SD)	2.2 (0.3)		2.2 (0.3)		2.2 (0.3)		2.2 (0.3)		2.2 (0.3)	
Min, Max	1.3, 3.3		1.4, 3.3		1.4, 3.3		1.4, 3.2		1.3, 3.3	
Weight at enrollment (lbs)										
Mean (SD)	11.8 (1.7)		11.8 (1.6)		12.0 (1.6)		11.8 (1.6)		11.8 (1.6)	
Min, Max	4.8, 17.0		7.4, 18.6		7.0, 18.9		8.0, 16.6		4.8, 18.9	

Source: 125324/0.3,m5.3.5.1, CSR-74251-report body.pdf, pages 51 and 52 (Table 8-7).

7.2.4.2 Nonstudy Concomitant Vaccinations

Table 50. Study 6096A1-3005. Subjects Who Received Non-Study Vaccinations

	13vPnC Pilot Scale Lot 1 N=489		13vPnC Pilot Scale Lot 2 N=488		13vPnC Manufacturing Scale Lot N=489		PCV7 N=246		Total N=1712	
Non-study vaccinations	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Before Infant Series	357	73.0	356	73.0	346	70.8	184	74.8	1243	72.6
Hepatitis B vaccines	357	73.0	356	73.0	344	70.3	183	74.4	1240	72.4
Rotavirus vaccines	1	0.2	1	0.2	2	0.4	3	1.0	7	0.4
Hepatitis B Immunoglobulin	0	0.0	1	0.2	0	0.0	0	0.0	1	0.1
Synagis Immunoglobulin	1	0.2	0	0.0	1	0.2	0	0.0	2	0.1
During Infant Series	402	82.8	397	81.4	402	82.2	207	84.1	1408	82.2
Rotavirus vaccines	400	81.8	395	80.9	400	81.8	206	83.7	1401	81.8
Influenza vaccine s	15	3.1	16	3.3	15	3.1	7	2.8	53	3.1
Prevnar	2	0.4	2	0.4	1	0.2	1	0.4	6	0.4
Hib vaccines	2	0.4	2	0.4	1	0.2	1	0.4	6	0.4
Hepatitis B vaccines	0	0.0	0	0.0	4	0.8	0	0.0	4	0.2
Pediarix	1	0.2	0	0.0	0	0.0	1	0.4	2	0.1
Pertussis vaccines	0	0.0	1	0.2	1	0.2	0	0.0	2	0.1
Poliomyelitis vaccines	0	0.0	1	0.2	0	0.0	0	0.0	1	0.1
Synagis Immunoglobulin	1	0.2	2	0.4	1	0.2	1	0.4	5	0.3
RSV Immunoglobulin	0	0.0	1	0.2	0	0.0	0	0.0	1	0.1

Source: 125324/0.3,m5.3.5.1, CSR-74251-report body.pdf, pages 183-186 (Tables 15.6 – 15.7).

7.2.4.3 Immunogenicity Endpoints/Outcomes

7.2.4.3.1 Post-dose 3 Pneumococcal Serotype Immunogenicity Outcomes

Post dose 3 Pneumococcal IgG Geometric Mean Concentrations

The differences between each possible 2-way comparison of vaccine lots and corresponding CIs, expressed as natural log-transformed geometric means, are shown in Table 51. The difference in the log transformed geometric mean responses for each of the serotypes among the three 13vPnC lots were < 0.693 and > -0.693, and therefore met the equivalency criterion for this primary endpoint.

Table 51. 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			Mfrg Scale Lot					
Serotype	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
PCV7												
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	1.3	(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)
Additional												
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	2.4	(2.21, 2.61)	402	2.1	(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	(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] n = Number of subjects with a determinate antibody concentration for the specified serotype.
b Confidence intervals (CIs) are back transformations of a confidence interval 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).

Table 52 presents pneumococcal IgG GMCs achieved by 13vPnC subjects in all 3 vaccine lots combined.

Table 52. Study 6096A1-3005. Post-dose 3 Pneumococcal IgG GMCs In the Three 13vPnC Lot Groups Combined

	Vaccine Group As Randomized		
	13vPnC		
Serotype	**N[a]**	**GMC[b]**	**95% CI[c]**
PCV7			
4	1213	1.46	(1.40, 1.52)
6B	1206	2.51	(2.35, 2.68)
9V	1210	1.09	(1.05, 1.13)
14	1172	5.09	(4.84, 5.35)
18C	1212	1.37	(1.31, 1.42)
19F	1205	2.15	(2.05, 2.24)
23F	1212	1.18	(1.11, 1.24)
Additional			
1	1209	1.78	(1.69, 1.86)
3	1190	0.56	(0.54, 0.59)
5	1207	1.24	(1.18, 1.30)
6A	1213	2.21	(2.10, 2.31)
7F	1210	2.57	(2.48, 2.68)
19A	1211	1.91	(1.82, 1.99)

[a] Number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] GMCs were calculated using all subjects with available data for the specified blood draw.
[c] CIs are back transforms of CIs 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 61 (Table 9-3).

Post-dose 3 Seroresponse Rates

Tables 53 and 54 presents post-dose 3 pneumococcal seroresponse rates at the 0.35 µg/mL and alternative 1.00 µg/mL cutoff levels for each of the 13 serotypes in the evaluable infant immunogenicity population; data from the three 13vPnC lot groups were combined.

Table 53. Study 6096A1-3005. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population, Data Combined for all three 13vPnC Lot Groups)

	Vaccine Group As Randomized			
	13vPnC			
Serotype	**N[a]**	**n[b]**	**%**	**95% CI[c]**
PCV7				
4	1213	1179	97.2	(96.1, 98.1)
6B	1206	1121	93.0	(91.4, 94.3)
9V	1210	1159	95.8	(94.5, 96.8)
14	1172	1158	98.8	(98.0, 99.3)
18C	1212	1178	97.2	(96.1, 98.0)
19F	1205	1183	98.2	(97.2, 98.9)
23F	1212	1077	88.9	(87.0, 90.6)
Additional				
1	1209	1182	97.8	(96.8, 98.5)
3	1190	872	73.3	(70.7, 75.8)
5	1207	1122	93.0	(91.4, 94.3)
6A	1213	1180	97.3	(96.2, 98.1)
7F	1210	1204	99.5	(98.9, 99.8)
19A	1211	1194	98.6	(97.8, 99.2)

[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: 125324/0.3,m5.3.5.1, CSR-74251-report body.pdf, page 216 (Table 15.18).

Table 54. Study 6096A1-3005. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 1.00µg/mL After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population, Data Combined for all three 13vPnC Lot Groups)

	Vaccine Group As Randomized			
	13vPnC			
Serotype	**N[a]**	**n[b]**	**%**	**95% CI[c]**
PCV7				
4	1213	858	70.7	(68.1, 73.3)
6B	1206	951	78.9	(76.4, 81.1)
9V	1210	674	55.7	(52.9, 58.5)
14	1172	1116	95.2	(93.8, 96.4)
18C	1212	833	68.7	(66.0, 71.3)
19F	1205	1029	85.4	(83.3, 87.3)
23F	1212	728	60.1	(57.2, 62.8)
Additional				
1	1209	909	75.2	(72.7, 77.6)
3	1190	254	21.3	(19.0, 23.8)
5	1207	728	60.3	(57.5, 63.1)
6A	1213	1032	85.1	(82.9, 87.0)
7F	1210	1123	92.8	(91.2, 94.2)
19A	1211	978	80.8	(78.4, 82.9)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥ 1.00 µg/mL for the given serotype.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.3,m5.3.5.1, CSR-74251-report body.pdf, page 219 (Table 15.21).

7.2.4.3.2 Post-dose 3 Concomitant Vaccine Immunogenicity Results

Seroresponse rates
Each of the co-primary objectives for the concomitant vaccine antigens was met.

Table 55. Study 6096A1-3005. Comparison of Subjects Achieving a Pre-specified antibody Concentration for Concomitant Vaccine Antigens After Dose 3 (Evaluable Infant Immunogenicity Population)

		Vaccine Group As Randomized									
		13vPnC				PCV7					
Concomitant Vaccine Antigen	Comparison level	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]	Difference[d]	(95% CI)[e]
Tetanus toxoid	≥ 0.01 IU/mL	184	181	98.4	(95.3, 99.7)	196	193	98.5	(95.6, 99.7)	-0.1	(-3.3, 3.0)
Poliovirus											
Type 1	≥ 1:8	183	183	100.0	(98.0, 100.0)	187	187	100.0	(98.0, 100.0)	0.0	(-2.1, 2.0)
Type 2	≥ 1:8	183	181	98.9	(96.1, 99.9)	187	186	99.5	(97.1, 100.0)	-0.6	(-3.4, 2.0)
Type 3	≥ 1:8	182	182	100.0	(98.0, 100.0)	187	186	99.5	(97.1, 100.0)	0.5	(-1.5, 3.0)
Hepatitis B	≥ 10.0 mIU/mL	153	153	100	(97.6, 100.0)	173	173	100.0	(97.9, 100.0)	0.0	(-2.4, 2.2)

[a] N = number of subjects with a determinate postinfant series antibody concentration to the given concomitant antigen.
[b] n = Number of subjects with an antibody concentration ≥ prespecified level for the given concomitant antigen.
[c] Exact 2–sided confidence interval based upon the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[e] Exact 2–sided confidence interval for the difference in proportions, 13vPnC – PCV7, expressed as a percentage.
Source: 125324/0.3,m5.3.5.1, CSR-74251-report body.pdf, page 70 (Table 9-7).

Geometric Mean Antibody Concentrations

The lower limit of the 95% confidence interval for the GMC ratios for tetanus toxoid, poliovirus, and hepatitis B vaccine antigens were all greater than 0.5. This was not a pre-specified study endpoint.

Table 56. Study 6096A1-3005. Comparison of Concomitant Vaccine Antigen GMC and GMTs After Dose 3 (Evaluable Infant Immunogenicity Population)

		Vaccine Group As Randomized							
		13vPnC			PCV7				
Concomitant Vaccine Antigen	**Units**	**N[a]**	**GMC/ GMT[b]**	**(95% CI)[c]**	**N[a]**	**GMC/ GMT[b]**	**(95% CI)[c]**	**Ratio[d]**	**(95% CI)[e]**
Tetanus toxoid	IU/mL	184	0.73	(0.65, 0.83)	196	0.77	(0.68, 0.86)	0.96	(0.80, 1.14)
Poliovirus									
Type 1	NA Titers	183	302.43	(256.66, 356.35)	187	330.61	(278.14, 392.98)	0.91	(0.72, 1.16)
Type 2	NA Titers	183	244.62	(202.10, 296.09)	187	261.76	(219.06, 312.78)	0.93	(0.72, 1.21)
Type 3	NA Titers	182	724.08	(606.25, 864.80)	187	545.30	(452.62, 656.96)	1.33	(1.03, 1.72)
Hepatitis B	mIU/mL	153	922.54	(768.51, 1107.44)	173	980.25	(832.87, 1153.72)	0.94	(0.74, 1.20)

NA: Neutralizing Antibody
[a] n = Number of subjects with a determinate antibody concentration for the specified concomitant antigen.
[b] Geometric mean concentrations (GMCs) for antibodies against tetnatus toxoid and heptatitis B antigens and anti-polio 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 concentrations.
[d] Ratio of GMCs or GMTs; 13vPnC to PCV7.
[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).
Source: 125324/0.3,m5.3.5.1, CSR-74251-report body.pdf, page 72 (Table 9-8)

7.2.4.3.3 Dose 4 Pneumococcal Serotype Immunogenicity Outcomes

Post-toddler dose data were not available for submission of clinical study report 74251.

7.2.4.4 Safety Outcomes

7.2.4.4.1 Immediate Reactions

Although immediate reactions were collected and reported along with other unsolicited adverse events, these events could not be idenitifed from the data submitted to the BLA. The specific time-to-onset of symptoms was not recorded, therefore reactions that occurred within 30 minutes of vaccination could not be identified.

Clinical Reviewer Note: CBER requested data regarding immediate reactions, however, the applicant indicated in amendment 11 to the BLA, that the time of observation was not recorded in the case report form. Therefore, the applicant could not identify those adverse events which occurred during the 30 minutes immediately following vaccination.

7.2.4.4.2 Solicited Local Reactions

There were no statistically significant differences between the two study groups. 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 57. Study 6096A1-3005. 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[a]					
	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[c]						
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[c]						
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).

7.2.4.4.3 Solicited Systemic Reactions

In both study groups, 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 3 (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 58. Study 6096A1-3005. 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).

Antipyretic Use
There were so statistically significant differences between the two study groups in the use of antipyretics to treat or prevent symptoms related to vaccination within 7 days of vaccination.

Table 59. Study 6096A1-3005. Subjects who received antipyretics to treat symptoms or to prevent symptoms within 7 days following each dose of 13vPnC or PCV7.

	Use of Antipyretics to Treat Symptoms		Use of Antipyretics to Prevent Symptoms	
Dose number	13vPnC n (%)	PCV7 n (%)	13vPnC n (%)	PCV7 n (%)
1	N[a]=1227 793 (64.6)	N=206 130 (63.1)	N=1276 910 (71.3)	N=214 157 (73.4)
2	N=1011 710 (70.2)	N=169 108 (63.9)	N=1080 811 (75.1)	N=185 139 (75.1)
3	N=952 643 (67.5)	N=160 114 (71.3)	N=978 711 (72.7)	N=167 122 (73.1)

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

7.2.4.4.4 Unsolicited Adverse Events

Overall, a similar proportion of subjects in each study group reported unsolicited adverse events following any of doses 1-3. During the infant series (i.e. within 30 days following any of doses 1-3), unsolicited adverse events were reported by 83.2% (1208/1452) and 85.2% (208/244) of subjects in the 13vPnC and PCV7 groups respectively. The most frequently reported adverse events during the infant series were upper respiratory tract infections (13vPnC: 40.4%, PCV7: 39.8%), otitis media (13vPnC: 27.8%, PCV7: 34.8%), bronchiolitis (13vPnC: 15.2, PCV7: 18.4), and cough (13vPnC: 11.2%, PCV7: 13.5).

Unsolicited adverse events occurring in at least 1% of 13vPnC subjects and in more 13vPnC subjects compared to PCV7 subjects following any of the first three infant series doses included the following: nasal congestion (8.6%, 6.1%), gastroesophageal reflux disease (4.5%, 4.1%), rhinorrhoea (4.4%, 3.7%), croup infections (3.9%, 3.3%), candidiasis (3.1%, 2.9%), otitis media acute (3.0%, 2.5%), wheezing (3.0%, 2.0%), rhinits (2.8%, 2.5%), RSV bronchiolitis (2.1%, 2.0%), pneumonia (2.1%, 1.6%), viral upper respiratory tract infection (2.0%, 0.8%), teething (1.7%, 0.8%), dermatitis contact (1.4%, 1.2%), candida nappy rash (1.4%, 1.2%), and heat rash (1.0%, 0.8%).

There were no statistically significant findings indicating a higher incidence of an adverse event in the 13vPnC group compared to the PCV7 group.

7.2.4.4.5 Serious Adverse Events

Three subjects (3005-002-000-000107, 3005-004-000320, and 3005-079-007651) died during the infant series phase of study 3005. Two deaths occurred in subjects that received 13vPnC vaccine and one death occurred in a subject that received PCV7. Narratives of subject deaths are provided in section 7.2.4.4.7. Overall, a similar proportion of subjects in each treatment group reported the occurrence of any serious adverse event.

Table 60. Study 6096A1-3005. Incidence of SAEs occurring after doses 1 to 3, by MedDRA system organ class and preferred term.

	Infant Series: Doses 1-3		
System Organ Class Preferred Term	**13vPnC N[a]=1452 n (%)**	**PCV7 N[a]=244 n (%)**	**p-value[b]**
Any event	53 (3.7)	15 (6.1)	0.077
Cardiac Disorders	2 (0.1)	0 (0.0)	>.99
Cyanosis	1 (0.1)	0 (0.0)	>.99
Pulmonary valve stenosis	1 (0.1)	0 (0.0)	>.99
Gastrointestinal Disorders	1 (0.1)	1 (0.4)	0.267
Haematochezia	1 (0.1)	0 (0.0)	>.99
Vomiting	0 (0.0)	1 (0.4)	0.144
General Disorders and Administration Site Conditions	5 (0.3)	4 (1.6)	0.029
Pyrexia	3 (0.2)	2 (0.8)	0.153
Sudden infant death syndrome	2 (0.1)	1 (0.4)	0.373
Irritability	0 (0.0)	1 (0.4)	0.144
Immune System Disorders	2 (0.1)	0 (0.0)	>.99
Allergy to vaccine	1 (0.1)	0 (0.0)	>.99
Food allergy	1 (0.1)	0 (0.0)	>.99
Infections and Infestations	42 (2.9)	10 (4.1)	0.315
Bronchiolitis	11 (0.8)	2 (0.8)	>.99
Respiratory syncytial virus bronchiolitis	11 (0.8)	2 (0.8)	>.99
Pneumonia	5 (0.3)	2 (0.8)	0.266
Respiratory syncytial virus infection	4 (0.3)	1 (0.4)	0.541
Urinary tract infection	3 (0.2)	2 (0.8)	0.153
Croup infectious	3 (0.2)	1 (0.4)	0.463
Gastroenteritis	3 (0.2)	1 (0.4)	0.463
Otitis media	3 (0.2)	0 (0.0)	>.99
Upper respiratory tract infection	2 (0.1)	0 (0.0)	>.99
Abscess oral	1 (0.1)	0 (0.0)	>.99
Influenza	1 (0.1)	0 (0.0)	>.99
Meningitis aseptic	1 (0.1)	0 (0.0)	>.99
Meningitis enteroviral	0 (0.0)	1 (0.4)	0.144
Respiratory tract infection viral	1 (0.1)	0 (0.0)	>.99
Urosepsis	1 (0.1)	0 (0.0)	>.99
Viral infection	1 (0.1)	0 (0.0)	>.99
Metabolism and Nutrition Disorders	4 (0.3)	2 (0.8)	0.209
Dehydration	4 (0.3)	2 (0.8)	0.209
Nervous System Disorders	1 (0.1)	0 (0.0)	>.99
Febrile convulsion	1 (0.1)	0 (0.0)	>.99
Respiratory, Thoracic and Mediastinal Disorders	9 (0.6)	1 (0.4)	>.99
Respiratory distress	4 (0.3)	1 (0.4)	0.541
Apparent life threatening event	2 (0.1)	0 (0.0)	>.99
Bronchial hyperreactivity	1 (0.1)	0 (0.0)	>.99
Hypoxia	1 (0.1)	0 (0.0)	>.99
Productive cough	1 (0.1)	0 (0.0)	>.99
Stridor	1 (0.1)	0 (0.0)	>.99
Skin and Subcutaneous Tissue Disorders	0 (0.0)	1 (0.4)	0.144
Petechiae	0 (0.0)	1 (0.4)	0.144

[a] Number of subjects reporting at least one event.
[b] Fisher exact test, 2-sided, used to calculate difference between vaccine groups in percentage of subjects reporting an event. p-values are not corrected for multiple comparisons.
Source: 125324/0.16,m5.3.5.1.3, Study Report Body Additional Safety Information, Response to May 21, 2009 Questions, page 95-97 (Tables 3-3).

Table 61. Study 6096A1-3005. Subjects Who Experienced SAEs Within 30 Days After Any of Doses 1-3 of 13vPnC

Site-Subject Number	13vPnC Vaccine Lot Group	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Action[a]	Outcome
001-000002	Pilot lot 1	3	Pneumonia	24	15	H, C, U	Resolved
			RSV infection	24	15	H, C, U	Resolved
			Respiratory distress	24	7	H	Resolved
003-000202	Pilot lot 1	1	Apparent life threatening event	1	1	N	Resolved
009-000793	Pilot lot 1	2	Viral infection	32	5	H, C	Resolved
018-001694	Pilot lot 1	1	RSV infection	2	9	H, C, ER, UT	Resolved
036-003433	Pilot lot 1	1	Bronchiolitis	1	3	H	Resolved
043-004120	Pilot lot 1	1	Bronchiolitis	50	16	H, C	Resolved
044-004255	Pilot lot 1	3	Bronchiolitis	1	13	H, C, ER, U	Resolved
044-004297	Pilot lot 1	3	Urinary Tract Infection	12	3	H, C, ER	Resolved
057-005495	Pilot lot 1	1	Bronchiolitis	30	34	H,C, U	Resolved
061-005916	Pilot lot 1	2	Pneumonia	16	13	H	Resolved
			RSV Bronchiolitis	16	13	H	Resolved
079-007648	Pilot lot 1	1	Upper respiratory tract infection	124	4	H, C	Resolved
086-008338	Pilot lot 1	1	RSV bronchiolitis	43	21	H, C, ER	Resolved
088-008545	Pilot lot 1	2	Bronchiolitis	22	12	H	Resolved
002-000108	Pilot lot 2	3	Abscess oral	27	C	H, C, UT	Persistent
002-000109	Pilot lot 2	1	Food allergy	55	C	H	Persistent
013-001196	Pilot lot 2	2	RSV bronchiolitis	45	5	H, C	Resolved
014-001276	Pilot lot 2	1	Croup infectious	67	4	H, ER	Resolved
		1	Respiratory distress	68	3	H, ER	Resolved
016-001471	Pilot lot 2	1	Urinary tract infection	49	11	H, C	Resolved
018-001683	Pilot lot 2	3	Croup infectious	29	4	H, C, ER, U	Resolved
		2	Otitis media	48	13	H, C, ER, U	Resolved
023-002190	Pilot lot 2	2	Hematochezia	59	6	H, UT	Resolved
023-002225	Pilot lot 2	2	Pneumonia	65	4	H	Resolved
029-002747	Pilot lot 2	1	Pulmonary valve stenosis	12	14	H, UT	Resolved
030-002843	Pilot lot 2	2	Pyrexia	44	7	U, C, ER	Resolved
		2	Bronchiolitis	46	5	H, C, ER	Resolved
		1	Gastroenteritis	11	46	H, C, ER	Resolved
		1	RSV bronchiolitis	56	16	H, C, ER	Resolved
030-002868	Pilot lot 2	1	Croup infectious	8	9	H, C, ER	Resolved
037-003541	Pilot lot 2	1	RSV infection	52	19	H, C, ER, U	Resolved
041-003953	Pilot lot 2	1	Pyrexia	17	2	H, C, ER	Resolved
		1	Bronchiolitis	17	2	H, C, ER,	Resolved
		1	Otitis media	17	42	H, C, ER	Resolved
044-004263	Pilot lot 2	1	Apparent life threatening event	38	3	H, ER	Resolved

044-004275	Pilot lot 2	2	Pyrexia	8	3	H, C	Resolved
059-005702	Pilot lot 2	2	RSV bronchiolitis	7	2	H, C, ER	Resolved
064-006181	Pilot lot 2	1	Otitis media	53	14	H, C, U	Resolved
		1	Dehydration	56	2	H, C, U	Resolved
065-006277	Pilot lot 2	2	Influenza	21	3	H, C, ER	Resolved
		2	RSV bronchiolitis	21	3	H, C, ER	Resolved
079-007647	Pilot lot 2	1	Respiratory distress	27	5	H, C	Resolved
079-007651	Pilot lot 2	2	Sudden infant death syndrome	3	1	N	Death
079-007657	Pilot lot 2	1	Respiratory tract infection viral	12	10	H, C	Resolved
079-007666	Pilot lot 2	2	RSV bronchiolitis	11	3	H, C	Resolved
091-008821	Pilot lot 2	2	Urosepsis	52	5	H, C	Resolved
		2	Febrile convulsion	52	5	W, H, C	Resolved
		2	Respiratory distress	53	1	C	Resolved
		2	Stridor	53	1	C	Resolved
001-000035	Manufacturing lot	1	Pneumonia	65	11	H, C, UT	Resolved
002-000104	Manufacturing lot	2	Gastroenteritis	65	2	H, C, UT	Resolved
004-000320	Manufacturing lot	1	Sudden infant death syndrome	14	1	N	Death
014-001280	Manufacturing lot	1	Productive cough	19	32	H	Resolved
016-001489	Manufacturing lot	3	Dehydration	26	7	H, C	Resolved
026-002487	Manufacturing lot	2	Pneumonia	18	11	H, C, ER, UT	Resolved
		2	RSV bronchiolitis	16	9	H, C	Resolved
		2	Dehydration	18	2	H, UT	Resolved
030-002857	Manufacturing lot	2	Allergy to vaccine	1	8	C, E, D	Resolved
037-003537	Manufacturing lot	1	RSV bronchiolitis	47	24	H, C, ER, UT	Resolved
038-003636	Manufacturing lot	2	Urinary tract infection	15	4	H, C, ER	Resolved
		2	Dehydration	15	2	H, C	Resolved
040-003830	Manufacturing lot	2	Bronchiolitis	2	17	H, C, ER	Resolved
042-004022	Manufacturing lot	3	Bronchiolitis	18	11	H, C, ER, UT	Resolved
059-005709	Manufacturing lot	1	RSV bronchiolitis	63	5	H, ER	Resolved
061-005914	Manufacturing lot	2	Bronchiolitis	9	3	H	Resolved
086-008339	Manufacturing lot	2	RSV infection	13	7	H, C, ER	Resolved
088-008531	Manufacturing lot	1	Bronchiolitis	65	18	H	Resolved
		1	Upper respiratory tract infection	65	18	H	Resolved
		1	Bronchial hyperreactivity	65	18	H	Resolved
088-008548	Manufacturing lot	2	RSV bronchiolitis	32	5	H, C	Resolved
		2	Hypoxia	32	2	H, C	Resolved
091-008844	Manufacturing lot	1	Meningitis aseptic	29	3	H	Resolved

RSV: Respiratory Syncytial Virus
[a] Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, Adverse Event Listings, pages 1-159.

Table 62. Study 6096A1-3005. Subjects Who Experienced SAEs Within 30 Days After Any of Doses 1-3 of PCV7

Site-Subject Number	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Action[a]	Outcome
001-000009	1	Pyrexia	47	10	H	Resolved
002-000107	1	Sudden infant death syndrome	13	1	N	Death
004-000327	2	Croup infectious	61	9	H, C, UT	Resolved
005-000396	1	Urinary tract infection	16	11	H, C, ER	Resolved
009-000808	1	RSV infection	26	8	H, C, U	Resolved
018-001672	2	Pyrexia	22	11	H, C, UT	Resolved
	2	Meningitis enteroviral	22	11	H, C, UT	Resolved
018-001690	2	Bronchiolitis	7	16	H, C, UT	Resolved
	2	Pneumonia	7	16	H, C, UT	Resolved
022-002084	1	Irritability	20	3	H, C, ER, UT	Resolved
	1	Petechiae	20	3	H, C, ER, UT	Resolved
030-002858	1	Urinary tract infection	22	9	H, C, ER	Resolved
032-003095	2	Bronchiolitis	37	25	H, C, ER	Resolved
	2	Pneumonia	56	9	H, C, UT	Resolved
042-004024	2	Vomiting	55	3	H, ER	Resolved
	2	Dehydration	55	3	H, C, ER	Resolved
044-004243	1	Gastroenteritis	58	3	H, C, ER, U	Resolved
063-006086	2	RSV bronchiolitis	20	49	H, C, ER, UT	Resolved
	2	Respiratory distress	15	54	H, C, ER, UT	Resolved
083-008041	3	Dehydration	18	3	H, C, UT	Resolved
091-008822	2	RSV bronchiolitis	30	2	H, ER	Resolved

RSV: Respiratory Syncytial Virus

[a] Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.

Source: 125324/0.1,m5.3.5.1, Adverse Event Listings, pages 160-191.

7.2.4.4.6 Safety-Related Discontinuations

Overall, 5 subjects were withdrawn because of adverse events. Treatment was discontinued due to an adverse event (allergy to vaccine) in one subjects; this subject was later withdrawn after data lock for the clinical study report.

Table 63. Study 6096A1-3005. Subject Withdrawal or Permanent Test Article Discontinuation Because of an Adverse Event During the Infant Series

Subject number	Vaccine Group	Preferred Term	Vax #	Time to Onset (days)	Duration (days)	Severity[a]	Action[b]	Outcome	SAE
091-008840	13vPnC Pilot lot 1	Pyrexia	2	1	1	Severe	W	Resolved	No
083-008063	13vPnC Pilot lot 2	Urticaria	2	4	6	Mild	W, C, U	Resolved	No
091-008821	13vPnC Pilot lot 2	Febrile convulsion	2	52	5	Severe	W, H, C	Resolved	Yes
083-008062	13vPnC MFR lot	Injection site reaction	2	1	2	Moderate	W	Resolved	No
030-002857	13vPnc MFR lot	Allergy to vaccine	2	1	8	Mild	C, E, D	Resolved	yes

[a] Severity assessed by the study investigator.
[b] Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.3,m5.3.5.1, CSR74251-report body.pdf, page s 136, 334-337 (Tables 15.89 - 15.92).

7.2.4.4.7 Clinical case narratives

Clinical case narratives are provided for subjects who died,had SAEs that were determined by the study investigator to possibly be related to the study vaccine, or had AEs resulting in withdrawal from the study.

Subject 6096A1-3005-002-000107

Thirteen days after receipt of the first dose of PCV7, this healthy 83 day old white, male infant was found supine, unresponsive, blue, and not breathing in the crib at day care. Resuscitative measured failed. The cause of death was reported as SIDS. Autopsy results were reported after data were locked for this CSR, concluding that the finding were consistent with SIDS.

Subject 6096A1-3005-004-00320

Fourteen days after receipt of the first dose of 13vPnC manufacturing scale lot, this 71 day old white, male infant was found unresponsive, blue, and not breathing by his Father in his crib. Resuscitative measures failed. An autopsy revealed that the subject died of undetermined causes. The autopsy report also revealed that the Father had drunk several beers and laid down in bed with the infant with multiple sheets and blankets after feeding him half a bottle of formula at 1am. The investigator concluded this infant died from sudden unexplained infant death.

Subject 6096A1-3005-040-003830

Four days after receipt of the 4th dose of 13vPnC manufacturing scale lot, this 12 month old male subject experienced bronchial hyperreactivity (reactive airway disease). The subject was hospitalized with a one day history of nasal flaring, cough, dyspnea, wheezing, and retractions. The subject was discharged and considered recovered on hospital day 3. This subject was also hospitalized for bronchiolitis 2 days after the second study dose lasting 17 days.

Subject6096A1-3005-079-007651

Three days after receipt of the second dose of 13vPnC pilot scale lot 2, this 127 day old white, female infant died. The infant was reportedly found unresponsive and cyanotic by the Father, who had been sleeping in bed with the infant. The cause of death was reported as asphyxiation or SIDS. Autopsy results describe no organic pathology, negative toxicology, and negative metabolic screenings. Parental cosleeping was identified as a possible contributor to the event. The opinion of the medical examiner agreed with the possibility of SIDS or accidental airway obstruction.

Subject 3005-030-002857

On the evening he received the second dose of 13vPnC manufacturing scale lot 2, this 4-month old Hispanic, male infant developed diffuse body rash and fussiness after vaccination with the second dose of 13vPnC manufacturing scale lot. The infant also had a fever of 104°F. On exam, the skin was blanchable with petechiae noted on the entire body except the face. The event was diagnosed as vaccine allergic reaction. The mother was advised to use topical hydrocortisone (0.5%) for the rash and the event resolved. The investigator determined that the event was mild and related to test article (both study vaccine and concomitant vaccine) administration. This event was considered "medically important," and therefore reported as an SAE. The subject was withdrawn from study participation after completing safety follow-up. No other adverse events were reported during the study or follow-up period.

Subject 3005-044-004255

One day after the 3rd dose of 13vPnC pilot lot 1, this approximately 6.5 month old Hispanic, male infant was hospitalized in respiratory distress and diagnosed with a RSV infection (not confirmed by a laboratory test) and bronchiolitis. A chest x-ray revealed ill-defined perihilar opacities consistent with viral or reactive airway disease. The infant was discharged the day after admission, and the event outcome was reported as resolved. Prior medical history includes candidiasis. In addition, the infant was noted to have a concurrent illness consisting of a 4-5 day history of an upper respiratory infection, cough, wheezing, and intermittent fever on the day of the 3rd study vaccination.

Subject 3005-044-004275
Eight days after the 2nd dose of 13vPnC pilot lot 2, this 4-month old white female subject was hospitalized with fever, nasal drainage, cough, fussiness, and decreased appetite. The SAE, coded as pyrexia and assessed as severe, began 1 day after vaccination and ranged from 100°F to 102°F. A chest x-ray revealed ill-defined central perihilar opacities consistent with viral or reactive airway disease. Laboratory test results revealed elevated neutrophils (68.4%; ref: 14-24%) and monocytes (17.4%; ref: 0-12%) and decreased lymphocytes (21.2%; ref: 44-71%). The subject was discharged the day after admission, and the event resolved.

Subject 3005-091-008821
Fifty-two days after the 2nd dose of 13vPnC pilot lot 2 and 15 days after surgical hypospadias repair, this 5 month old white male infant was hospitalized with urosepsis and febrile seizure. Tympanic temperature was noted to be 103°F. Urine culture grew significant levels of *Enterobacter cloacae* and blood cultures grew enteric gram negative rods of 2 colony types (unspeciated). Urological evaluation revealed a 7 mm right renal cyst, grade 3-4 vesiculoureteral reflux in the left renal system, and a bladder diverticulum. The subject was treated for his fever, seizure, and urosepsis. Seizure activity ceased after treatment. On hospital day #2, the subject developed stridor and respiratory distress which resolved the same day and which were attributed to intercurrent viral illness. Brief seizure activity was noted during this episode, which resolved on its own. On hospital day #5, the subject was discharged. The subject was withdrawn because he no longer met study eligibility requirements.

Subject 3005-083-8062
On the evening of the 2nd dose of 13vPnC manufacturing lot, this 4-month old white, Hispanic infant developed a moderate local injection site reaction at the site of ActHIB administration which resolved the next day. The subject was not hospitalized and the event was not considered a serious adverse event. The investigator decided to withdraw the subject from the study due to the adverse event.

Subject 3005-083-8063
Four days after the 2nd dose of 13vPnC pilot lot 2, this 4-month old white male infant developed mild urticaria. The event was preceded by a pruritic rash on the scalp about 19 days prior to the event and postviral cough about one week prior to the event. The subject was not hospitalized and the event was not considered a serious adverse event. The investigator decided to withdraw the subject due to the adverse event.

Subject 3005-091-8840
On the evening of the 2nd dose of 13vPnC pilot lot 1, this 4-month old black female infant developed a severe fever of 104.9°F which resolved the same day. The subject was not hospitalized and the event was not considered a serious adverse event. A preceding mild viral illness was reported about 2 weeks prior to receipt of the 2nd study dose. The investigator decided to withdraw the subject due to the adverse event.

7.2.4.5 Summary and Conclusions

7.2.4.5.1 Safety
Prevnar 13 safety data following doses 1-3 from study 3005 demonstrated no imbalance in the rates of serious adverse events compared to Prevnar recipients. Serious adverse events were reported in 3.7% and 6.1% of 13vPnC and PCV7 subjects respectively during the infant series. Overall, rates of solicited local and systemic adverse events were similar between Prevnar 13 and Prevnar. In addition, no consistent trends were identified. As in study 004, tenderness and irritability were the most frequently reported solicited local and systemic adverse events, respectively. Moderate fever (defined as > 39°C and ≤ 40.0°C) occurred in a statistically significantly higher percentage of Prevnar 13 recipients (3.4%) compared to Prevnar recipients (0%). Among Prevnar 13 recipients, mild fever (defined as ≥ 38.0°C and ≤ 39.0°C) peaked after dose 2, while moderate fever peaked after dose 3. One subject reported a febrile seizure during the infant series; the event, which occurred 52 days post-dose 2, was temporally related to a post-surgical infection (Iurosepsis). There were no reports of febrile seizures within 30 days of doses 1-3. There were 3 deaths that occurred in this

study, two Prevnar 13 recipients and 1 Prevnar recipient; each death was suspected to be caused by sudden infant death syndrome.

7.2.4.5.2 Immunogenicity

Immune responses induced by 3 independently produced lots of Prevnar 13 (two pilot scale lots and one manufacturing scale lot) were shown to be equivalent when measured one month after the 3rd study dose. Each of the co-primary objectives for the concomitant vaccine antigens, including tetanus, poliovirus types 1, 2, and 3, and hepatitis B were met.

7.2.5 Study 3005 Safety Addendum

Clinical Reviewer Note: Toddler and 6-month follow-up safety data for study 3005 were submitted on December 2nd 2009 as amendment 57 to the BLA. The submission was not a complete toddler dose clinical study report. The tables below summarize the data submitted in amendment 57. Post-dose 4 solicited safety data are presented along with infant series data.

7.2.5.1 Populations Enrolled/Analyzed

7.2.5.1.1 Subject Disposition and Follow-Up

Of the 1289 13vPnC recipients who completed the infant series, 67 were withdrawn after the infant series but before the toddler dose, and 1220 were administered dose 4.

Table 64. Study 6096A1-3005. Summary of Toddler Dose and 6-month Follow-up Subject Disposition

	13vPnC Pilot Scale Lot 1 N=489		13vPnC Pilot Scale Lot 2 N=488		13vPnC Manufacturing Scale Lot N=489		PCV7 N=246		Total N=1712	
	n	%	n	%	n	%	n	%	n	%
Subjects randomized[a]	489	100.0	488	100.0	489	100.0	246	100.0	1712	100.0
Completed infant series	435	89.0	427	87.5	427	87.3	218	88.6	1507	88.0
Withdrawn after infant series	20	4.1	29	5.9	18	3.7	9	3.7	76	4.4
Unknown[b]	0	0.0	1[b]	0.2	1	0.2	1	0.4	3	0.2
Reasons for withdrawal:										
Parent / legal guardian request	4	0.8	11	2.3	6	1.2	3	1.2	24	1.4
Failed to return	7	1.4	6	1.2	5	1.0	1	0.4	19	1.1
Lost to follow-up	5	1.0	5	1.0	5	1.0	2	0.8	17	1.0
Protocol violation	2	0.4	4	0.8	2	0.4	2	0.8	10	0.6
Adverse event[c]	2	0.4	2	0.4	0	0.0	0	0.0	4	0.2
Investigator request	0	0.0	0	0.0	0	0.0	1	0.4	1	0.1
Other	0	0.0	1	0.2	0	0.0	0	0.0	1	0.1
Vaccinated Toddler Dose	415	84.9	397	81.4	408	83.4	208	84.6	1428	83.4
Completed Toddler Dose	408	83.4	391	80.1	404	82.6	200	81.3	1403	82.0
Withdrawn During Toddler Dose	7	1.4	6	1.2	4	0.8	8	3.3	25	1.5
Reasons for withdrawal:										
Lost to follow-up	4	0.8	1	0.2	1	0.2	3	1.2	9	0.5
Failed to return	2	0.4	2	0.4	1	0.2	3	1.2	8	0.5
Parent/legal guardian request	0	0.0	3	0.6	2	0.4	1	0.4	6	0.4
Protocol violation	1	0.2	0	0.0	0	0.0	1	0.4	2	0.1
Withdrawn after toddler dose	5	1.0	7	1.4	11	2.2	4	1.6	26	1.5
Reasons for withdrawal										
Lost to follow-up	4	0.8	7	1.4	11	2.2	4	1.6	26	1.5
Adverse event	1	0.2	0	0.0	0	0.0	0	0.0	1	0.1
Completed study	403	82.4	384	78.7	393	80.4	196	79.7	1376	80.4
Entered 6-month follow-up[d]	425	86.9	415	85.0	418	85.5	206	83.7	1464	85.5
Completed 6-month follow-up[d]	417	85.3	406	83.2	406	83.0	201	81.7	1430	83.5

Infant series = dose 1 to blood draw after dose 3. Toddler dose = toddler vaccination to blood draw.
Subjects 3005-012-001101, 3005-013-001200, 3005-081-007846 were prerandomized but not consented.
[a] The values in this row are used as the denominators for percentages.
[b] Subjects 3005-039-003725, 3005-044-004265, and 3005-063-006093 did not have completed study forms for the after the infant series period, and thus were marked "unknown."
[c] Subjects 031-002945 and 091-008825 experienced a febrile convulsion 58 and 69 days, respectively, after the third dose of 13vPnC Pilot Lot 1. Subjects 005-000395 experienced a food allergy 88 days after dose 3 of 13vPnC Pilot Lot 2. Subject 086-008336 experienced a febrile convulsion 37 days after dose 3 of 13vPnC Pilot Lot 2. See narratives for further details.
[d] A telephone contact attempted for all subjects 6-months after their last vaccination.
Source: 125324/0.57,m1.11 efficacy-info-amendment.pdf, pages 6 and 7 (Tables 2-1 and 2-2).

7.2.5.1.2 Subject Demographics

Demographics of the toddler dose safety population were similar to the demographics of the infant series population.

Table 65. Toddler Dose Safety Population Demographic Characteristics

	13vPnC Pilot Scale Lot 1 N=489		13vPnC Pilot Scale Lot 2 N=488		13vPnC Manufacturing Scale Lot N=489		PCV7 N=246		Total N=1712	
	n	%	n	%	n	%	n	%	n	%
Gender										
Male	221	53.3	215	54	227	55.9	115	55	778	54.5
Female	194	46.7	183	46	179	44.1	94	45	650	45.5
Unknown										
Race										
White	343	82.7	334	83.9	326	80.3	180	86.1	1183	82.8
Black	42	10.1	41	10.3	46	11.3	18	8.6	147	10.3
Other	21	5.1	20	5	23	5.7	7	3.3	71	5
Asian	6	1.4	2	0.5	8	2	3	1.4	19	1.3
Native Hawaiian or other Pacific Islander	2	0.5	1	0.3	1	0.2	0	0.0	4	0.3
American Indian or Alaska Native	1	0.2	0	0.0	2	0.5	1	0.5	4	0.3
Ethnicity										
Non-Hispanic and Non-Latino	358	86.3	346	86.9	345	85	176	84.2	1225	85.8
Hispanic or Latino	57	13.7	52	13.1	61	15	33	15.8	203	14.2
Age at enrollment (months)										
Mean (SD)	12.4 (0.4)		12.4 (0.4)		12.4 (0.3)		12.4 (0.4)		12.4 (0.4)	
Min, Max	12.1, 15.1		12.0, 15.7		12.0, 14.9		12.0, 14.4		12.0, 15.7	

Source: 125324/0.57,m1.11 efficacy-info-amendment.pdf, page 10 (Table 2-5).

Similar to study 004, rates of erythema and induration increased following each subsequent dose and were highest after the fourth dose. A statistically significantly higher proportion of PCV7 recipients experienced erythema and induration compared to 13vPnC recipients after dose 4. Rates of any tenderness were consistenly high (~57-67%) following each dose in both study groups. Rates of severe tenderness were lowest following the fourth dose. Tenderness was the most frequently reported local adverse event followed by erythema and induration. There were no reports of severe erythema or induration.

7.2.5.2 Immediate Reactions

Although immediate reactions were collected and reported along with other unsolicited adverse events, these events could not be idenitifed from the data submitted to the BLA. The specific time-to-onset of symptoms was not recorded, therefore reactions that occurred within 30 minutes of vaccination could not be identified.

7.2.5.3 Solicited Local Reactions

Table 66. Study 6096A1-3005. 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[a]							
	Dose 1		Dose 2		Dose 3		Dose 4	
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 %	13vPnC N[a]=603-826 %	PCV7 N[a]=93-131 %
Erythema[c]								
Any	22.5	22.8	33.4	30.1	37.7	39.4	42.6*	52.9*
0.5 - 2.0 cm	21.3	21.7	32.0	28.8	35.8	38.5	39.2*	50.0*
2.5 - 7.0 cm	1.7	1.2	2.8	3.1	5.1	7.8	10.6*	21.2*
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Induration[c]								
Any	18.5	18.2	25.3	17.7	26.5	30.5	31.5*	43.6*
0.5 - 2.0 cm	15.7	16.2	23.8	17.7	24.8	29.1	28.9*	41.1*
2.5 - 7.0 cm	4.8	3.6	3.5	3.9	4.0	7.0	8.5*	17.8*
> 7.0 cm	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
Tenderness								
Any	63.0	67.0	66.2	64.8	59.5	64.7	57.3	63.4
Interferes with limb movement	10.0	12.9	9.8	11.4	8.9	11.9	6.7	4.1

* 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] 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); 125324/0.57,m1.11 efficacy-info-amendment.pdf, page 13 (Table 3-1).

The duration of local reactions in the Prevnar 13 group ranged from 1-42 days for tenderness, 1-15 days for erythema, and 1-11 days for induration. In the Prevnar group, the duration of reactions was 1-8 days for tenderness and erythema and 1-11 days for induration.

7.2.5.4 Solicited Systemic Reactions

Rates of fever were highest after dose 2 among 13vPnC recipients and after dose 3 among PCV7 recipients. One 13vPnC subject reported fever > 40°C after each of the first three doses and one PCV7 subject reported fever > 40°C after dose 1 and 3. Six 13vPnC subjects (1%) reported fever > 40°C after dose 4. The frequency of hives increased with each subsequent dose in both groups and was highest after dose 4.

Table 67. Study 6096A1-3005. Percentage of subjects with solicited systemic adverse events within 7 days after each vaccination.

	Safety Populations by Dose							
	Dose 1		Dose 2		Dose 3		Dose 4	
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 (%)	**13vPnC** N[a]=586-943 n (%)	**PCV7** N[a]=93-160 n (%)
Fever[b]								
38.0°C ≤ x ≤ 39.0°C	24.3	26.0	35.1	28.0	28.5	32.6	28.8	29.9
39°C < x ≤ 40.0°C	0.6	1.2	3.4	0.0*	3.9	6.2	4.4	5.3
> 40°C	0.1	0.6	0.1	0.0	0.1	0.9	1.0	0.0
Decreased appetite	48.9	49.0	48.5	49.4	48.2	50.0	51.9	50.4
Irritability	86.4	87.6	85.8	81.1	80.9	84.4	81.8	80.0
Increased sleep	71.2	72.6	66.8	63.3	58.0	51.4	47.8	47.6
Decreased sleep	44.4	46.4	47.5	48.4	47.1*	56.5*	46.9	42.7
Hives (urticaria)	0.7	0.0	1.3	0.8	1.5	1.8	2.1	5.2

* 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); 125324/0.57,m1.11 efficacy-info-amendment.pdf, page 16 (Table 3-4).

The duration of fever ≥ 38.0°C ranged from 1-12 days among Prevnar 13 recipients and 1-6 days in Prevnar recipients.

There were so statistically significant differences between the two study groups in the use of antipyretics to treat or prevent symptoms related to vaccination within 7 days of vaccination.

Table 68. Study 6096A1-3005. Subjects who received antipyretics to treat symptoms or to prevent symptoms within 7 days following each dose of 13vPnC or PCV7.

	Use of Antipyretics to Treat Symptoms		Use of Antipyretics to Prevent Symptoms	
Dose number	13vPnC n (%)	PCV7 n (%)	13vPnC n (%)	PCV7 n (%)
1	N[a]=1227 793 (64.6)	N=206 130 (63.1)	N=1276 910 (71.3)	N=214 157 (73.4)
2	N=1011 710 (70.2)	N=169 108 (63.9)	N=1080 811 (75.1)	N=185 139 (75.1)
3	N=952 643 (67.5)	N=160 114 (71.3)	N=978 711 (72.7)	N=167 122 (73.1)
4	N=845 532 (63.0)	N=127 82 (64.6)	N=889 637 (71.7)	N=150 108 (72.0)

[a] Number of subjects reporting yes for at least 1 day or no for all days
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); 125324/0.57,m1.11 efficacy-info-amendment.pdf, page 16 (Table 3-4).

7.2.5.5 Unsolicited Adverse Events

Overall, a similar proportion of subjects in each study group reported unsolicited adverse events following dose 4. Unsolicited adverse events were reported by 36.2% (438/1210) and 36.5% (76/208) of subjects in the 13vPnC and PCV7 groups respectively. The most frequently reported adverse events following the toddler dose were otitis media (13vPnC: 5.8%, PCV7: 9.6%, p=0.045), upper respiratory tract infection (13vPnC: 5.1%, PCV7: 5.3%), pyrexia (13vPnC: 3.1%, PCV7: 4.3%), and diarrhea (13vPnC: 3.1%, PCV7: 3.8%).

Unsolicited adverse events occurring in at least 1% of 13vPnC subjects and in more 13vPnC subjects compared to PCV7 subjects following the toddler dose included the following: nasopharyngitis (1.0%, 0.5%), viral rash (1.0%, 0.5%), sinusitis (1.0%, 0.0%), dermatitis diaper (2.6%, 2.4%), rash (2.2%, 1.0%), and eczema (1.4%, 0.0%).

7.2.5.6 Serious Adverse Events

No deaths were reported from the post-infant series blood draw through the 6-month follow-up period. No statistically significant differences between vaccine groups were noted in the incidence of SAEs. SAEs were reported among 1.7% of 13vPnC subjects and 1.2% of PCV7 subjects from > 30 days after the 3rd dose until just before the 4th dose; 0.7% of PCV7 subjects and 0.5 of PCV7 subjects within 30 days of the 4th dose; and 1.5% of 13vPnC subjects and 2.9% of PCV7 subjects during the 6-month follow-up period.

Table 69. Study 6096A1-3005. Subjects who Experienced SAEs Within 30 Days After Dose 4

Site-Subject Number	Vaccine Group	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Outcome
013-001196	13vPnC Pilot lot 2	Skull fracture	39	C	MO	Persisted
017-001579	13vPnC Pilot lot 1	Dehydration	33	C	SE	Persisted
023-002173	13vPnC MFR Lot	Urinary tract infection	33	3	MO	Resolved
023-002173	13vPnC MFR Lot	Viral rash	34	10	MO	Resolved
040-003830	13vPnC MFR Lot	Bronchial hyperreactivity	4	14	MO	Resolved
041-003937	13vPnC Pilot lot 1	Rectal abscess	7	35	MI	Resolved
049-004709	13vPnC MFR Lot	Pyelonephritis	13	8	MO	Resolved
059-005702	13vPnC Pilot lot 2	Cellulitis pharyngeal	26	4	SE	Resolved
074-007169	PCV7	Bronchiolitis	2	3	MO	Resolved
074-007169	PCV7	Pneumonia	2	3	MO	Resolved
074-007169	PCV7	Respiratory syncytial virus infection	2	3	MO	Resolved
075-007255	13vPnC Pilot lot 1	Febrile convulsion	13	2	MO	Resolved
075-007255	13vPnC Pilot lot 1	Injection site rash	11	5	MO	Resolved
088-008540	13vPnC MFR Lot	Near drowning	15	2	LT	Resolved

[a] C = Continuing.
[b] Mild (MI), moderate (MO), severe (SE), or life-threatening (LT).
Source: 125324/0.70, m1.11, Clinical-Response to December 22, 2009 Request for SAEs for 6096A1-3005, page 2, Table 1-1 and AE.xpt dataset.

Table 70. Study 6096A1-3005. Subjects who Experienced SAEs During the 6-Month Follow-Up

Site-Subject Number	Vaccine Group	Preferred Term (MedDRA)	Time to Onset From Dose 4 (Days)	Duration (Days)	Severity	Action Taken	Outcome
001-000023	13vPnC Pilot Lot 1	Endocarditis bacterial	114	41	SE	W,H,C	Resolved
002-000105	PCV7	Dehydration	163	2	MO	H	Resolved
009-000808	PCV7	Upper respiratory tract infection	104	8	SE	H,C,ER	Resolved
009-000809	13vPnC MFR Lot	Respiratory syncytial virus infection	90	13	SE	H,C,U	Resolved
013-001182	13vPnC MFR Lot	Near drowning	84	114	LT	H,C,UT	Resolved
016-001480	PCV7	Gastroenteritis	65	6	SE	H	Resolved
017-001579	13vPnC Pilot Lot 1	Gastroenteritis	101	74	SE	H,C	Resolved
018-001669	13vPnC MFR Lot	Asthma	202	20	SE	H,C,UT	Resolved
018-001669	13vPnC MFR Lot	Gastroenteritis	208	5	MO	H,C,UT	Resolved
018-001669	13vPnC MFR Lot	Respiratory syncytial virus infection	202	20	SE	H,C,UT	Resolved
018-001676	13vPnC Pilot Lot 2	Asthma	132	4	MO	H,C,U	Resolved

018-001676	13vPnC Pilot Lot 2	Cellulitis	131	21	SE	H,C,ER,U	Resolved
018-001684	13vPnC Pilot Lot 1	Asthma	45	6	SE	H,C,ER,U	Resolved
032-003080	13vPnC Manufacturing Lot	Pneumonia	184	12	MO	H,C	Resolved
032-003123	13vPnC Pilot Lot 1	Asthma	131	9	MO	H,C	Resolved
032-003123	13vPnC Pilot Lot 1	Pneumonia	131	16	MO	H,C	Resolved
038-003633	PCV7	Croup infectious	149	1	MO	H,C,ER	Resolved
038-003640	PCV7	Otitis media	76	8	MO	H,C,ER	Resolved
038-003640	PCV7	Pneumonia	76	15	MO	H,C,ER	Resolved
038-003647	PCV7	Asthma	115	8	SE	H,C,ER	Resolved
038-003647	PCV7	Otitis media acute	115	8	MO	H,C,ER	Resolved
042-004019	13vPnC Pilot Lot 2	Croup infectious	51	2	SE	H,C,UT	Resolved
042-004027	13vPnC Pilot Lot 1	Cellulitis	98	5	SE	H,C,UT	Resolved
044-009224	13vPnC Pilot Lot 2	Foreign body trauma	120	3	SE	H,C,UT	Resolved
049-004716	13vPnC Pilot Lot 1	Periorbital cellulitis	131	6	MO	H,C,U	Resolved
049-004721	13vPnC MFR Lot	Otitis media	133	22	MO	H,C	Resolved
059-005691	13vPnC Pilot Lot 2	Failure to thrive	104	9	SE	H,C,U	Resolved
067-006488	13vPnC MFR Lot	Intussusception	189	1	LT	ER	Resolved
074-007162	13vPnC Pilot Lot 2	Febrile convulsion	145	3	SE	H	Resolved
074-007162	13vPnC Pilot Lot 2	Upper respiratory tract infection	145	3	SE	H	Resolved
074-007169	PCV7	Asthma	48	C	MO	H	Persisted
074-007169	PCV7	Otitis media	48	6	MO	H	Resolved
079-007669	13vPnC Pilot Lot 2	Bronchiolitis	179	2	MO	H,C,ER	Resolved
079-007669	13vPnC Pilot Lot 2	Respiratory syncytial virus bronchiolitis	111	3	MO	H,C,ER	Resolved
084-008147	13vPnC MFR Lot	Pneumonia	175	15	SE	H	Resolved
086-008332	13vPnC MFR Lot	Febrile convulsion	31	1	SE	C,ER	Resolved
088-008546	13vPnC Pilot Lot 2	Accidental overdose	162	4	SE	H,C	Resolved

[a] C = Continuing.
[b] Mild (MI), moderate (MO), severe (SE), or life-threatening (LT).
[c]Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.70, m1.11, Clinical-Response to December 22, 2009 Request for SAEs for 6096A1-3005, pages 3-5, Table 1-2.

7.2.5.7 Safety Related Discontinuations

Table 71. Study 6096A1-3005. Study Withdrawal and Test Article Discontinuation After the Post-Infant Series Blood Draw Due to an Adverse Event

Subject number	Vaccine Group	Preferred Term	Vax #	Time to Onset (days)	Duration (days)	Severity[a]	Action[b]	Outcome	SAE
031-002945	13vPnC Lot 1	Febrile convulsion	3	58	1	Mild	W, U, D	Resolved	No
091-008825	13vPnC Lot 1	Febrile convulsion	3	69	69	Severe	W, H, C, D	Resolved	Yes
005-00395	13vPnC Lot 2	Food allergy	3	88	-	Moderate	W, C, U, T	Persistent	No
086-008336	13vPnC Lot 2	Convulsion	3	37	-	Moderate	W, ER, U	Persistent	No

[a] Severity abbreviation: Life - life-threatening.

[b] Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page s170-173 (Tables 10-20 – 10-25.).

There were no withdrawals because of an adverse event following the toddler dose. During the 6-month follow-up period, one subject was withdrawn due to an event reported as endocarditis bacterial. This event is described in the narratives.

7.2.5.8 Clinical Case Narratives

Clinical case narratives are provided for subjects who had SAEs that were determined by the study investigator to possibly be related to the study vaccine or AEs resulting in study withdrawal.

Subject 6096A1-3005-005-000395
Eighty-eight days after the 3rd dose of 13vPnC pilot lot 2, this 8-month old female infant developed an egg allergy. The infant was treated with concomitant medications and was withdrawn from the study. Medical history was significant for premature birth and gastrointestinal reflux. The event was categorized as moderate, was not considered serious and did not result in hospitalization.

Subject 6096A1-3005-031-0002945
Fifty-eight days after the 3rd dose of 13vPnC pilot lot 1, this 8-month old Hispanic male infant developed a febrile seizure determined to be mild in severity. The event did not result in hospitalization and was not considered serious. The event resolved the same day. The subject was withdrawn due to the event.

Subject 6096A1-3005-040-003830
Four days after dose 4 of 13vPnC manufacturing lot, this 12-month old male Hispanic infant developed reactive airway disease requiring hospitalization, albuterol sulfate and ipratropim bromide nebulization, and prednisone. The subject remained afebrile and fed well throughout the 2 day hospitalization. The subject was started on fluticasone via aerochamber and discontinued prednisone. The investigator and medical monitor considered this event possibly related to test article/concomitant vaccine administration. The subject's family history is notable for asthma in a twin sibling. The adverse event did not result in withdrawal from the study and the subject completed the study.

Subject 6096A1-3005-086-8336
Thirty-seven days after dose 3 of 13vPnC pilot lot 2, this 6-month old female infant developed seizures. The subject was not hospitalized and the event was not considered serious. The investigator determined the seizure was moderate in severity. The subject was withdrawn because of the adverse event and the event remained persistent at the time that the 6-month safety follow-up was completed.

Subject 6096A1-3005-086-8825
Sixty-nine days after dose 3 of 13vPnC pilot lot 1, this 8-month old female infant developed a febrile seizure lasting ~ 10 minutes with a temperature of 101.3°F). In the emergency room, the subject experienced a second febrile seizure lasting ~ 15 minutes with a temperature of 104°F. Laboratory tests revealed elevated WBC count of 25,900 and a CXR was consistent with a viral bronchitis. The event resolved and the subject was discharged on hospital day 3. An EEG performed about 3 months later was significant for two negative spike waves in the left occipital region during sleep. The neurologist considered the symptoms and EEG finding consistent with febrile seizure, but also considered the possibility of myoclonic epilepsy; therefore, a follow-up consultation and EEG after 6 months was recommended. The subject was withdrawn because a history of febrile seizure was an exclusion criterion. The subject's medical history is significant for bilateral pelviectasis (moderate-right renal, mild-left renal), and for acquired dacryostenosis.

Subject 3005-001-000023
One-hundred fourteen days after the 4th dose of 13vPnC pilot lot 1, this 16-month old Hispanic male child developed a fever of 102°F which was treated with antipyretics. The next day, the child developed a fever of 105.3°F and vomiting, which continued during the nightime over the next 2 days. The parents noted the subjects's lips appeared purple during the espisodes of fever. On the fifth day since fever onset, he was seen by a primary care physician who noted a newly developed heart murmur; blood cultures were obtained for microbial culture. On day 6, he was admitted to the children's hospital emergency room. An echocardiogram showed a large performation of the anterior mitral valve leaflet with possible vegetation causing severe mitral insufficiency; good biventricular systolic function was noted. The subject was diagnosed with acute bacterial endocarditis, mitral valve regurgitation, and patent foramen ovale. Blood cultures were positive for *Kingella kingae*. The subject was treated in the hospital (including the need for a red blood cell transfusion) and subsequently underwent mitral valve repair, including removal of the vegetation on the anterior leaflet of the mitral valve, autologous pericardial patch, repair of anterior defect of the mitral valve, and direct suture closure of the patent foramen ovale. Two weeks after admission, the subject was discharged. The SAE was considered to be resolved about three weeks after discharge, at which time the subject was withdrawn from the study because of this adverse event.

7.2.5.9 Summary and Conclusions Regarding Study 3005 Post-Infant Series Safety Addendum
Among 13vPnC recipients, 1203 completed the toddler dose, 1180 completed the study, and 1229 completed the 6-month follow-up. . No deaths were reported from the post-dose 3 blood draw through the 6-month safety follow-up. An abbreviated study report including fourth dose Prevnar 13 safety data demonstrated no imbalance in the rates of serious adverse events compared to Prevnar recipients. Overall, during the time period from > 30 days after the 3rd dose until just before the 4th dose, SAEs were reported in 1.7% of 13vPnC subjects and 1.2% of PCV7 subjects. SAEs were reported in 0.7% of 13vPnC subjects and 0.5% of PCV7 subjects within 30 days of dose 4; and SAEs were reported in 1.5% and 2.9% of 13vPnC and PCV7 subjects respectively during the 6-month follow-up period.

Similar to study 004, rates of erythema and induration increased following each subsequent dose and were highest after the fourth dose. A statistically significantly higher proportion of PCV7 recipients experienced erythema and induration compared to 13vPnC recipients after dose 4. Rates of any tenderness were consistenly high (~57-67%) following each dose in both study groups. There were no reports of severe erythema or induration after dose 4.

Rates of fever were highest after dose 2 among 13vPnC recipients and after dose 3 among PCV7 recipients. One 13vPnC subject reported fever > 40°C after each of the first three doses and one PCV7 subject reported fever > 40°C after dose 1 and 3. Six 13vPnC subjects (1%) reported fever > 40°C after dose 4. The frequency of hives increased with each subsequent dose in both groups and was highest after dose 4. Use of antipyretics after dose 4 was similar to use following doses 1-3.

There were no withdrawals due to an adverse event following dose 4. During the 6-month follow-up period, one subject was withdrawn due to an event reported as endocarditis bacterial. An additional event to note involved a 12-month male infant with a family history notable for asthma in a twin sibling who developed reactive airways disease four days after the fourth dose of Prevnar 13 (manufacturing lot); the event required hospitalization and administration of prednisone.

8.0 Final Formulation Study

8.1 Clinical Study Protocol # 6096A1-009

Clinical trials.gov registry identifier: NCT00366548

CSR # 71892: infant series analyses
CSR # 74276: 4th dose and 6-month safety follow-up analyses

Protocol Title: A phase 3, randomized, double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine manufactured with and without polysorbate 80 in healthy infants given in a 2, 3, 4, and 12-month schedule with routine pediatric vaccinations in Poland.

8.1.1 Objective/Rationale

This study was designed to evaluate the safety and immunogenicity of 13vPnC formulated with polysorbate 80 (P80) compared to 13vPnC without P80. P80, a nonionic surfactant used –b(4)------- proteins, has been shown to result in a more robust manufacturing process. It is used in several U.S. licensed vaccines (e.g. Infanrix, Pediarix, Tripedia, Havrix, Twinrix, Boostrix, Gardasil, and Rotateq), but is not a component of Prevnar. The decision on whether or not to include P80 in the final 13vPnC formulation was to be based on data from this study.

8.1.1.1 Primary objective

To demonstrate that the immune responses to the 13 common pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 13vPnC with P80 are noninferior to the immune responses induced by 13vPnC without P80, when measured one month after the 3rd dose.

8.1.1.2 Safety objective

To evaluate the acceptability of the safety profile of the 13vPnC vaccine with P80 and the 13vPnC vaccine without P80, as measured by the incidence rates of local injection site reactions, systemic events, and adverse events (AEs).

8.1.1.3 Secondary objective

To assess the pneumococcal immune response induced by 13vPnC with P80 relative to the immune response induced by 13vPnC without P80 when measured 1 month after the 4th dose.

8.1.2 Design Overview

Table 72. Study design 009: Parallel-group, randomized, double-blind, multi-center study

Population n= 500 (Planned enrollment)	Vaccine	Dosing Schedule	Concomitant Vaccines	Blood Draws
n= 250	13vPnC with P80	2, 3, 4, and 12 mo	DTaP-IPV-PRP-T (Pentaxim) at 2, 3, and 4 mo Hep B Vaccine (Engerix-B) at 2 mo MMR (Priorix) at 12 mo	1 mo post-dose 3 Pre-dose 4 1 mo post-dose 4
n= 250	13vPnC without P80			

Source: 125324/0.1,m5.3.5.1, CSR-71892-protocol-amend.pdf

8.1.3 Protocol

8.1.3.1 Population

8.1.3.1.1 Study Period

The study period was from November 14, 2006 to June 4, 2008. May 7, 2007 was the date of the last infant series blood draw and the end of the infant series phase of the study.

8.1.3.1.2 Study sites and recruitment

Study 6096A1-009 was conducted at 15 sites in Poland.

8.1.3.1.3 Inclusion Criteria

The inclusion criteria for study 009 were identical to the criteria in study 004.

8.1.3.1.4 Exclusion Criteria

Prior vaccination with or a contraindication to vaccination with measles, mumps, rubella, varicella, and Hepatitis A vaccines were not exclusionary criteria in study 009. A history of culture-proven invasive disease caused by Hib or confirmed measles, mumps, rubella, or varicella was also not an exclusionary criterion. All other exclusion criteria in study 009 were identical to those in study 004.

8.1.3.1.5 Criteria for Temporarily Delaying Vaccine Administration

The criteria for temporarily delaying vaccine administration were identical to those in study 004.

8.1.3.1.6 Criteria for Withdrawal of a Subject From the Study

The criteria for withdrawal of a subject from study 009 were identical to those in study 004.

8.1.3.2 Concomitant medications

Antipyretic medications were permitted to prevent or treat symptoms related to study vaccination, and this information was collected on days 1 to 4 after vaccination. Data on the use of other concomitant medications, other than antipyretic medications, were not collected.

8.1.3.3 Vaccine administration

Mandatory vaccines in this study included 13vPnC with P80, 13vPnC without P80, Pentaxim, Engerix-B, and Priorix. The formulation and lot number for each study vaccine is described below:

13vPnC with polysorbate 80 (13vPnC+P80): Each 0.5mL dose contains 2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4ug saccharide for 6B individually conjugated to cross-reacting material 197 (CRM_{197}). The total concentration of CRM_{197} is approximately 29ug. The final formulation contains 0.02% P80, 5mM succinate buffer and 0.125 mg aluminum as AlPO4. The vaccine is formulated as a liquid and appears as a homogeneous, white suspension after shaking. The vaccine was filled in containers identical to those containing 13vPnC-P80. Route: intramuscular (IM), anterolateral left thigh. Lot number: 7-5095-001A.

13vPnC without polysorbate 80 (13vPnC-P80): Each 0.5mL dose contains 2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4ug saccharide for 6B individually conjugated to cross-reacting material 197 (CRM_{197}). The total concentration of CRM_{197} is approximately 29ug per 0.5 ml dose. The final formulation contains 5mM succinate buffer and 0.125 mg aluminum as AlPO4. The vaccine is formulated as a liquid and appears as a homogeneous, white suspension after shaking. The vaccine was filled in containers that were identical to those containing 13vPnC+P80. Route: intramuscular (IM), anterolateral left thigh. Lot number: 7-5093-003A.

DTaP-IPV- PRP-T [Pentaxim; Sanofi Pasteur S.A.]: This vaccine is not licensed in the U.S. Each 0.5mL dose contains diphtheria toxoid (≥ 30 IU), tetanus toxoid (≥ 40 IU), and *Bordetella pertussis* antigens (PT 25µg and FHA 25µg), IPV type 1 [40 D-antigen units (DU)] type 2 (8 DU), and type 3 (32 DU), and 10µg Hib purified capsular polysaccharide (PRP) conjugated to tetanus protein. The vaccine must be reconstituted by injecting the 0.5mL suspension of the combined diphtheria, tetanus, acellular pertussis, and poliomyelitis vaccine into the vial of the Hib conjugate vaccine powder. It appears as a cloudy whitish suspension after reconstitution. Route: intramuscular injection after reconstitution into anterolateral right thigh. Lot number: Z2166-2 (doses 1-3); A2061-1 (dose 4).

Hepatitis B [Engerix-B, GSK]: Each 0.5 mL dose contains hepatitis B virus surface antigen (10.0µg), adsorbed on 0.25 mg aluminum as aluminum hydroxide. The final formulation contains 9mg/mL NaCl and phosphate buffers (0.98mg/mL disodium phosphate dehydrate and 0.71mg/mL sodium dihydrogen phosphate dehydrate). The purified surface antigen of the virus is produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology. The final product has no more than 5% of yeast protein. The vaccine is supplied as a sterile suspension for intramuscular administration. It must be shaken before administration. Route: intramuscular injection into anterolateral right thigh, at least 4-5 cm apart from Pentaxim injection site. Lot number: AHBVB138AI.

MMR [Priorix; GSK.]: This vaccine is not licesensed in the U.S. Priorix is a sterile lyophilized mixed preparation containing attenuated measles, mumps, and rubella viruses. Each 0.5mL dose of the reconstituted vaccine contains not less than a $10^{3..0}$ cell culture infective dose 50% ($CCID_{50}$) of the Schwarz measles virus strain, not less than $10^{3.7}$ $CCID_{50}$ of the RIT 4385 mumps virus strain, and not less than $10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus strain. The lyophilized vaccine also contains lactose, neomycin sulphate, amino acids, and sorbitol and mannitol as stabilizers. Each virus strain is separately obtained by propagation in either chick embryo tissue cultures (mumps and measles) or MRC5 human diploid cells (rubella). The manufacture of this product includes exposure to bovine derived materials. The vaccine appears as a white to slightly pink pellet for reconstitution with sterile water for injection diluent. Route: injected subcutaneously into anterolateral right thigh. Lot number: A69CA683A.

- BCG vaccine: from birth up to 28 days before the 1st study dose; after the post-dose 3 blood draw; up to 14 days before study dose 4; and after the post-dose 4 blood draw.
- Hepatitis B vaccine: from birth up to 14 days before the 1st study dose; after the post-dose 3 blood draw, up to 14 days before study dose 4; and after the post-dose 4 blood draw.
- Rotavirus vaccine could be given concomitantly with 13vPnC.
- Influenza vaccine: beginning 7 days after the 3rd study dose until 14 days before study dose 4, and beginning 7 days after the 4th study dose
- Varicella vaccine: after post-dose 4 blood draw
- If recommended by a health authority, meningitis C vaccination could be given 14 days before study vaccination or after the 4 day observation period following each vaccination
- A booster dose of Pentaxim could have been given according to the Polish schedule after the post-dose 4 blood draw (dose provided by applicant for administration at discretion of the investigator)
- A dose of Engerix-B could have been given according to the Polish schedule at 6-7 months of age, after the post-dose 3 blood draw (dose provided by applicant for administration at discretion of investigator)

No other vaccines were to be administered concomitantly with the study vaccine. The name and date of administration of any nonstudy vaccine administered before or during the study period was recorded.

8.1.3.4 Endpoints

8.1.3.4.1 Primary Immunogenicity Endpoint

Proportion of subjects with pneumococcal serotype-specific IgG antibody concentrations ≥ 0.35 µg/mL 1 month post-dose 3

8.1.3.4.2 Secondary Immunogenicity Endpoints

11. Proportion of subjects achieving pneumococcal serotype-specific IgG antibody concentrations ≥ 0.35 µg/mL at 1 month post-dose 4
12. Pneumococcal serotype-specific IgG GMC at 1 month post-dose 3 and 1 month post-dose 4

8.1.3.4.3 Safety Endpoint

The primary endpoints for safety comparisons include incidence rates of solicited local injection site reactions, solicited systemic events (including fever and use of antipyretic medications), and other unsolicited AEs occurring within 4 days after each vaccination.

Solicited local reactions collected included erythema, induration, and tenderness at the site of the pneumococcal vaccine injection. Solicited systemic events included fever (rectal temperature ≥ 38.0°C and use of antipyretic medications to treat and to prevent symptoms, decreased appetite, irritability, increased sleep, and decreased sleep.

8.1.3.5 Surveillance

8.1.3.5.1 Immunogenicity Monitoring

Blood samples were obtained for immunogenicity analyses one month (28-42 days) after the third dose, prior to the fourth dose, and one month (28-42 days) after the fourth dose for all subjects.

Pneumococcal antibody response:
ELISA was performed to measure IgG antibody concentrations specific to each of the 13 pneumococcal serotypes were determined for each blood sample. The ELISA assay employed ----b(4)---------- Results will be reported as µg/mL. Pneumococcal IgG ELISA was performed by Early Phase Programs – Clinical Testing and Assay Development (EPP_CTAD) by Wyeth at Pearl River, NY.

8.1.3.5.2 Safety Surveillance / Monitoring

Safety monitoring in study 009 was identical to safety monitoring in study 004, except solicited local and systemic events were monitored for 4 days rather then 7 days in study 009.

Table 73. Study 6096A1-009 flowchart

Visit No.	1	2	3	4	5	6	7
Visit ID	2-Month Visit	3-Month Visit	4-Month Visit	5-Month Visit	12 Month Visit	13 Month Visit	18 Month Visit
Study Interval	Vaccine dose 1	Vaccine dose 2	Vaccine dose 3	Post-infant series	Vaccine dose 4	Post-toddler dose	6-Month Follow-up
Visit Window	42-98 days of age	28-42 days after visit 1	28-42 days after visit 2	28-42 days after visit 3	365-425 days of age	28-42 days after visit 5	165-210 days after last study vaccine
Informed consent	X						
Review inclusion/ exclusion/delay criteria	X						
Medical Hx/PE	X						
Core rectal temp	X	X	X		X		
Randomization	X						
Study vaccination & 30 minute observation	X	X	X		X		
Pentaxim vaccination	X	X	X				
Engerix-B vaccination	X						
Priorix vaccination					X		
Confirm continued eligibility		X	X	X	X	X	
AE collection	⟷ x ⟶				⟷ x ⟶		
SAE collection	⟷ x ⟶						
Obtain 5 mL blood sample				X	X (before 4th dose)	X	
E-diary, thermometer, calipers provided	X	X	X		X		
Assess acute reactions	Day 1 to 4*	Day 1 to 4	Day 1 to 4		Day 1 to 4		
Use of antipyretic medication	Day 1 to 4	Day 1 to 4	Day 1 to 4		Day 1 to 4		
Telephone call							X

*Day of vaccination is considered day 1. Source: 125324/0.1,m5.3.5.1, CSR-71892-protocol-amend, pages 23 (Table 8.0-1)

8.1.3.6 Statistical considerations

Blinding:
This is a double blind study. The appearance of 13vPnC+P80 and 13vPnC-P80 was identical. Unblinding occurred at analysis of the infant series data for the purposes of regulatory submission. The interim analyses were performed by the study statistician who was provided with randomized vaccine information as well as actual vaccine packaging assignment information for the primary analysis. Results of unblinded assay data were not to be available to applicant personnel involved with the study except as necessary to perform the interim analyses. The database was unblinded for the final analysis of the 6-month follow-up data.

Before analysis was performed, a blinded statistical review of the database occurred to ensure that the planned analyses could be performed, that the data were as expected and that no underlying statistical assumptions were violated.

Randomization:
Eligible subjects were prospectively randomized in a 1:1 allocation into 1 of 2 treatment groups using the ---b(4)---------- system developed for Wyeth. The –b(4)---- system uses a block random assignment scheme for each site separately based on a random assignment schedule generated by Wyeth. Subjects were registered in the Wyeth Clinical Operations Randomization Environment, version II (CORE II) system before they could be randomly assigned. Only subjects who withdrew before randomization could be replaced with additional subjects.

8.1.3.6.1 Sample Size/Statistical Power
Sample size estimation was based on the proportion of responders for pneumococcal serotypes from study 6096A1-003. The study planned to enroll 500 subjects (250 per group) in order to ensure 444 evaluable subjects (222 per group). This sample size is estimated to provide at least 90% overall power to declare non-inferiority for all 13 pneumococcal antigens using a 2-sided, type I error of 0.05 and a non-inferiority criterion of -0.10. A dropout rate of 10% was assumed.

8.1.3.6.2 Study Cohorts Analyzed
Five analysis populations were defined for the immunogenicity analyses: formulation, evaluable infant, all-available infant, evaluable toddler, and all-available toddler. The latter four analysis populations in study 009 were defined very similarly to study 004 with the following exceptions:

- Evaluable infant immunogenicity population:
  - Study 009 subjects had an additional criterion to be ≥ 42 to ≤ 98 days of age on the first day of vaccination for the first infant interim analysis
  - The required time frame for the post-dose 3 blood draw was 28 to 42 days after dose 3. In study 004, the required time frame was 27 to 56 days post-dose 3.
- Evaluable toddler immunogenicity population:
  - Study 009 subjects were required to be ≥ 366 to ≤ 425 days of age on the first day of vaccination; whereas in study 004, subjects were required to be ≥ 364 to ≤ 456 days of age on the first day of vaccination.
  - The required time frame for the post-dose 4 blood draw was 28 to 42 days after dose 4. In study 004, the required time frame was 27 to 56 days post-dose 4.

If no important differences were noted between the evaluable toddler and all-available toddler immunogenicity populations, a single all-available toddler immunogenicity analysis was to be performed.

Subjects eligible for inclusion in the formulation decision population had to meet criteria for a clean patient group. Subjects who were screened and received at least one dose of study vaccine had to have all queries related to study vaccination visits resolved. Subjects who completed visit 4 and whose sera were sent for assaying had to have all queries related to this visit resolved.

8.1.3.6.3 Statistical Analyses

Version 2 of the statistical analysis plan (SAP) dated 16-Nov-07 outlined statistical analyses for this study.

8.1.3.6.3.1 Immunogenicity analyses:

Primary analysis:
To demonstrate that the antibody response to each of the 13 common pneumococcal serotypes one month after the 3rd 13vPnC+P80 dose is non-inferior to the corresponding antibody response after the 3rd dose of 13vPnC-P80. [antibody response: proportion of subjects achieving IgG antibody concentration ≥ 0.35 µg/mL]
Criteria for non-inferiority: Lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC+P80 group – *p*13vPnC-P80 group) > -0.1; *p* is the percentage of subjects with pneumococcal serotype-specific IgG concentration ≥ 0.35 ug/mL

Secondary analyses:

1. To demonstrate that the antibody response to each of the 13 common pneumococcal serotypes one month after the 3rd or 4th 13vPnC+P80 dose is non-inferior to the corresponding antibody response one month after the 3rd or 4th 13vPnC-P80 dose respectively. [antibody response: log of geometric mean IgG antibody concentration]
   Criteria for non-inferiority: Lower limit of the 2-sided 95% CI for the GMC ratio (*p*13vPnC group – *p*PCV7 group) > 0.5 (2-fold criterion)

2. To demonstrate that the antibody response to each of the 13 common pneumococcal serotypes one month after the 4th 13vPnC+P80 dose is non-inferior to the corresponding antibody response after the 4th dose of 13vPnC-P80. [antibody response: proportion of subjects achieving IgG antibody concentration ≥ 0.35 µg/mL]
   Criteria for non-inferiority: Lower limit of the 2-sided 95% CI for the difference in two proportions (*p*13vPnC+P80 group – *p*13vPnC-P80 group) > -0.1; *p* is the percentage of subjects with pneumococcal serotype-specific IgG concentration ≥ 0.35 ug/mL

8.1.3.6.3.2 Safety analyses:

- Safety analysis will be based on the actual study vaccine received.
- Analysis populations:
  - All participants who received at least 1 dose of study vaccine were included in the safety population. Subjects lacking safety data for a particular vaccination were excluded from that analysis.
  - Separate safety populations were defined for each vaccination. An additional infant series safety population, consisting of any subject in the dose 1, dose 2, or dose 3 safety population, was also created.
- AEs were categorized according to MedDRA terminology.

Interim analyses:
Two interim analyses were planned. The initial interim analysis (termed the formulation decision analysis) was conducted when post-dose 3 immunogenicity data was available from approximately 150 evaluable subjects per group. The 2-sided type I error was 0.002 and the non-inferiority criteria was -0.10. The second interim analysis (termed the infant series analysis) was planned after the immunogenicity data from the post-dose 3 blood draw was available from all subjects.

If non-inferiority was declared based on the initial interim analysis, then no additional subjects were to have immunologic assays performed on the blood sample collected 1 month after dose 3 and no second interim analysis was to be conducted. If non-inferiority was not declared, then the second interim analysis (the primary analysis) was to be performed using assay results from all subjects. The 2-sided type I error was 0.05, and the same non-inferiority criteria were used for the second interim analysis. Type I error was permitted to exceed 0.05; using 0.002 and 0.05 resulted in an overall alpha of 0.051.

8.1.3.7 Changes in the Study Protocol (Protocol Amendments) and in the Planned Analyses

The original protocol (dated 1-Jun-06) was amended on 3-Jul-06 to allow two changes: (1) HBVAXPRO vaccine, which was not available for purchase, was replaced with Engerix-B vaccine; and (2) meningitis C vaccine was permitted to be given 14 days before study vaccination or after the 4-day post-vaccination observation period. In addition, the applicant noticed that some AEs were reported outside of the protocol-specified time points and thus were not required to be reported at those times. The applicant excluded these events from the primary safety analyses for consistency with analyses of other studies. Secondary analyses were performed including these non-protocol required events.

The original SAP (dated 4-Apr-07) was amended on 16-Nov-07 to expand the age range of the protocol specified age range for inclusion in the evaluable infant immunogenicity population for the 2nd infant interim analysis; the age range was expanded by 1 day on each side. The protocol did not explicitly describe how to calculate age for study eligibility requirements, and some investigators considered the date of birth as day 1 while others considered it day 0.

8.1.4 Results

8.1.4.1 Populations Enrolled/Analyzed

A total of 500 subjects were randomized into this study at 15 sites and 250 subjects to each group.

8.1.4.1.1 Subject Disposition and Follow-up

Table 74. Study 6096A1-009. Summary of Subject Disposition

	13vPnC+P80 N=250		13vPnC-P80 N=250		Total N=500	
	n	%	n	%	n	%
Subjects randomized	250	100.0	250	100.0	500	100.0
Subjects vaccinated						
Dose 1	250	100.0	250	100.0	500	100.0
Dose 2	246	98.4	249	99.6	495	99.0
Dose 3	246	98.4	247	98.8	193	98.6
Dose 4	240	96.0	244	97.6	484	96.8
Withdrawn during infant series	4	1.6	5	2.0	9	1.8
Reasons for withdrawal:						
Adverse event	1	0.4	3	1.2	4	0.8
Protocol violation	0	0.0	1	0.4	1	0.2
Parent / legal guardian request	3	1.2	1	0.4	4	0.8
Completed infant series	246	98.4	245	98.0	491	98.2
Withdrawn after infant series	6	2.4	1	0.4	7	1.4
Reasons for withdrawal:						
Parent/legal guardian request	3	1.2	1	0.4	4	0.8
Adverse event	2	0.8	0	0.0	2	0.4
Lost to follow-up	1	0.4	0	0.0	1	0.2
Completed toddler dose	240	96.0	244	97.6	484	96.8
Withdrawn after toddler dose	1	0.4	2	0.8	3	0.6
Reason for withdrawal						
Lost to follow-up	1	0.4	1	0.4	2	0.4
Parent/legal guardian request	0	0.0	1	0.4	1	0.2
Completed study	239	95.6	242	96.8	481	96.2
Entered 6-month follow-up[j]	240	96.0	247	98.8	487	97.4
Completed 6-month follow-up[k]	237	94.8	245	98.0	482	96.4

Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant, page 37 (Table 8-1); CSR-74276-report-body, pages 36 -37 (Tables 8-1 and 8-2).

Table 75. Study 6096A1-009. Summary of Safety, Infant Series Immunogenicity and Toddler Immunogenicity Populations

	13vPnC+P80 N=250		13vPnC-P80 N=250		Total N=500	
	n	%	n	%	n	%
Randomized	250	100.0	250	100.0	500	100.0
Dose 1 Safety Population						
Dose 2 Safety Population						
Dose 3 Safety Population						
Dose 4 Safety Population						
All-available infant immunogenicity population	245	98.0	245	98.0	490	98.0
Subjects excluded from all-available infant immunogenicity population because no postinfant assay result for any pneumococcal serotype or concomitant antigen	5	2.0	5	2.0	10	2.0
Evaluable infant immunogenicity population	238	95.2	238	95.2	476	95.5
Subjects excluded from the evaluable infant immunogenicity population[a]	12	4.8	12	4.8	24	4.8
Not in all available infant immunogenicity population	5	2.0	5	2.0	10	2.0
Received vaccine other than randomized	1	0.4	1	0.4	2	0.4
Did not receive all pneumococcal study vaccinations	4	1.6	3	1.2	7	1.4
Blood draw > 42 days after the infant series	6	2.4	5	2.0	11	2.2
Received prohibited vaccines	0	0.0	1	0.4	1	0.2
Not eligible for study	1	0.4	1	0.4	2	0.4
All-available toddler immunogenicity population	241	96.4	244	97.6	491	98.2
Subjects excluded from all-available toddler immunogenicity population before dose 4 administration[b]	5	2.0	1	0.4	6	1.2
Evaluable toddler immunogenicity population	227	90.8	238	95.2	465	93.0
Subjects excluded from the evaluable toddler immunogenicity population[a]	19	7.6	7	2.8	26	5.2
Not in all-available toddler immunogenicity population	5	2.0	1	0.4	6	1.2
Blood draw > 43 days after the toddler dose	8	3.2	4	1.6	12	2.4
Withdrew before toddler vaccination	6	2.4	1	0.4	7	1.4
Received vaccine other than randomized	2	0.8	1	0.4	3	0.6
Age > 425 days on day of dose 4	3	1.2	0	0.0	3	0.6
Not eligible for the study	0	0.0	1	0.4	1	0.2

[a] Subjects may have been excluded for more than 1 reason.
[b] Subject 009-005-000435 had a pretoddler blood draw but was not vaccinated and thereby was included in the all-available toddler immunogenicity population and excluded from the evaluable toddler immunogenicity population.
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant, page 45 (Table 9-2).

The formulation decision population consisted of a subset of 386 subjects of the 500 enrolled subjects. Table 76 summarizes the formulation decision analysis populations.

Table 76. Study 6096A1-009. Summary of Formulation Decision (First Interim Analysis) Populations[a]

	13vPnC+P80 N=192		13vPnC-P80 N=194		Total N=386	
	n	%	n	%	n	%
Subjects eligible for inclusion in formulation decision analysis	192	100	194	100	386	100.0
All-available infant immunogenicity population	175	91.1	178	91.8	353	91.5
Subjects excluded from all-available infant immunogenicity population because no postinfant assay result for any pneumococcal serotype or concomitant antigen	17	8.9	16	8.2	33	8.5
Evaluable infant immunogenicity population	174	90.6	176	90.7	350	90.7
Subjects excluded from the evaluable infant immunogenicity population[a]	18	9.4	18	9.3	36	9.3
Not in all available infant immunogenicity population	17	8.9	16	8.2	33	8.5
Blood draw > 42 days after the infant series	1	0.5	3	1.5	4	1
Vaccine received at dose 1 other than randomized	1	0.5	0	0	1	0.3
Vaccine received at dose 2 other than randomized	0	0	1	0.5	1	0.3

[a] Subjects may have been excluded for more than 1 reason.
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant, page 44 (Table 9-1), CSR-74276-report-body, pages 46-47 (Table 9-1).

8.1.4.1.2 Subject Demographics

The demographic characteristics of the formulation decision immunogenicity analysis populations were similar to data in Table 6, except for a higher proportion of males (52-53%) in each of the two study groups.

Table 77. Study 6096A1-009. Demographic Characteristics for All Subjects by Randomized Group

	13vPnC+P80 N=250		13vPnC-P80 N=250		Total N=500	
	n	%	n	%	n	%
Gender						
Male	128	51.2	128	51.2	256	51.2
Female	122	48.8	122	48.8	244	48.8
Race						
White	250	100.0	250	100.0	500	100.0
Ethnicity						
Non-Hispanic and Non-Latino	250	100.0	249	99.6	499	99.8
Unknown	0	0.0	1	0.4	1	0.2
Age at enrollment (months)						
Mean (SD)	2.1 (0.5)		2.1 (0.5)		2.1 (0.5)	
Min, Max	1.4, 3.3		1.4, 3.2		1.4, 3.3	
Weight at enrollment (lbs)						
Mean (SD)	5.3 (0.8)		5.4 (0.7)		5.4 (0.8)	
Min, Max	3.7, 9.1		3.8, 7.9		3.7, 9.1	

Source: 125324/0.1,m5.3.5.1, CSR-71892-report-body-infant.pdf, page 151 (Table 14.22).

8.1.4.2 Nonstudy Concomitant Vaccinations

Table 78. Study 6096A1-009. Subjects Who Received Non-Study Vaccinations

	13vPnC+P80 (N=250)		13vPnC-P80 (N=250)		Total (N=500)	
Non-study vaccinations	**n**	**%**	**n**	**%**	**n**	**%**
BCG before infant series	234	93.6	232	92.8	466	93.2
Hepatitis B vaccine						
Before infant series	234	93.6	232	92.8	466	93.2
During infant series	54	21.6	54	21.6	108	21.6
Before toddler dose	148	59.2	138	55.2	286	57.2
At toddler dose	0	0.0	1	0.4	1	0.2
Rotavirus vaccine						
During infant series	9	3.6	8	3.2	17	3.4
Before toddler dose	0	0.0	1	0.4	1	0.2
Meningococcal vaccines polysaccharide						
During infant series	0	0.0	1	0.4	1	0.2
Before toddler dose	10	4.0	8	3.2	18	3.6
At toddler dose	21	8.4	21	8.4	42	8.4
Meningococcal conjugate vaccine before 4th dose	1	0.4	0	0.0	1	0.2
Influenza vaccine at toddler dose	2	0.8	0	0.0	2	0.4
Pentavac at toddler dose	198	79.2	203	81.2	401	80.2
Varicella vaccine at toddler dose	0	0.0	3	1.2	3	0.6
Infanrix IPV+HIB I before toddler dose	0	0.0	1	0.4	1	0.2
Pneumococcal conjugate vaccine before toddler dose	0	0.0	1	0.4	1	0.2

Source: 125324/0.1,m5.3.5.1, CSR-71892-report body.pdf, pages 147-148, (Tables 14.18-14.19), CSR-74276-report-body, pages 107-108 (Tables 15.7-15.8).

8.1.4.3 Immunogenicity Endpoints/Outcomes

8.1.4.3.1 Post-dose 3 Pneumococcal Serotype Immunogenicity Outcomes

Post-dose 3 Seroresponse Rates, First Interim Analysis
Serotypes 4, 6B, 9V, 14, 19F, 23F, and 6A failed to meet the -10% non-inferiority criterion based on the lower limit of the 99.8% conficence interval. A second analysis (see Table 81) was performed on a larger sample size.

Table 79. Study 6096A1-009. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population, First Interim Analysis)

	Vaccine Group As Randomized							
	13vPnC+P80 N[a]=174			13vPnC-P80 N[a]=176				
Serotype	n[b]	%	99.8% CI[c]	n[b]	%	(99.8% CI)[c]	Difference[d]	(99.8% CI)[e]
PCV7								
4	161	92.5	(84.4, 97.3)	164	93.2	(85.3, 97.7)	-0.7	(-10.2, 8.7)
6B	99	56.9	(44.9, 68.3)	112	63.6	(51.8, 74.4)	-6.7	(-22.8, 9.5)
9V	167	96.0	(89.1, 99.1)	174	98.9	(93.8, 100.0)	-2.9	(-10.4, 3.3)
14	162	93.1	(85.1, 97.6)	171	97.2	(91.0, 99.6)	-4.1	(-12.9, 3.6)
18C	169	97.1	(90.8, 99.6)	173	98.3	(92.8, 99.9)	-1.2	(-8.3, 5.2)
19F	165	94.8	(87.5, 98.6)	172	97.7	(91.8, 99.8)	-2.9	(-11.0, 4.2)
23F	148	85.1	(75.1, 92.2)	162	92.0	(83.8, 97.0)	-7.0	(-18.3, 3.7)
Additional								
1	166	95.4	(88.3, 98.9)	164	93.2	(85.3, 97.7)	2.2	(-6.3, 11.2)
3	170	97.7	(91.8, 99.8)	175	99.4	(94.9, 100.0)	-1.7	(-8.4, 3.8)
5	162	93.1	(85.1, 97.6)	165	93.8	(86.1, 98.0)	-0.6	(-10.0, 8.4)
6A	147	84.5	(74.4, 91.8)	151	85.8	(76.1, 92.7)	-1.3	(-13.6, 10.8)
7F	171	98.3	(92.7, 99.9)	175	99.4	(94.9, 100.0)	-1.2	(-7.5, 4.3)
19A	171	98.3	(92.7, 99.9)	176	100.0	(96.2, 100.0)	-1.7	(-7.9, 3.2)

[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+P80 – 13vPnC-P80) expressed as a percentage.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC+P80 – 13vPnC-P80, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, page 50 (Table 9-4).

Post dose 3 Pneumococcal IgG Geometric Mean Concentrations, First Interim Analysis
The lower limit of the 99.8% CI for the GMC ratio was greater than 0.5 for all serotypes, which was the non-inferiority criterion for this secondary study endpoint. A second anlaysis (see Table 82) was performed on a larger sample size.

Table 80. Study 6096A1-009. Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population, First Interim Analysis)

	Vaccine Group As Randomized					
	13vPnC+P80 N[a]=174		13vPnC-P80 N[a]=176			
Serotype	GMC[b]	99.8% CI[c]	GMC[b]	(99.8% CI)[c]	GMC Ratio[d]	(99.8% CI)[e]
PCV7						
4	1.49	(1.18, 1.87)	1.55	(1.24, 1.95)	0.96	(0.69, 1.32)
6B	0.47	(0.34, 0.63)	0.53	(0.38, 0.74)	0.88	(0.56, 1.37)
9V	1.53	(1.28, 1.82)	1.63	(1.39, 1.92)	0.93	(0.73, 1.19)
14	2.00	(1.54, 2.59)	2.33	(1.87, 2.90)	0.86	(0.61, 1.20)
18C	1.96	(1.61, 2.37)	1.99	(1.69, 2.35)	0.98	(0.76, 1.26)
19F	1.43	(1.13, 1.82)	1.76	(1.48, 2.10)	0.81	(0.61, 1.09)
23F	0.95	(0.76, 1.20)	1.16	(0.94, 1.43)	0.82	(0.60, 1.12)
Additional						
1	1.44	(1.18, 1.76)	1.59	(1.29, 1.97)	0.91	(0.68, 1.21)
3	1.60	(1.36, 1.88)	1.74	(1.51, 2.01)	0.92	(0.74, 1.14)
5	1.28	(1.04, 1.57)	1.31	(1.08, 1.60)	0.98	(0.74, 1.30)
6A	0.94	(0.74, 1.18)	1.05	(0.84, 1.32)	0.89	(0.65, 1.23)
7F	1.93	(1.63, 2.29)	1.88	(1.60, 2.21)	1.03	(0.81, 1.29)
19A	2.78	(2.32, 3.34)	3.09	(2.61, 3.66)	0.90	(0.70, 1.15)

[a] Number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
[c] Confidence intervals (CI) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC+P80 to 13vPnC-P80.
[e] CIs for the ratio are back transforms of confidence levels based on the Student t distribution for the mean difference of the logarithms of the concentrations (13vPnC+P80-13vPnC-P80).
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, pages 51-52 (Table 9-5 and 9-6).

Because the first interim analysis failed to demonstrate non-inferiority, a second interim analysis of infant series data was performed.

Post-dose 3 Seroresponse Rates, Second Interim Analysis
In this secnd analysis, the -10% non-inferiority criterion was based on the lower limit of the 95% CI. The non-inferiority criterion was met for 11 of 13 serotypes. Serotypes 6B and 23F failed to meet the pre-specified primary objective of demonstrating noninferior immune responses.

Table 81. Study 6096A1-009. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population, Second Interim Analysis)

	Vaccine Group As Randomized							
	13vPnC+P80 N[a]=238			13vPnC-P80 N[a]=238				
Serotype	n[b]	%	95% CI[c]	n[b]	%	(95% CI)[c]	Difference[d]	(95% CI)[e]
PCV7								
4	222	93.3	(89.3, 96.1)	224	94.1	(90.3, 96.7)	-0.8	(-5.4, 3.7)
6B	145	60.9	(54.4, 67.2)	158	66.4	(60.0, 72.4)	-5.5	(-14.2, 3.3)
9V	231	97.1	(94.0, 98.8)	232	97.5	(94.6, 99.1)	-0.4	(-3.7, 2.8)
14	225	94.5	(90.8, 97.1)	232	97.5	(94.6, 99.1)	-2.9	(-6.9, 0.7)
18C	233	97.9	(95.2, 99.3)	233	97.9	(95.2, 99.3)	0.0	(-3.0, 3.0)
19F	228	95.8	(92.4, 98.0)	234	98.3	(95.8, 99.5)	-2.5	(-6.1, 0.6)
23F	205	86.1	(81.1, 90.3)	220	92.4	(88.3, 95.5)	-6.3	(-12.1, -0.7)
Additional								
1	228	95.8	(92.4, 98.0)	220	92.4	(88.3, 95.5)	3.4	(-0.9, 7.9)
3	233	97.9	(95.2, 99.3)	236	99.2	(97.0, 99.9)	-1.3	(-4.1, 1.1)
5	224	94.1	(90.3, 96.7)	220	92.4	(88.3, 95.5)	1.7	(-3.0, 6.4)
6A	206	86.6	(81.6, 90.6)	205	86.1	(81.1, 90.3)	0.4	(-5.8, 6.7)
7F	235	98.7	(96.4, 99.7)	237	99.6	(97.7, 100.0)	-0.8	(-3.2, 1.2)
19A	235	98.7	(96.4, 99.7)	238	100.0	(98.5, 100.0)	-1.3	(-3.6, 0.3)

[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+P80 – 13vPnC-P80) expressed as a percentage.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC+P80 – 13vPnC-P80, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, page 55 (Table 9-7).

Post dose 3 Pneumococcal IgG Geometric Mean Concentrations, Second Interim Analysis
The lower limit of the 95% CI for the GMC ratio was greater than 0.5 for all serotypes, which was the non-inferiority criterion for this secondary study endpoint.

Table 82. Study 6096A1-009. Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population, Second Interim Analysis).

	Vaccine Group As Randomized					
	13vPnC+P80 N[a]=238		13vPnC-P80 N[a]=238			
Serotype	GMC[b]	95% CI[c]	GMC[b]	(95% CI)[c]	GMC Ratio[d]	(95% CI)[e]
PCV7						
4	1.47	(1.30, 1.65)	1.53	(1.36, 1.72)	0.96	(0.81, 1.13)
6B	0.51	(0.44, 0.60)	0.57	(0.48, 0.68)	0.90	(0.72, 1.14)
9V	1.46	(1.34, 1.60)	1.51	(1.38, 1.65)	0.97	(0.85, 1.10)
14	2.37	(2.06, 2.73)	2.48	(2.20, 2.80)	0.96	(0.79, 1.15)
18C	1.84	(1.67, 2.03)	1.87	(1.71, 2.04)	0.98	(0.86, 1.13)
19F	1.46	(1.30, 1.65)	1.75	(1.60, 1.91)	0.84	(0.72, 0.97)
23F	0.93	(0.83, 1.05)	1.11	(1.00, 1.24)	0.84	(0.71, 0.98)
Additional						
1	1.39	(1.26, 1.55)	1.48	(1.32, 1.66)	0.94	(0.81, 1.10)
3	1.50	(1.38, 1.63)	1.62	(1.49, 1.75)	0.93	(0.83, 1.04)
5	1.26	(1.13, 1.40)	1.30	(1.16, 1.44)	0.97	(0.83, 1.13)
6A	0.99	(0.88, 1.12)	1.04	(0.92, 1.17)	0.96	(0.81, 1.13)
7F	1.98	(1.81, 2.15)	1.89	(1.73, 2.06)	1.05	(0.93, 1.18)
19A	2.68	(2.44, 2.95)	2.94	(2.69, 3.21)	0.91	(0.80, 1.04)

[a] Number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
[c] Confidence intervals (CI) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC+P80 to 13vPnC-P80.
[e] CIs for the ratio are back transforms of confidence levels based on the Student t distribution for the mean difference of the logarithms of the concentrations (13vPnC+P80-13vPnC-P80).
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, pages 56 and 158 (Tables 9-8 and 14.29).

8.1.4.3.2 Dose 4 Pneumococcal Serotype Immunogenicity Outcomes

Post-dose 4 Seroresponse rates ≥ 0.35µg/mL
Each of the 13 vaccine serotypes elicited post-dose 4 antibody responses in the 13vPnC+P80 group that met the -10% non-inferiority criterion when compared to the corresponding antibody responses in the 13vPnC-P80 group. This was a secondary study endpoint.

Table 83. Study 6096A1-009. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After Dose 4 (Evaluable Toddler Immunogenicity Population).

	Vaccine Group As Randomized									
	13vPnC+P80				13vPnC-P80					
Serotype	N[a]	n[b]	%	95% CI[c]	N[a]	n[b]	%	(95% CI)[c]	Difference[d]	(95% CI)[e]
PCV7										
4	226	225	99.6	(97.6, 100.0)	238	237	99.6	(97.7, 100.0)	0.0	(-2.1, 1.9)
6B	225	224	99.6	(97.5, 100.0)	237	235	99.2	(97.0, 99.9)	0.4	(-1.7, 2.6)
9V	226	225	99.6	(97.6, 100.0)	238	238	100.0	(98.5, 100.0)	-0.4	(-2.4, 1.1)
14	226	225	99.6	(97.6, 100.0)	238	237	99.6	(97.7, 100.0)	0.0	(-2.1, 1.9)
18C	226	226	100.0	(98.4, 100.0)	238	237	99.6	(97.7, 100.0)	0.4	(-1.2, 2.3)
19F	226	224	99.1	(96.8, 99.9)	237	234	98.7	(96.3, 99.7)	0.4	(-2.0, 2.9)
23F	226	223	98.7	(96.2, 99.7)	238	237	99.6	(97.7, 100.0)	-0.9	(-3.4, 1.1)
Additional										
1	226	226	100.0	(98.4, 100.0)	238	236	99.2	(97.0, 99.9)	0.8	(-0.8, 3.0)
3	223	212	95.1	(91.3, 97.5)	236	223	94.5	(90.8, 97.0)	0.6	(-3.7, 4.9)
5	226	225	99.6	(97.6, 100.0)	238	238	100.0	(98.5, 100.0)	-0.4	(-2.4, 1.1)
6A	226	225	99.6	(97.6, 100.0)	237	237	100.0	(98.5, 100.0)	-0.4	(-2.4, 1.2)
7F	226	226	100.0	(98.4, 100.0)	238	238	100.0	(98.5, 100.0)	0.0	(-1.7, 1.6)
19A	226	226	100.0	(98.4, 100.0)	238	238	100.0	(98.5, 100.0)	0.0	(-1.7, 1.6)

[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.
[d] Difference in proportions (13vPnC+P80 – 13vPnC-P80) expressed as a percentage.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC+P80 – 13vPnC-P80, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body.pdf, pages 51 (Tables 9-3).

Clinical Reviewer Note: GMCs are the preferred endpoint for the post-dose 4 analysis of immune responses. The proportion of children achieving the 0.35 µg/mL antibody concentration after the fourth dose at 12-15 months of age is less useful in evaluating of immune responses at this timepoint, as it is a low bar for these comparisons. The proportion of subjects achieving the 0.35 µg/mL antibody concentration is high in both groups, which limits the ability to determine differences, if any, between the products.

Post-dose 4 Pneumococcal IgG Geometric Mean Concentrations
Each of the 13 vaccine serotypes elicited post-dose 4 IgG GMCs in the 13vPnC+P80 group that met the non-inferiority criterion (GMC ratio > 0.5) when compared to the corresponding IgG GMCs in the 13vPnC-P80 group. This was a secondary study endpoint.

Table 84. Study 6096A1-009. Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 4 (Evaluable Toddler Immunogenicity Population).

	Vaccine Group As Randomized							
	13vPnC+P80			13vPnC-P80				
Serotype	N[a]	GMC[b]	95% CI[c]	N[a]	GMC[b]	(95% CI)[c]	Ratio[d]	(95% CI)[e]
PCV7								
4	226	5.25	(4.65, 5.92)	238	5.38	4.78, 6.07)	0.97	(0.82, 1.15)
6B	225	9.89	(8.70, 11.23)	237	10.65	(9.40, 12.06)	0.93	(0.78, 1.11)
9V	226	3.01	(2.73, 3.31)	238	3.10	(2.80, 3.42)	0.97	(0.85, 1.11)
14	226	11.72	(10.26, 13.40)	238	11.95	(10.42, 13.71)	0.98	(0.81, 1.19)
18C	226	3.40	(3.06, 3.78)	238	3.10	(2.79, 3.45)	1.10	(0.94, 1.27)
19F	226	9.63	(8.45, 10.97)	237	10.27	(8.99, 11.73)	0.94	(0.78, 1.13)
23F	226	3.88	(3.44, 4.38)	238	4.15	(3.73, 4.62)	0.94	(0.80, 1.10)
Additional								
1	226	6.03	(5.36, 6.78)	238	6.11	(5.43, 6.87)	0.99	(0.84, 1.17)
3	223	1.09	(0.99, 1.20)	236	1.16	(1.05, 1.29)	0.94	(0.81, 1.08)
5	226	3.80	(3.41, 4.23)	238	3.98	(3.59, 4.41)	0.95	(0.82, 1.11)
6A	226	7.48	(6.66, 8.40)	237	8.19	(7.38, 9.09)	0.91	(0.78, 1.07)
7F	226	5.36	(4.89, 5.88)	238	4.95	(4.50, 5.44)	1.08	(0.95, 1.24)
19A	226	13.20	(11.88, 14.67)	238	13.02	(11.88, 14.27)	1.01	(0.88, 1.16)

[a] Number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
[c] Confidence intervals (CI) are back transforms of CIs based on Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC+P80 to 13vPnC-P80.
[e] CIs for the ratio are back transforms of confidence levels based on the Student t distribution for the mean difference of the logarithms of the concentrations (13vPnC+P80-13vPnC-P80).
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body.pdf, page 56 (Table 9-5).

Pre-dose 4 Pneumococcal IgG GMCs

Approximately 6 months after the 3rd dose and before administration of the 4th dose, IgG GMCs were similar between the two study groups for each serotype. This was not a pre-specified study endpoint.

Table 85. Study 6096A1-009. Pneumococcal IgG Geometric Mean Concentrations (µg/mL) Before Toddler Dose (Evaluable Toddler Immunogenicity Population).

	Vaccine Group As Randomized					
	13vPnC+P80			13vPnC-P80		
Serotype	N[a]	GMC[b]	95% CI[c]	N[a]	GMC[b]	(95% CI)[c]
PCV7						
4	227	0.35	(0.31, 0.39)	238	0.37	(0.33, 0.41)
6B	222	0.58	(0.51, 0.65)	229	0.68	(0.60, 0.76)
9V	227	0.38	(0.35, 0.42)	238	0.41	(0.37, 0.45)
14	225	1.82	(1.57, 2.11)	238	2.17	(1.87, 2.51)
18C	227	0.32	(0.29, 0.35)	238	0.32	(0.29, 0.35)
19F	224	0.67	(0.58, 0.77)	237	0.76	(0.67, 0.86)
23F	224	0.21	(0.19, 0.24)	236	0.25	(0.23, 0.29)
Additional						
1	227	0.54	(0.49, 0.60)	238	0.56	(0.51, 0.62)
3	217	0.14	(0.13, 0.16)	228	0.18	(0.16, 0.20)
5	226	0.67	(0.59, 0.75)	234	0.73	(0.66, 0.81)
6A	225	0.53	(0.47, 0.59)	237	0.63	(0.56, 0.70)
7F	227	0.81	(0.74, 0.88)	238	0.84	(0.76, 0.91)
19A	225	1.02	(0.89, 1.17)	236	1.02	(0.89, 1.15)

[a] 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] Confidence intervals (CIs) are back transformations of a confidence interval
based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body.pdf, page 53-55 (Table 9-4).

Pre-dose 4 Pneumococcal Seroresponse Rates

Similarly, approximately 6 months after the 3rd dose and before administration of the fourth dose, the proportion of subjects achieving an IgG antibody concentration ≥ 0.35µg/mL was similar between the two study groups for each vaccine serotype. This was not a pre-specified study endpoint.

Table 86. Study 6096A1-009. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL 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]
PCV7										
4	234	107	45.7	(39.2, 52.3)	237	123	51.9	(45.3, 58.4)	-0.0	(-2.1, 1.9)
6B	229	167	72.9	(66.7, 78.6)	228	179	78.5	(72.6, 83.7)	0.4	(-1.7, 2.6)
9V	234	122	52.1	(45.5, 58.7)	237	135	57.0	(50.4, 63.4)	-0.4	(-2.4, 1.1)
14	232	215	92.7	(88.5, 95.7)	237	224	94.5	(90.8, 97.0)	-0.0	(-2.1, 1.9)
18C	234	98	41.9	(35.5, 48.5)	237	107	45.1	(38.7, 51.7)	0.4	(-1.2, 2.3)
19F	231	188	81.4	(75.8, 86.2)	236	204	86.4	(81.4, 90.5)	0.4	(-2.0, 2.9)
23F	230	72	31.3	(25.4, 37.7)	235	79	33.6	(27.6, 40.0)	-0.9	(-3.4, 1.1)
Additional										
1	234	174	74.4	(68.3, 79.8)	237	170	71.7	(65.5, 77.4)	0.8	(-0.8, 3.0)
3	225	32	14.2	(9.9, 19.5)	227	35	15.4	(11.0, 20.8)	0.6	(-3.7, 4.9)
5	233	189	81.1	(75.5, 85.9)	233	191	82.0	(76.4, 86.7)	-0.4	(-2.4, 1.1)
6A	232	156	67.2	(60.8, 73.2)	236	181	76.7	(70.8, 81.9)	-0.4	(-2.4, 1.2)
7F	234	210	89.7	(85.1, 93.3)	237	213	89.9	(85.3, 93.4)	0.0	(-1.7, 1.6)
19A	232	211	90.9	(86.5, 94.3)	235	213	90.6	(86.2, 94.0)	0.0	(-1.7, 1.6)

[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.

8.1.4.4 Safety Outcomes

Antipyretic Use

There were no statistically significant differences between the two study groups in the use of antipyretic drugs for either prevention or treatment of fever.

Table 87. Study 6096A1-009. Subjects who received antipyretics to treat symptoms or to prevent symptoms within 4 days following each dose of 13vPnC or PCV7.

	Use of Antipyretics to Treat Symptoms		Use of Antipyretics to Prevent Symptoms	
Dose number	13vPnC+P80 n (%)	13vPnC-P80 n (%)	13vPnC+P80 n (%)	13vPnC-P80 n (%)
1	N[a]=180 27 (15.0)	N[b]=181 33 (18.2)	N[b]=179 27 (15.1)	N[b]=180 32 (17.8)
2	N=174 27 (15.5)	N=174 27 (15.5)	N=172 29 (16.9)	N=172 28 (16.3)
3	N=164 25 (15.2)	N=170 23 (13.5)	N=164 25 (15.2)_	N=170 19 (11.2)
4	N=172 37 (21.5)	N=168 26 (15.5)	N=171 32 (18.7)	N=171 26 (15.2)

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

Source: 125324/0.1,m5.3.5.1, CSR71892-report body-infant.pdf, page 78-79 (Tables 10-8 to 10-10); CSR74276-report-body.pdf, page 66 (Table 10-2).

8.1.4.4.1 Immediate Reactions

Although immediate reactions were collected and reported along with other unsolicited adverse events, these events could not be idenitifed from the data submitted to the BLA. The specific time-to-onset of symptoms was not recorded, therefore reactions that occurred within 30 minutes of vaccination could not be identified.

8.1.4.4.2 Solicited Local Reactions

Erythema was the most frequently reported local adverse event. The incidence of erythema peaked after dose 3 in the 13vPnC+P80 group and peaked after dose 4 in the 13vPnC-P80 group. The incidence of swelling and tenderness peaked after dose 3 and dose 4 respectively in both study groups. The incidence of local reactions after each dose was generally higher among 13vPnC-P80 subjects compared to 13vPnC+P80 subjects. A statistically significantly higher proportions of subjects in the 13vPnC+P80 group than in the 13vPnC-P80 experienced the following local reactions:

- First interim analysis: moderate erythema after dose 3, mild swelling after dose 2, and any tenderness after dose 2.
- Second interim analysis: any erythema after dose 1 and dose 2, moderate erythema after dose 3, mild erythema after dose 4, and any and mild swelling after dose 2.

Table 88. Study 6096A1-009. Percentage of subjects with solicited local adverse events, by severity, at the 13vPnC+P80 or 13vPnC-P80 injection site within 4 days after each vaccination, First Interim Analysis.

	Safety Populations by Dose[a]					
	Dose 1		Dose 2		Dose 3	
Graded Local Reaction	**13vPnC+P80** N[a]=179-181 %	**13vPnC-P80** N[a]=177-183 %	**13vPnC+P80** N[a]=172-180 %	**13vPnC-P80** N[a]=170-178 %	**13vPnC+P80** N[a]=163-169 %	**13vPnC-P80** N[a]=165-177 %
Erythema[b]						
Any	32.0	39.9	37.8	48.3	46.2	50.3
0.5 - 2.0 cm	30.9	35.0	37.8	46.3	46.2	46.3
2.5 - 7.0 cm	1.7	5.6	1.2	3.5	3.0	9.7*
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0
Swelling[b]						
Any	21.8	30.1	25.8	35.4	35.8	38.3
0.5 - 2.0 cm	18.4	22.8	20.9	31.2*	30.9	32.7
2.5 - 7.0 cm	10.1	15.4	12.6	14.0	14.0	17.8
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0
Tenderness						
Any	24.9	32.6	24.4	35.8*	24.6	22.4
Interferes with limb movement	2.2	4.5	0.6	0.6	1.2	1.2

[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 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.
* Indicates statistically significant difference between two study groups.
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, pages 66-68 .(Tables 10-2 to 10-4).

Table 89. Study 6096A1-009. Percentage of subjects with solicited local adverse events, by severity, at the 13vPnC+P80 or 13vPnC-P80 injection site within 4 days after each vaccination (Second Interim Analysis for doses 1-3).

	Safety Populations by Dose							
	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Local Reaction	**13vPnC+ P80 N[a]=235-238 %**	**13vPnC- P80 N[a]=231-239 %**	**13vPnC+ P80 N[a]=220-232 %**	**13vPnC- P80 N[a]=221-231 %**	**13vPnC+ P80 N[a]=203-216 %**	**13vPnC- P80 N[a]=211-226 %**	**13vPnC+ P80 N[a]=159-178 %**	**13vPnC -P80 N[a]=164-200 %**
Erythema[b]								
Any	29.8	39.5*	38.8	48.5*	46.8	50.0	42.1	52.0
0.5 - 2.0 cm	28.2	35.7	38.4	47.0	46.5	46.9	35.8	46.4*
2.5 - 7.0 cm	2.1	4.3	1.4	3.2	3.9	9.0*	12.8	19.7
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6
Swelling[b]								
Any	22.9	30.5	25.0	36.4*	36.7	38.2	29.9	34.8
0.5 - 2.0 cm	18.2	24.2	20.3	31.9*	32.5	33.5	26.6	29.8
2.5 - 7.0 cm	11.9	14.4	11.2	14.3	13.9	17.5	12.2	19.9
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tenderness								
Any	27.7	32.9	26.8	32.8	24.8	23.1	42.1	43.1
Interferes with limb movement	2.1	4.3	0.9	0.5	1.5	1.9	2.5	1.2

[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 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.
* Indicates statistically significant difference between two study groups. P-values calculated by Fisher exact test, 2 sided. p-values are not corrected for multiple comparisons.
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, pages 70-72, (Tables 10-5 to 10-7); CSR-74276-report-body, page 64 (Table 10-1).

8.1.4.4.3 Solicited Systemic Reactions

In both study groups, irritability was the most frequently reported solicited systemic adverse event. Mild and moderate fever peaked after dose 3 in both study groups. There were no cases of severe fever > 40°C. A statistically significantly higher proportion of subjects in the 13vPnC-P80 group experienced decreased appetite after dose 2 and increased sleep after dose 4.

Table 90. Study 6096A1-009. Percentage of subjects with solicited systemic adverse events within 4 days after each vaccination, First Interim Analysis.

	Safety Populations by Dose					
	Dose 1		Dose 2		Dose 3	
Graded Systemic Events	**13vPnC+P80** N[a]=179-184 %	**13vPnC-P80** N[a]=179-185 %	**13vPnC+P80** N[a]=172-182 %	**13vPnC-P80** N[a]=170-179 %	**13vPnC+P80** N[a]=163-171 %	**13vPnC-P80** N[a]=165-177 %
Fever[b]						
38.0°C ≤ x ≤ 39.0°C	15.0	18.2	19.9	16.9	21.6	18.9
39°C < x ≤ 40.0°C	0.6	0.6	1.2	0.0	1.2	1.2
> 40°C	0.0	0.0	0.0	0.0	0.0	0.0
Decreased appetite	22.1	20.3	15.7	23.1	21.0	20.8
Irritability	50.5	55.4	46.4	52.5	44.4	48.0
Increased sleep	46.7	51.9	35.2	41.8	26.5	27.5
Decreased sleep	32.6	30.4	22.2	25.7	25.3	23.5

[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. No other systemic event other than fever was graded.
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, page 78-79 (Tables 10-8 to 10-10).

Table 91. Study 6096A1-009. Percentage of subjects with solicited system adverse events within 4 days after each vaccination (Second Interim Analysis for doses 1-3).

	Safety Populations by Dose							
	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Systemic Events	**13vPnC+ P80** N[a]=235-242 %	**13vPnC- P80** N[a]=233-242 %	**13vPnC+ P80** N[a]=221-232 %	**13vPnC- P80** N[a]=221-232 %	**13vPnC+ P80** N[a]=203-215 %	**13vPnC- P80** N[a]=211-226 %	**13vPnC+ P80** N[a]=160-184 %	**13vPnC- P80** N[a]=164-198 %
Fever[b]								
38.0°C ≤ x ≤ 39.0°C	33 (14.0)	38 (16.2)	41 (18.3)	39 (17.0)	41 (19.7)	45 (20.6)	39 (22.9)	31 (18.0)
39°C < x ≤ 40.0°C	1 (0.4)	1 (0.4)	2 (0.9)	1 (0.5)	2 (1.0)	2 (0.9)	4 (2.5)	3 (1.8)
> 40°C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	51 (21.5)	53 (22.4)	36 (16.3)	54 (24.1)*	45 (21.4)	46 (20.7)	45 (26.2)	53 (29.0)
Irritability	132 (55.0)	132 (55.2)	120 (51.7)	125 (53.9)	98 (45.6)	113 (50.0)	91 (49.5)	111 (56.1)
Increased sleep	112 (46.3)	127 (52.5)	83 (35.9)	90 (39.3)	54 (25.8)	61 (27.6)	33 (19.0)	56 (30.8)*
Decreased sleep	85 (35.7)	70 (29.7)	56 (24.7)	60 (26.4)	53 (25.4)	53 (24.4)	33 (19.4)	46 (25.6)

* 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. No other systemic event other than fever was graded.
Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, page 80-81 (Tables 10-11 to 10-13); CSR-74276-report-body, page 66 (Table 10-2).

8.1.4.4.4 Unsolicited Adverse Events

During the infant series, unsolicited adverse events were reported by 47.6% (91/191) and 46.1% (89/193) of subjects in the 13vPnC+P80 and 13vPnC-P80 groups respectively during the first interim analysis. At the second interim analysis (the primary analysis), 52.2% (130/249) and 48.4% (121/250) of subjects in the 13vPnC+P80 and 13vPnC-P80 groups respectively reported unsolicited AEs. During the 30 day period following the toddler dose, unsolicited adverse events were reported by 23.0% (55/239) and 32.4% (79/244) of subjects in the 13vPnC+P80 and 13vPnC-P80 groups respectively. There were no statistically significant differences in the rates of reported AE preferred terms between the two study groups.

The most frequently reported adverse events during the infant series were bronchitis (10%), rhinitis (8-9%), pharyngitis (6-7%), upper respiratory tract infection (5-7%), nasopharyngitis (5%), and dermatitis atopic (3-6%). Following the toddler dose, the most frequently reported adverse events were pharyngitis (4-8%), upper respiratory tract infections (4-7%), and rhinitis (3-4%).

8.1.4.4.5 Serious Adverse Events

No subjects died during the study. There were no statistically significant differences in rates of SAEs between the two groups.

Table 92. Study 6096A1-009. Incidence of SAEs during infant series by MedDRA system organ class and preferred term.

	Vaccine Group (as Administered)						
	13vPnC+P80 N=249			13vPnC-P80 N=250			
System Organ Class\ Preferred Term	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	p-Value[c]
Any event	15	6.0	22	21	8.4	31	0.387
Blood and lymphatic system disorders	0	0.0	0	1	0.4	1	>.99
Anaemia	0	0.0	0	1	0.4	1	>.99
Gastrointestinal disorders	3	1.2	3	3	1.2	3	>.99
Diarrhoea	2	0.8	2	2	0.8	2	>.99
Gastrooesophageal reflux disease	1	0.4	1	0	0.0	0	0.499
Vomiting	0	0.0	0	1	0.4	1	>.99
Immune system disorders	1	0.4	1	0	0.0	0	0.499
Hypersensitivity	1	0.4	1	0	0.0	0	0.499
Infections and infestations	11	4.4	16	17	6.8	23	0.331
Bronchitis	4	1.6	4	9	3.6	9	0.260
Pneumonia	8	3.2	8	3	1.2	3	0.141
Bronchopneumonia	0	0.0	0	3	1.2	3	0.248
Gastroenteritis	2	0.8	2	1	0.4	1	0.623
Respiratory tract infection	1	0.4	1	1	0.4	1	>.99
Rhinitis	0	0.0	0	2	0.8	2	0.499
Laryngitis	1	0.4	1	0	0.0	0	0.499
Meningitis meningococcal	0	0.0	0	1	0.4	1	>.99
Meningococcal sepsis	0	0.0	0	1	0.4	1	>.99
Pneumonia primary atypical	0	0.0	0	1	0.4	1	>.99
Urinary tract infection	0	0.0	0	1	0.4	1	>.99
Nervous system disorders	0	0.0	0	1	0.4	1	>.99
Hydrocephalus	0	0.0	0	1	0.4	1	>.99
Renal and urinary disorders	0	0.0	0	1	0.4	1	>.99
Hydronephrosis	0	0.0	0	1	0.4	1	>.99
Respiratory, thoracic and mediastinal disorders	1	0.4	1	2	0.8	2	>.99
Pneumonia aspiration	1	0.4	1	1	0.4	1	>.99
Sleep apnoea syndrome	0	0.0	0	1	0.4	1	>.99
Skin and subcutaneous tissue disorders	1	0.4	1	0	0.0	0	0.499
Urticaria	1	0.4	1	0	0.0	0	0.499

[a] Number of subjects reporting at least 1 event. [b] The total number of events. Multiple events may be reported by 1 subject.
[c] Fisher exact test, 2-sided. p-values are not corrected for multiple comparisons.

Source: 125324/0.1,m5.3.5.1, CSR-71892-report body-infant.pdf, page 98 (Table 10-21).

Table 93. Study 6096A1-009. Incidence of SAEs after the infant series by MedDRA system organ class and preferred term.

	Vaccine Group (as Administered)						
	13vPnC+P80 N=249			**13vPnC-P80 N=250**			
System Organ Class\ Preferred Term	**No. of Subjects[a]**	**%**	**No. of Events[b]**	**No. of Subjects[a]**	**%**	**No. of Events[b]**	**p-Value[c]**
Any event	24	9.6	43	16	6.4	25	0.192
Blood and lymphatic system disorders	1	0.4	2	0	0.0	0	0.499
Leukocytosis	1	0.4	1	0	0.0	0	0.499
Splenomegaly	1	0.4	1	0	0.0	0	0.499
Gastrointestinal disorders	5	2.0	5	4	1.6	4	0.751
Diarrhoea	4	1.6	4	3	1.2	3	0.724
Dyspepsia	1	0.4	1	0	0.0	0	0.499
Inguinal hernia, obstructive	0	0.0	0	1	0.4	1	>.99
General disorders and administration site conditions	0	0.0	0	1	0.4	1	>.99
Pyrexia	0	0.0	0	1	0.4	1	>.99
Hepatobiliary disorders	1	0.4	1	0	0.0	0	0.499
Hepatitis	1	0.4	1	0	0.0	0	0.499
Immune system disorders	1	0.4	1	0	0.0	0	0.499
Alloimmunisation	1	0.4	1	0	0.0	0	0.499
Infections and infestations	17	6.8	25	11	4.4	13	0.251
Gastroenteritis	4	1.6	4	3	1.2	3	0.724
Pneumonia	6	2.4	6	1	0.4	1	0.068
Bronchitis	5	2.0	5	1	0.4	1	0.122
Laryngitis	1	0.4	1	2	0.8	2	>.99
Pharyngitis	2	0.8	2	1	0.4	1	0.623
Urinary tract infection	1	0.4	1	2	0.8	2	>.99
Nasopharyngitis	1	0.4	1	1	0.4	1	>.99
Viral infection	2	0.8	2	0	0.0	0	0.248
Infectious mononucleosis	1	0.4	1	0	0.0	0	0.499
Otitis media	1	0.4	1	0	0.0	0	0.499
Pneumonia primary atypical	0	0.0	0	1	0.4	1	>.99
Respiratory tract infection	0	0.0	0	1	0.4	1	>.99
Staphylococcal bacteraemia	1	0.4	1	0	0.0	0	0.499
Injury, poisoning and procedural complications	3	1.2	3	1	0.4	1	0.372
Head injury	2	0.8	2	0	0.0	0	0.248
Limb traumatic amputation	0	0.0	0	1	0.4	1	>.99
Thermal burn	1	0.4	1	0	0.0	0	0.499
Investigations	0	0.0	0	1	0.4	2	>.99
Ultrasound kidney abnormal	0	0.0	0	1	0.4	2	>.99
Metabolism and nutrition disorders	1	0.4	1	0	0.0	0	0.499
Dehydration	1	0.4	1	0	0.0	0	0.499
Nervous system disorders	1	0.4	3	0	0.0	0	0.499
Febrile convulsion	1	0.4	3	0	0.0	0	0.499
Psychiatric disorders	1	0.4	2	0	0.0	0	0.499
Breath holding	1	0.4	2	0	0.0	0	0.499
Renal and urinary disorders	0	0.0	0	1	0.4	2	>.99
Hypercalciuria	0	0.0	0	1	0.4	1	>.99
Renal tubular disorder	0	0.0	0	1	0.4	1	>.99
Respiratory, thoracic and mediastinal disorders	0	0.0	0	1	0.4	1	>.99
Bronchospasm	0	0.0	0	1	0.4	1	>.99

Skin and subcutaneous tissue disorders	0	0.0	0	1	0.4	1	>.99
Urticaria	0	0.0	0	1	0.4	1	>.99

[a] Number of subjects reporting at least 1 event.
[b] Multiple events may be reported by 1 subject.
[c] Fisher exact test, 2-sided, used to calculate difference between vaccine groups in percentages of subjects reporting an event. p-values are not corrected for multiple comparisons.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body.pdf, page 78-80 (Table 10-9).

Table 94. Study 6096A1-009. Incidence of SAEs after the 4th dose by MedDRA system organ class and preferred term.

	Vaccine Group (as Administered)						
	13vPnC+P80 N=249			**13vPnC-P80 N=250**			
System Organ Class\ Preferred Term	**No. of Subjects[a]**	**%**	**No. of Events[b]**	**No. of Subjects[a]**	**%**	**No. of Events[b]**	**p-Value[c]**
Any event	3	1.3	3	2	0.8	2	0.683
Gastrointestinal disorders	1	0.4	1	1	0.4	1	>.99
Diarrhoea	1	0.4	1	0	0.0	0	0.495
Gastritis	0	0.0	0	1	0.4	1	>.99
General disorders and administration site conditions	1	0.4	1	0	0.0	0	0.495
Fibrosis	1	0.4	1	0	0.0	0	0.495
Infections and infestations	1	0.4	1	1	0.4	1	>.99
Bronchitis	0	0.0	0	1	0.4	1	>.99
Laryngitis	1	0.4	1	0	0.0	0	0.495

[a] Number of subjects reporting at least 1 event.
[b] Multiple events may be reported by 1 subject.
[c] Fisher exact test, 2-sided, used to calculate difference between vaccine groups in the % of subjects reporting an event. p-values are not corrected for multiple comparisons.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body.pdf, page 81 (Table 10-10).

Table 95. Study 6096A1-009. Incidence of SAEs collected at the 6-month follow-up by MedDRA system organ class and preferred term.

	Vaccine Group (as Administered)						
	13vPnC+P80 N=249			13vPnC-P80 N=250			
System Organ Class\ Preferred Term	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	p-Value[c]
Any event	13	5.2	18	14	5.6	17	>.99
Blood and lymphatic system disorders	1	0.4	1	0	0.0	0	0.499
Anaemia	1	0.4	1	0	0.0	0	0.499
Gastrointestinal disorders	3	1.2	3	4	1.6	4	>.99
Diarrhoea	3	1.2	3	4	1.6	4	>.99
Infections and infestations	8	3.2	11	7	2.8	8	0.800
Pneumonia	3	1.2	3	3	1.2	3	>.99
Bronchitis	1	0.4	1	2	0.8	2	>.99
Laryngitis	3	1.2	3	0	0.0	0	0.123
Pharyngitis	2	0.8	2	0	0.0	0	0.248
Bronchopneumonia	1	0.4	1	0	0.0	0	0.499
Gastroenteritis	0	0.0	0	1	0.4	1	>.99
Gastroenteritis rotavirus	0	0.0	0	1	0.4	1	>.99
Sepsis	1	0.4	1	0	0.0	0	0.499
Urinary tract infection	0	0.0	0	1	0.4	1	>.99
Injury, poisoning and procedural complications	2	0.8	2	0	0.0	0	0.248
Head injury	1	0.4	1	0	0.0	0	0.499
Radius fracture	1	0.4	1	0	0.0	0	0.499
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.4	1	0	0.0	0	0.499
Renal neoplasm	1	0.4	1	0	0.0	0	0.499
Nervous system disorders	0	0.0	0	2	0.8	2	0.499
Balance disorder	0	0.0	0	1	0.4	1	>.99
Hydrocephalus	0	0.0	0	1	0.4	1	>.99
Renal and urinary disorders	0	0.0	0	1	0.4	3	>.99
Calculus urinary	0	0.0	0	1	0.4	1	>.99
Renal tubular disorder	0	0.0	0	1	0.4	2	>.99

[a] Number of subjects reporting at least 1 event.
[b] Multiple events may be reported by 1 subject.
[c] Fisher exact test, 2-sided, used to calculate difference between vaccine groups in the % of subjects reporting an event. p-values are not corrected for multiple comparisons.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body.pdf, page 82 (Table 10-11).

Table 96. Study 6096A1-009. 13vPnC+P80 Subjects Who Experienced SAEs Within 30 Days After Any of Doses 1-3

Site-Subject Number	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Action	Outcome
005-000409	3	Bronchitis	3	13	H, C	Resolved
	3	Pneumonia	3	13	H, C	Resolved
005-000422	2	Gastroenteritis	12	5	H, C	Resolved
005-000432	3	Gastroenteritis	31	4	H, C	Resolved
	3	Pneumonia	26	11	H, C	Resolved
007-000606	1	Hypersensitivity	24	2	H, C	Resolved
007-000621	1	Respiratory tract infection	30	6	H, C	Resolved
007-000632	3	Pneumonia	15	19	H, C	Resolved
009 000802	3	Diarrhoea	32	16	H, C	Resolved
009-000813	2	Bronchitis	35	11	H, C	Resolved
	2	Pneumonia	35	11	H, C	Resolved
010 000931	3	Pneumonia aspiration	25	26	H, C, U	Resolved
012 001102	2	Pneumonia	17	13	H, C	Resolved
012-001106	2	Diarrhoea	35	6	H, C	Resolved
	2	Bronchitis	35	6	H, C	Resolved
	2	Laryngitis	30	3	H, C	Resolved
013 001215	1	Gastrooesophageal reflux disease	32	21	H, C, W	Resolved
	1	Pneumonia	32	21	H, C, W	Resolved
013-001231	1	Urticaria	15	6	H, C	Resolved
111-001307	2	Pneumonia	12	14	H, C	Resolved
111-001317	1	Bronchitis	11	24	H, C	Resolved
	1	Pneumonia	11	24	H, C	Resolved

Source: 125324/0.1,m5.3.5.1, CSR-74276-report body-infant.pdf, page 290 (Table 14.151).

Table 97. Study 6096A1-009. 13vPnC-P80 Subjects Who Experienced SAEs Within 30 Days After Any of Doses 1-3

Site-Subject Number	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Action[a]	Outcome
001 000011	1	Pneumonia aspiration	11	11 MILD	H	Resolved
003 000204	3	Urinary tract infection	6	21	H, C	Resolved
	3	Hydronephrosis	6	21	H, C	Resolved
004 000327	3	Diarrhoea	20	7	H, C	Resolved
005 000411	3	Bronchitis	8	9	H, C, U	Resolved
005-000415	3	Bronchitis	17	14	H, C, U	Resolved
005-000420	3	Bronchitis	2	6	H, C, W	Resolved
006 000507	1	Vomiting	20	1	H	Resolved
006-000529	3	Bronchopneumonia	6	11	H, C	Resolved
007 000612	3	Pneumonia	23	54	H, C	Resolved
007-000622	1	Respiratory tract infection	30	6	H, C	Resolved
007-000628	1	Anaemia	21	108	H, C, UT	Resolved
	1	Rhinitis	21	3	H, C	Resolved
	1	Sleep apnoea syndrome	21	1	H	Resolved
009 000804	1	Bronchitis	44	19	H, C	Resolved
	1	Pneumonia	44	19	H, C	Resolved
009-000835	1	Bronchitis	4	10	H, C	Resolved
	1	Bronchopneumonia	32	17	H, C	Resolved
010 000916	3	Bronchitis	26	11	C, UT, H	Resolved
	3	Bronchopneumonia	26	11	C, UT, H	Resolved
	3	Rhinitis	26	11	C, UT, H	Resolved
011-001014	2	Bronchitis	24	29	H, C	Resolved
011-001036	2	Meningitis meningococcal	8	37	H, C, D	Resolved
	2	Meningococcal sepsis	8	37	H, C, D	Resolved
	2	Hydrocephalus	62	10	H, C, D	Resolved
012-001114	3	Bronchitis	9	8	H	Resolved
	3	Gastroenteritis	13	4	H	Resolved
013-001204	2	Bronchitis	34	10	H, C	Resolved
014-001417	1	Diarrhoea	24	12	H, C	Resolved
111-001314	1	Pneumonia primary atypical	7	10	H, C	Resolved
111-001333	2	Pneumonia	9	18	H, C, ER	Resolved

[a] Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body-infant.pdf, page 291-292 (Table 14.152).

Table 98. Study 6096A1-009. 13vPnC+P80 Subjects Who Experienced SAEs > 30 days After Dose 3 and Before Dose 4

Site-Subject Number	Dose #	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Action	Outcome
002-000117	3	Diarrhoea	75	8	Severe	H, C	Resolved
	3	Pneumonia	70	20	Severe	H, C, UT	Resolved
004-000305	3	Pharyngitis	100	8	Moderate	H, C	Resolved
004-000317	3	Dyspepsia	146	5	Moderate	H	Resolved
004-000323	3	Diarrhoea	172	19	Moderate	H	Resolved
	3	Bronchitis	172	19	Moderate	H	Resolved
004-000324	3	Nasopharyngitis	35	9	Moderate	H	Resolved
004-000335	3	Bronchitis	101	9	Moderate	H	Resolved
005-000412	3	Head injury	135	4	Mild	H	Resolved
005-000435			60	1	Moderate	H	Resolved
	3	Breath holding	167	1	Moderate	H, W	Resolved
005-000437	3	Diarrhoea	36	9	Moderate	H, C	Resolved
	3	Pneumonia	33	12	Mild	H, C, U	Resolved
006-000512	3	Dehydration	207	2	Moderate	H, C	Resolved
007-000620	3	Pneumonia	127	11	Severe	H, C	Resolved
007-000635	3	Diarrhoea	201	10	Severe	H, C	Resolved
009-000802	3	Pneumonia	33	15	Moderate	H, C	Resolved
009-000831	3	Bronchitis	94	9	Moderate	H, C	Resolved
	3	Pneumonia	94	9	Moderate	H, C	Resolved
010-000901	3	Gastroenteritis	238	5	Moderate	H, C, UT	Resolved
010-000911	3	Thermal burn	239	3	Moderate	H, C	Resolved
010-000920	3	Gastroenteritis	214	8	Moderate	H, C, UT	Resolved
011-001012			213	3	Moderate	H, C	Resolved
	3	Pharyngitis	129	11	Moderate	H, C	Resolved
	3	Pneumonia	223	15	Moderate	H, C	Resolved
	3	Staphylococcal	129	1	Moderate	H, C	Resolved
	3	bacteraemia	213	1	Moderate	H, C	Resolved
	3	Febrile convulsion	223	1	Moderate	H, C	Resolved
011-001040		Bronchitis	275	10	Moderate	H	Resolved
		Gastroenteritis	275	10	Moderate	H	Resolved
		Otitis media	275	4	Moderate	H	Resolved
	3	Viral infection	270	8	Moderate	H	Resolved
012-001106		Bronchitis	206	8	Moderate	H, C	Resolved
	3	Laryngitis	206	8	Moderate	H, C	Resolved
012-001109	3	Head Injury	94	2	Mild	H	Resolved
012-001121	3	Gastroenteritis	224	6	Moderate	H, C	Resolved
013-001209	3	Urinary tract infection	53	4	Mild	H, C	Resolved
014-001416		Leukocytosis					
		Splenomegaly	247	C	Moderate	H, C, W	Persisted
		Hepatitis	247	131	Moderate	H, C	Resolved
		Alloimmunisation	247	22	Moderate	H, C	Resolved
		Infectious	247	22	Mild	H	Resolved
		mononucleosis	247	22	Moderate	H, C	Resolved
	3	Viral infection	247	22	Moderate	H, C	Resolved

Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body-infant.pdf, page 144-145 (Table 15.40).

Table 99. Study 6096A1-009. 13vPnC-P80 Subjects Who Experienced SAEs > 30 days After Dose 3 and Before Dose 4

Site-Subject Number	Dose #	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Action	Outcome
002-000116	3	Limb traumatic amputation	194	4	Moderate	H, C	Resolved
003-000210	3	Gastroenteritis	128	6	Moderate	H, C	Resolved
005-000411	3	Gastroenteritis	126	10	Moderate	H, C	Resolved
	3	Urinary tract infection	208	11	Moderate	H, C	Resolved
006-000518	3	Laryngitis	287	4	Moderate	H, C	Resolved
006-000525	3	Laryngitis	274	4	Mild	H, C	Resolved
007-000603	3	Pneumonia	80	18	Severe	H, C	Resolved
007-000608	3	Diarrhoea	229	3	Moderate	H, C	Resolved
008-000712	3	Bronchitis	92	9	Moderate	H, C	Resolved
	3	Gastroenteritis	92	9	Moderate	H, C	Resolved
	3	Bronchospasm	92	9	Moderate	H, C	Resolved
009-000826	3	Pneumonia primary atypical	121	13	Moderate	H, C	Resolved
010-000932	3	Nasopharyngitis	206	16	Moderate	H, C, UT	Resolved
	3	Urticaria	206	16	Moderate	H, C, UT	Resolved
011-001014	3	Inguinal hernia, obstructive	145	3	Moderate	H	Resolved
011-001035	3	Ultrasound kidney abnormal	204	3	Mild	H	Resolved
	3		255	2	Mild	H	Resolved
	3	Hypercalciuria	204	3	Mild	H	Resolved
	3	Renal tubular disorder	255	2	Mild	H	Resolved
012-001105	3	Diarrhoea	112	8	Mild	H, C	Resolved
	3	Urinary tract infection	110	10	Moderate	H, C	Resolved
013-001219	3	Pyrexia	92	3	Moderate	H, C	Resolved
	3	Pharyngitis	92	3	Moderate	H, C	Resolved
014-001430	3	Respiratory tract infection	111	8	Mild	H	Resolved
111-001340	3	Diarrhoea	243	18	Moderate	H, C, ER	Resolved

[a]Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body-infant.pdf, page 148 (Table 15.42).

Table 100. Study 6096A1-009. 13vPnC+P80 Subjects Who Experienced SAEs Within 30 Days After Dose 4

Site-Subject Number	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Action	Outcome
006-000516	4	Fibrosis	23	1	Moderate	H,	Resolved
009-000821	4	Diarrhoea	11	11	Moderate	H, C	Resolved
010-000933	4	Laryngitis	8	8	Moderate	H, C, U	Resolved

[a]Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR-74276-report body-infant.pdf, page 150 (Table 15.44).

Table 101. Study 6096A1-009. 13vPnC-P80 Subjects Who Experienced SAEs Within 30 Days After Dose 4

Site-Subject Number	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Action	Outcome
004-000309	4	Gastritis	21	3	Moderate	H	Resolved
011-001044	4	Bronchitis	14	14	Moderate	H, C	Resolved

[a]Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR74276-report body-infant.pdf, page 152 (Table 15.46).

Table 102. Study 6096A1-009. 13vPnC+P80 Subjects Who Experienced SAEs During the 6-Month Follow-Up

Site-Subject Number	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Action	Outcome
004-000305	4	Pneumonia	111	10	Moderate	H, C	Resolved
004-000316	4	Diarrhoea	112	7	Moderate	H, C, ER	Resolved
004-000317	4	Diarrhoea	158	10	Moderate	H, C	Resolved
006-000508	4	Bronchopneumonia	176	7	Moderate	H, C	Resolved
006-000517	4	Renal neoplasm	212	C	Severe	H, C	Persisted
006-000519	4	Laryngitis	54	4	Moderate	H, C	Resolved
006-000522	4	Head injury	163	4	Mild	H	Resolved
007-000616	4	Laryngitis	38	5	Severe	H, C	Resolved
010-000933	4	Laryngitis	133	7	Moderate	H, C, UT	Resolved
	4	Pharyngitis	133	7	Moderate	H, C, UT	Resolved
011-001033	4	Bronchitis	85	25	Moderate	H, C	Resolved
	4	Pneumonia	85	25	Moderate	H, C	Resolved
014-001402	4	Radius fracture	231	C	Moderate	H	Persisted
111-001308	4	Pneumonia	100	11	Severe	H, C, ER	Resolved
111-001330	4	Anaemia	151	40	Mild	H, C	Resolved
	4	Diarrhoea	151	16	Moderate	H, C	Resolved
	4	Pharyngitis	151	16	Moderate	H, C	Resolved
	4	Sepsis	151	16	Severe	H, C	Resolved

[a]Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR74276-report body-infant.pdf, page 154 (Table 15.48).

Table 103. Study 6096A1-009. 13vPnC-P80 Subjects Who Experienced SAEs During the 6-Month Follow-Up

Site-Subject Number	Dose #	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Action	Outcome
002-000106	4	Pneumonia	107	6	Moderate	H, C	Resolved
002-000116	4	Diarrhoea	88	4	Moderate	H, C	Resolved
003-000207	4	Pneumonia	64	9	Moderate	H, C	Resolved
004-000340	4	Bronchitis	60	10	Moderate	H	Resolved
005-000411	4	Urinary tract infection	39	6	Moderate	H, C	Resolved
007-000628	4	Diarrhoea	74	3	Severe	H, C	Resolved
007-000629	4	Balance disorder	43	5	Mild	H	Resolved
010-000936	4	Gastroenteritis	107	6	Moderate	H, C, UT	Resolved
011-001035	4	Calculus urinary	71	2	Mild	H	Resolved
	4	Renal tubular disorder	71	2	Mild	H	Resolved
	4		152	3	Mild	H	Resolved
011-001036	2	Hydrocephalus	62	10	Severe	H, C, W, D	Resolved
012-001103	4	Pneumonia	128	7	Moderate	H, C	Resolved
012-001108	4	Bronchitis	128	11	Moderate	H	Resolved
	4	Gastroenteritis rotavirus	128	11	Moderate	H	Resolved
014-001418	4	Diarrhoea	223	6	Severe	H	Resolved
014-001429	4	Diarrhoea	149	6	Severe	H	Resolved

[a]Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR74276-report body-infant.pdf, page 156 (Table 15.50).

8.1.4.4.6 Safety-Related Discontinuations

Four subjects were withdrawn during the infant series because of AEs. In addition, one subject (009-007-000612) in the 13vPnc-P80 group was withdrawn because the subject no longer met the study eligibility criteria; this subject required prolonged systemic steroid therapy for treatment of bilateral pneumonia with bronchospasm which required hospitalization.

Table 104. Study 6096A1-009. Subjects Withdrawn or With Permanent Test Article Discontinuation Because of an Adverse Event

Subject number	Vaccine Group	Preferred Term	Dose #	Time to Onset (days)	Duration (days)	Severity[a]	Action[b]	Outcome	SAE
During infant series									
013-001215	13vPnC+P80	Gastroesophageal reflux disease Pneumonia	1 1	32 32	21 21	Moderate Moderate	H, C, W H, C, W	Resolved Resolved	Yes Yes
005-000420	13vPnC-P80	Bronchitis (treatment-related AE)	3	2	6	Moderate	H, C, W	Resolved	Yes
007-000625	13vPnC-P80	Hypertonia	2	1	202	Moderate	UT, D	Resolved	No
011-001036	13vPnC-P80	Meningococcal meningitis Meningococcal sepsis Hydrocephalus	2 2 2	8 8 8	37 37 10	Severe Severe Severe	H, C, D H, C, D H, C, D	Resolved Resolved Resolved	Yes Yes Yes
Post-dose 3 visit and before dose 4									
005-000435	13vPnC+P80	Breath holding	3	167	1	Moderate	H, W	Resolved	Yes
014-001416	13vPnC+P80	Leukocytosis	3	247	C	Moderate	H, C, W	Persisted	Yes
6-Month Follow-Up									
011-001036	13vPnC-P80	Hydrocephalus	2	62	10	Severe	H, C, W, D	Resolved	Yes

[a] Severity abbreviations: Mod: moderate, Sev: severe.
[b] Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR71892-report body-infant.pdf, pages 308-310 (Tables 15.154 – 15.156); CSR74276-report-body.pdf, pages 158 and 162-167 (Tables 15.52 and 15.53)

8.1.4.4.7 Clinical Case Narratives

Clinical case narratives are provided for subjects who had SAEs that were determined by the study investigator to possibly be related to the study vaccine or AEs resulting in withdrawal from the study.

Subject 009-013-001215: Gastroesophageal reflux disease and pneumonia

A 3 month old girl, 1 month after 13vPnC+P80 dose 2, was diagnosed with bronchitis which progressed to pneumonia and required hospitalization. The subject was also diagnosed with gastroesophageal reflux disease. The subject was treated with antibiotics for approximately 10 days, but experienced worsening of symptoms prior to discharge. The subject completed another 10 day course of antibiotics and was then discharged home. The subject was withdrawn due to the prolonged episode of respiratory illness and parental concern.

Subject 009-005-000420: 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 temporal association between the event and vaccine administration.

Subject 009-007-000625: Hypertonia
A 3 month old girl, on the day of 13vPnC-P80 dose 2 (prior to vaccination), was found to have moderate hypertonia. A review of the medical history revealed a maternal history of arterial hypertension diagnosed in the antenatal period (treated with methyldopa) and diabetes diagnosed at 20 weeks gestation. The disorder was considered related to intrauterine hypoaemic brain injury. The mother was electively hospitalized at 38 weeks gestation. Delivery was by Caesarean section due to fetal distress. The infant was born in good condition with an Apgar score of 9/10. A cranial ultrasound performed after study dose 2 showed evidence of intrauterine fetal anoxia. The subject was noted to have persistent moderate hypertonia at 7 months of age. The infant was withdrawn because of clinical features consistent with a chronic neurological disorder.

Subject 009-011-001036: 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. The subject responded to antibiotic and vasopressor treatment. Cranial ultrasonography revealed slight symmetrical enlargement of the ventricles with hyper-echogenic fluid and thickened ventricular ependyma. The subject was started on sodium valproate on the advice of the neurologist. The subject had occasional spasms, mainly of the lower limbs; quadriparetic spasticity, predominantly of the lower limbs and right side of the body; features of left facial nerve palsy; and poor auditory and visual responses. Repeat cranial ultrasonography revealed enlargement of the subdural spaces with increased fluid echogenicity, suggestive of a subdural effusion (possibly subdural empyema). A subdural tap was performed via the fontanelle on day 36, and fluid obtained that was negative on culture. Computerized tomography (CT) of the head revealed generalized cortical/subcortical atrophy. The subject was discharged home on day 43, and re-admitted on day 61 due to increased intracranial pressure. 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.

Subject 009-005-000435: Breath holding
At 6-months of age, a male infant who was enrolled with a past history of hyperbilirubinemia, nasopharyngitis, and pneumonia, developed breath-holding spells 60 days after the third dose of 13vPnC+P80 and Pentaxim; he was hospitalized the same day. Physical exam and neurological evaluation were noted to be normal. A cranial ultrasound was notable for small dilation of the subarachnoid space and an EEG was unremarkable. The infant's condition improved and he was discharged on hospital day 8 with advice for a neurology workup after 3 months. Other reported AEs included bronchitis starting on day 8 after study dose 3 and resolving after 13 days. Approximately 5.5 months after the 3rd study vaccination, the infant developed and was hospitalized for a second bout of breath-holding spells. The infant's physical exam and blood tests were noted to be normal. An EEG revealed focal spikes in the temporal and parietal region. The infant was discharged on hospital day 4 and referred for a neurology workup. The infant was withdrawn from the study 4.5 months after the second bout of breath-holding spells.

Subject 009-014-001416: Leukocytosis
A 1 year old boy, 247 days after the 3rd dose of 13vPnC+P80, Pentaxim, and Engerix B, was hospitalized due to a 7-day history of pyrexia (40^{o}C) and papular rash of the face. Blood investigations revealed an elevated WBC count and elevated aspartate aminotransferase and alanine transferase levels. The subject was diagnosed with viral infection, hepatitis, mononucleosis, alloimmunization, leukocytosis,and splenomegaly. He was treated with cefuroxime sodium, amikacin, sulfate, allopurinol as hyperuricemia prophylaxis,and intravenousfluids for dehydration. The subject was discharged approximately after 3 weeks after the events of hepatitis, mononucleosis, alloimmunization, and viral infection resolved. Splenomegaly resolved approximately one year after the third study dose was administered. The

subject was withdrawn due to the adverse event of leukocytosis at about this time. This subject also experienced bronchitis approximately two weeks after the second study vaccinations.

Subject 009-007-000612: Pneumonia
A 4-month old girl with a history of congenital laryngeal stridor, 2 months after 13vPnC-P80 dose 3, was hospitalized with a diagnosis of bilateral pneumonia with wheezing. The subject was started on broad-spectrum antibiotics, bronchodilators, and 2 weeks of intravenous dexamentasone. A culture of the subject's respiratory secretions grew *Klebsiella pneumoniae*. The subject was withdrawn at the because of the prolonged course of systemic steroids exclusion criterion. At 7.5 months of age, the subject was seen in the clinic and was noted to have ongoing respiratory symptoms.

8.1.4.5 Summary and Conclusions
The safety and immunogenicity of 13vPnC with (+) or without (-) P80 was assessed in this study. A total of 500 Polish infants (n=250 per vaccine formulation) were vaccinated at 2, 3, 4 and 12 months of age. Study 009 is relevant to U.S. licensure of Prevnar 13 because it evaluated the safety and immunogenicity of Prevnar 13 with and without the addition of polysorbate 80 to the final formulation. The clinical data from this study, in conjunction with P80 manufacturing process improvements, supported the applicant's selected 13vPnC+P80 formulation. Clinical data from studies -3005 and -3000 were used to support manufacturing and formulation bridging of 13vPnC final production scale and formulation. Post-dose 3 IgG antibody responses were the primary outcome measures. OPA responses were evaluated in a subset of study -3000 participants.

Except for injection site tenderness post-dose 3, local reactions following +P80 vaccination occurred less often than after –P80 vaccination. Irritability, the most frequent systemic reaction, was reported by 44.4%-50.5% of +P80 participants and 48.0%-56.1% of –P80 participants. Treatment use of acetaminophen/ibuprofen was highest after dose 4 (21.5%) in the +P80 group, and highest after dose 1 (18.2%) in the –P80 group. The incidence of severe tenderness (interfering with limb movement) in each study group coincided with treatment use. In both groups, moderate fever (>39.0C - 40.0C) was most frequent after dose 4 (+P80, 2.5%; -P80, 1.8%). No participant reported a temperature > 40.0C.

Immunogenicity analyses were based on the evaluable infant immunogenicity population for the third 13vPnC dose. Except for two serotypes, 13vPnC+80 was comparable to 13vPnC-P80. For serotypes, 6B (LL 95%CI -14.2), and 23F (LL95%CI -12.1), the lower limit of the 95% confidence interval for the difference in seroresponse rate $\geq$ 0.35ug/mL exceeded the ≤ -10% non-inferiority (NI) criteria by a small margin. Of note, the 6B seroresponse rate observed for both study groups (13vPnC + P80, 60.9%; 13vPnC - P80, 66.4%) was lower than the expected 88% rate achieved for PCV7. The significance of these findings for serotypes 6B and 23F on the use of Prevnar 13 without P80 on a 2, 4, 6, 12-15 month schedule in U.S. study 004 are unclear. All serotypes met the lower 95% confidence limit of ≤ 0.5 NI criteria for the GMC ratio post-doses 3 and 4, both secondary study endpoints.

9.0 Catch-Up Studies

9.1 Clinical Study Protocol # 6096A1-3002

Clinical trials.gov registry identifier: NCT00452452

CSR #71057

Protocol Title: A Phase 3, Open-Label, Multicenter Trial in Poland Evaluating the Safety, Tolerability, and Immunogenicity of a 13vPnC Vaccine in Healthy Older Infants and Children Who Are Naive to Previous Vaccination With Pneumococcal Conjugate (PnC) Vaccine.

9.1.1 Objective/Rationale

This study evaluates the safety and immunogenicity of three 13vPnC catch-up vaccination schedules when administered to older infants and children naïve to previous vaccination with Prevnar.

The 3 schedules schedules evaluated are currently recommended for Prevnar. Effectiveness of these PCV7 catch-up schedules was estimated to be 93% to 98% in infants and young children who started their PCV7 series late in their first year or after their first birthday.[26] Unpublished data from PCV7 catch up studies showed on average, 18.7% to 23.8% of children < 2 years of age had prevaccination antibody concentrations exceeding 0.35µg/mL for the 7 serotypes combined. In children 2-5 years of age, 34.5% to 51.4% had average prevaccination antibody concentrations exceeding this endpoint. Therefore, pre- and post-vaccination blood samples were collected for the 24 month to 5 year age group (group 3).

In Poland, 2000-2001 nasopharyngeal carriage data in children 6 months to 5 years of age showed that Prevnar covered ~ 80% of pneumococcal isolates. Thirty-six percent of these isolates were nonsusceptible to penicillin, and 11.8% were fully penicillin resistant and expressed multiresistant phenotypes. Data from 1993-1994 showed that all pneumococcal isolates from children in Poland were fully susceptible to penicillin.

9.1.1.1 Primary objective

To assess the pneumococcal immune response induced by 3 catch-up 13vPnC vaccination schedules, when measured 1 month after the last scheduled dose of 13vPnC. The 3 schedules are as follows:

- Group I: infants enrolled at 7 to < 12 months of age and given 3 doses of 13vPnC;
- Group II: children enrolled at 12 to < 24 months of age and given 2 doses of 13vPnC; and
- Group III: children enrolled at 24 to < 72 months of age and given 1 dose of 13vPnC.

9.1.1.2 Safety objective

To evaluate the acceptability of the safety profile of 13vPnC vaccine as measured by incidence rates of local reactions, systemic events, and adverse events (AEs).

9.1.2 Design Overview

This is an open-label, non-randomized, non-controlled, multicenter trial evaluating the immune response in older infants and children after completion of the following 3 catch-up vaccination schedules:

- doses of 13vPnC administered 1 month (28-42 days) apart with a booster dose at 12-16 months of age (at least 2 months after 2nd dose) administered to children enrolled at 7 to < 12 months of age.
- doses of 13vPnC administered at least 2 months (56-70 days) apart administered to children enrolled at 12 to < 24 months of age.
- 1 dose of 13vPnC administered to children enrolled at 24 months to 5 years (<72 months) of age.

9.1.3 Protocol

9.1.3.1 Population

9.1.3.1.1 Study Period
The study period was July 12, 2007 through March 31, 2008.

9.1.3.1.2 Study sites and recruitment
Study 6096A1-3002 was conducted at 9 sites in Poland.

9.1.3.1.3 Inclusion Criteria
1. Healthy children aged 7 to < 72 months of age at time of enrollment
2. Available for entire study period
3. Parent(s) / legal guardian(s) reachable by phone and able to complete all relevant study procedures

9.1.3.1.4 Exclusion Criteria
1. Previous vaccination with licensed or investigational pneumococcal vaccine
2. Previous anaphylactic reaction to any vaccine or vaccine-related component
3. Contraindication to vaccination with pneumococcal vaccines
4. Bleeding diathesis or condition associated with prolonged bleeding time contraindicating IM injection
5. Known or suspected immune deficiency or suppression
6. History of culture-proven IPD
7. Major known congenital malformation or serious chronic disorder
8. Significant disorders (neurological, seizure, stable or evolving)
9. Receipt of blood products or gamma-globulin (including monoclonal antibodies) in the last 3 months. Topical and inhaled corticosteroids were permitted.
10. Participation in another investigational or interventional trial (purely observational studies acceptable).
11. Child is direct first or second-generation descendent of study site personnel.

9.1.3.2 Concomitant medications
The study permitted antipyretic medications to treat or prevent vaccine-related symptoms. The study did not collect data on use of concomitant medications other than antipyretic medications.

9.1.3.3. Vaccine administration
Children received the following study vaccine as per protocol. The study did not permit concurrent administration of licensed or other investigational vaccines with the test article.

13vPnC: Each 0.5ml dose contains 2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4ug saccharide for 6B individually conjugated to CRM_{197}. The total concentration of CRM_{197} is 29ug. The final formulation contains 5mM succinate buffer and 0.125 mg elemental aluminum as AlPO4. The vaccine is formulated as a liquid, appears as a homogeneous, white suspension after shaking, and is supplied in single-dose syringes. Route: intramuscular, anterolateral left thigh or left deltoid according to local practice. Lot number: 7-5093-006A.

9.1.3.4 Endpoints

9.1.3.4.1 Primary Immunogenicity Endpoint
Proportion of subjects achieving a serotype-specific IgG antibody concentration ≥ 0.35µg/mL (with corresponding 2-sided 95% CI), measured 1 month after the last scheduled 13vPnC dose.

Clinical Reviewer Note: Functional OPA antibody levels were not evaluated in study 3002, therefore OPA data are not available to assess the catch-up schedules.

9.1.3.4.2 Primary Safety Endpoints

Proportion of subjects reporting unsolicited AEs, solicited local reactions, or solicited systemic events, including fever (temp ≥ 38.0°C) and the use of antipyretic medications to treat and to prevent symptoms. Solicited AEs were prospectively collected for 4 days after each vaccination.

9.1.3.5 Surveillance

9.1.3.5.1 Immunogenicity Monitoring

Blood samples (5mL) were collected 1 month (28-42 days) after the last scheduled 13vPnC dose in groups 1 and 2. In group 3, a 5mL blood sample was collected prior to and 1 month (28-42 days) after 13vPnC vaccination. Serotype specific IgG concentrations to the 13 serotypes in the 13vPnC vaccine were determined for each blood sample. GMCs were calculated with corresponding 2-sided 95% CIs by age group for each serotype. Pneumococcal IgG ELISA assays were performed by Early Phase Programs-Clinical Testing Assay Development (EPP-CTAD) Wyeth, Pearl River.

9.1.3.5.2 Safety Surveillance Monitoring

- Immediate acute reactions were assessed for 30 minutes after each vaccination.
- Solicited AEs prospectively collected by electronic diary for 4 days after vaccination. End dates captured for reactions persisting beyond day 4.
  - Local reactions: erythema, induration, and tenderness at the injection site were monitored daily for 4 days after each vaccination. Erythema and swelling diameters were measured in caliper units from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number.
  - Erythema and induration grading scale: Mild: 0.5 ≤ x ≤ 2.0 cm; moderate, 2.5 ≤ x ≤ 7.0 cm; and severe, >7.0 cm.
  - Systemic events: decreased appetite, irritability, increased sleep, and decreased sleep were monitored for 4 days after each vaccination.
  - Temperature grading scale: absent: < 38.0°C; mild: ≥ 38.0 to ≤ 39.0°C; moderate: > 39.0 to ≤ 40.0°C; severe: > 40.0°C.
- Serious adverse events (SAEs) recorded from signing of the informed consent form (ICF) to the last study visit (28-42 days after last dose)
- Unsolicited AEs were recorded as follows:
  - Group I: from signing of the ICF to one month post-dose 2 and from the dose 3 visit until the last study visit (post-dose 3 visit). New chronic medical conditions diagnosed since the last study visit were also recorded at the dose 3 visit.
  - Group II: from signing of the ICF to the last study visit (the post-dose 2 study visit).
  - Group III: from signing of the ICF until the last study visit (the post-dose 1 study visit).

9.1.3.6 Statistical considerations

9.1.3.6.1 Sample Size

Sample size estimation for group 1 in study 6096A1-3002 was based on the proportion of responders in the PCV7 group in Wyeth study D118-16. Sample size estimations for groups 2 and 3 were based on the proportion of responders in the PCV7 group in Wyeth study D118-P18. Assuming a drop out rate of 10%, the study aimed to enroll 90, 112, and 152 subjects into Groups 1, 2, and 3 respectively; this would ensure 80, 100, and 144 evaluable subjects in Groups 1, 2, and 3 respectively. With these selected sample sizes, the study would be able to estimate the proportion of responders with a maximum margin of error of 4.8%, 4.3%, and 5% for groups 1, 2, and 3 respectively.

9.1.3.6.2 Study Cohorts Analyzed

For the immunogenicity analyses, 2 analysis populations were defined. The all-available immunogenicity population will include all subjects with at least 1 valid and determinate assay result. The evaluable immunogenicity population is the primary analysis population and includes subjects who:

- Were eligible for the study
- Were 7 to < 12 months of age (inclusive) on the 1st day of vaccination if enrolled in group 1.
- Were 12 to < 24 months of age (inclusive) on the 1st day of vaccination if enrolled in group 2.
- Were 24 to < 72 months of age (inclusive) on the day of vaccination if enrolled into group 3.
- Received all required study vaccinations
- Had at least 1 valid and determinate post-dose 3 assay result contributing to planned analysis.
- Had a post-vaccination blood draw within the required time frame (27 to 56 days after the last vaccination in all groups). Group 3 subjects were also required to have a blood draw before vaccination at 24 to < 72 months of age.
- Received no prohibited vaccines.
- Had no other major protocol violations as determined by the global clinical program leader or global medical monitor.

The safety population included all participants who received at least 1 dose of the study vaccine. The study also included separate safety populations for groups 1, 2, and 3. Subjects with no safety data for a particular vaccination were excluded from that analysis.

9.1.3.7 Changes in Study Protocol (Protocol Amendments) and in Planned Analyses

There were no major changes to the protocol.

9.1.4 Results

9.1.4.1 Populations Enrolled/Analyzed

Nine study centers enrolled a total of 355 subjects: 90 subjects in group 1, 112 subjects in group 2, and 153 subjects in group 3. The all available immunogenicity population consisted of 351 subjects; the evaluable immunogenicity population consisted of 346 subjects; and the safety population consisted of 354 subjects.

9.1.4.1.1 Subject Disposition and Follow-up

Table 105: Study 6096A1-3002 Summary of Subject Disposition

	Group 1 7 to < 12 months	Group 2 12 to < 24 months	Group 3 24 to < 72 months	Total
Number of subjects enrolled	90	112	153	355
Number of subjects vaccinated				
Dose 1	90	112	152[a]	354
Dose 2	90	112	N/A	202
Dose 3	89	N/A	N/A	89
Completed study vaccination(s)	88	112	152	352
Number of subjects withdrawn	2	0	1	3
Reasons for withdrawal:				
Protocol violation	0	0	1	1
Parent / legal guardian request	1	0	0	1
Lost to follow-up	1	0	0	1
All-available immunogenicity population	88	111	152	351
Subjects excluded from all-available immunogenicity population because of no postvaccination assay result	2	1	1	4
Evaluable immunogenicity population	84	110	152	346
Subjects excluded from evaluable immunogenicity population				
Not in all-available immunogenicity population	2	1	1	4
Age < 7 months, < 12 months, or < 24 months on day of first dose (according to age group)	4	0	0	4
Blood draw > 56 days after last scheduled vaccination	0	1	0	1

[a] Subject 3002-009-000831 in group 3 was discovered to be ineligible after enrollment but before vaccination due to a history of pneumococcal infection.
Source: 125324/0.2, m5.3.5.2, CSR71057-report body.pdf, pages 33 and 45 (Table 8-1 and 9-1)

Protocol violations that did not result in exclusion from the evaluable immunogenicity population included the following: 11 subjects who received dose 2 outside the specified time windows (one group 1 subject received dose 2 between 42 to 56 after dose 1, and 10 group 2 subjects 2 received dose 2 > 70 days after dose 1), 4 group 1 subjects who received dose 3 at visit 3[3] instead of visit 4, and 2 group 1 subjects who received product with another package number at dose 3.

[3] Group 1 participants were to receive their 2nd dose of 13vPnC at visit 2 and their 3rd dose of 13vPnC at visit 4. Visit 3 (the post-dose 2 visit) was to occur 28 to 42 days after visit 2. Visit 4 was to occur at least 28 days after visit 3 and at 12 to 16 months of age. Therefore, children who received dose 3 at visit 4 would have received dose 3 less than 2 months after dose 2 and possibly at < 12 months of age. This could result in what should be considered a major violation because this departs from the schedule that was to be assessed according to the study objectives.

9.1.4.1.2 Subject Demographics

Evaluable immunogenicity population demographics
Prior to the first vaccination, 86.2% of subjects had normal physical exams.

Table 106: Demographic characteristics of the evaluable immunogenicity population (as enrolled)

	Group 1 7 to < 12 months N=84 n (%)	Group 2 12 to < 24 months N=110 n (%)	Group 3 24 to < 72 months N=152 n (%)	Total N=346 n (%)
Gender				
Male	40 (47.6)	52 (47.3%)	79 (52.0%)	171 (49.4%)
Female	44 (52.4%)	58 (52.7%)	73 (48.0%)	175 (50.6%)
Race				
Caucasian	84 (100%)	110 (100%)	152 (100%)	346 (100%)
Ethnicity				
Non-Hispanic and Non-Latino	84 (100%)	110 (100%)	152 (100%)	346 (100%)
Age at dose 1 (months)				
Mean (SD)	8.8 (± 1.5)	17.6 (± 3.5)	42.1 (± 13.1)	-
Age at dose 2 (months)				
Mean (SD)	9.8 (±1.5)	19.6 (± 3.5)	N/A	-
Age at dose 3 (months)				
Mean (SD)	12.8 (± 1.1)	N/A	N/A	-
Weight at enrollment (kg)				
Mean (SD)	9.0 (± 1.3)	11.4 (± 1.7)	16.7 (± 3.8)	-

Source: 125324/0.2,m5.3.5.2, CSR71057-report body.pdf, page 43.

9.1.4.2 Immunogenicity Endpoints/Outcomes

Response rates were similar among the 3 groups, except for a lower response rate for serotype 14 in group 3.

Table 107. Study 6096A1-3002. Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After Vaccination (Evaluable Infant Immunogenicity Population)

	13vPnC Group As Enrolled											
	13vPnC Group 1 7 to < 12 months enrolled Post-dose 3				13vPnC Group 2 12 to < 24 months enrolled Post-dose 2				13vPnC Group 3 24 to < 72 months enrolled Post-dose 1			
Serotype	N[a]	n[b]	%	95% CI[b]	N[a]	n[b]	%	95% CI[b]	N[a]	n[b]	%	95% CI[b]
PCV7												
4	84	84	100.0	(95.7, 100.0)	110	110	100.0	(96.7, 100.0)	151	150	99.3	(96.4, 100.0)
6B	83	82	98.8	(93.5, 100.0)	110	110	100.0	(96.7, 100.0)	150	149	99.3	(96.3, 100.0)
9V	83	82	98.8	(93.5, 100.0)	104	103	99.0	(94.8, 100.0)	148	146	98.6	(95.2, 99.8)
14	84	84	100.0	(95.7, 100.0)	108	108	100.0	(96.6, 100.0)	135	119	88.1	(81.5, 93.1)
18C	83	83	100.0	(95.7, 100.0)	109	109	100.0	(96.7, 100.0)	151	149	98.7	(95.3, 99.8)
19F	84	82	97.6	(91.7, 99.7)	110	110	100.0	(96.7, 100.0)	147	144	98.0	(94.2, 99.6)
23F	84	83	98.8	(93.5, 100.0)	110	102	92.7	(86.2, 96.8)	151	141	93.4	(88.2, 96.8)
Additional												
1	83	83	100.0	(95.7, 100.0)	108	108	100.0	(96.6, 100.0)	149	144	96.6	(92.3, 98.9)
3	83	82	98.8	(93.5, 100.0)	108	108	100.0	(96.6, 100.0)	149	145	97.3	(93.3, 99.3)
5	84	82	97.6	(91.7, 99.7)	107	106	99.1	(94.9, 100.0)	152	150	98.7	(95.3, 99.8)
6A	84	84	100.0	(95.7, 100.0)	110	108	98.2	(93.6, 99.8)	150	150	100.0	(97.6, 100.0)
7F	84	84	100.0	(95.7, 100.0)	108	108	100.0	(96.6, 100.0)	142	141	99.3	(96.1, 100.0)
19A	84	84	100.0	(95.7, 100.0)	110	110	100.0	(96.7, 100.0)	150	150	100.0	(97.6, 100.0)

[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. Antibody concentrations were measured after vaccination 3 for group 1, after vaccination 2 for group 2, and after vaccination for group 3.
[c] Exact 2-sided confidence interval based upon the observed proportion of subjects.
Source: 125324/0.11,m5.3.5.2, CSR71057-report body.pdf, page 47 (Table 9-2).

With the exception of serotype 19A, group 3 achieved lower GMCs compared to groups 1 and 2. The GMC for serotype 14 was particularly low in group 3 compared to groups 1 and 2.

Table 108. Study 6096A1-3002. Pneumococcal IgG GMCs (µg/mL) After Vaccination (Evaluable Infant Immunogenicity Population)

	13vPnC Group As Enrolled								
	13vPnC Group 1 7 to < 12 months enrolled Post-dose 3			13vPnC Group 2 12 to < 24 months enrolled Post-dose 2			13vPnC Group 3 24 to < 72 months enrolled Post-dose 1		
Serotype	**N[a]**	**GMC[b]**	**(95% CI[c])**	**N[a]**	**GMC[b]**	**(95% CI[c])**	**N[a]**	**GMC[b]**	**(95% CI[c])**
PCV7									
4	84	3.63	(3.11, 4.23)	110	4.28	(3.78, 4.86)	151	3.37	(2.95, 3.85)
6B	83	4.77	(3.90, 5.84)	110	3.38	(2.81, 4.06)	150	3.41	(2.80, 4.16)
9V	83	2.56	(2.21, 2.96)	104	3.08	(2.69, 3.53)	148	2.67	(2.32, 3.07)
14	84	8.04	(6.95, 9.30)	108	6.45	(5.48, 7.59)	135	2.24	(1.71, 2.93)
18C	83	2.77	(2.39, 3.23)	109	3.71	(3.29, 4.19)	151	2.56	(2.17, 3.03)
19F	84	2.88	(2.35, 3.54)	110	3.07	(2.68, 3.51)	147	2.53	(2.14, 2.99)
23F	84	2.16	(1.82, 2.55)	110	1.98	(1.64, 2.39)	151	1.55	(1.31, 1.85)
Additional									
1	83	2.88	(2.44, 3.39)	108	2.74	(2.37, 3.16)	149	1.78	(1.52, 2.08)
3	83	1.94	(1.68, 2.24)	108	1.86	(1.60, 2.15)	149	1.42	(1.23, 1.64)
5	84	2.85	(2.34, 3.46)	107	2.16	(1.89, 2.47)	152	2.33	(2.05, 2.64)
6A	84	3.72	(3.12, 4.45)	110	2.62	(2.25, 3.06)	150	2.96	(2.52, 3.47)
7F	84	5.30	(4.54, 6.18)	108	5.99	(5.40, 6.65)	142	4.92	(4.26, 5.68)
19A	84	4.77	(4.28, 5.33)	110	4.94	(4.31, 5.65)	150	6.03	(5.22, 6.97)

[a] n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] GMCs were calculated using all subjects with available data for the specified blood draw. GMCs were measured after vaccination 3 for group 1, after vaccination 2 for group 2, and after vaccination for group 3.
[c] Confidence intervals (CIs) are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.11,m5.3.5.2, CSR71057-report body.pdf, page 48 (Table 9-3).

9.1.4.3 Safety Outcomes

9.1.4.3.1 Immediate Reactions

Although immediate reactions were collected and reported along with other unsolicited adverse events, these events could not be idenitifed from the data submitted to the BLA. The specific time-to-onset of symptoms was not recorded, therefore reactions that occurred within 30 minutes of vaccination could not be identified.

9.1.4.3.2 Solicited Local Reactions Reported Within 4 Days of Vaccination

The most common solicited local reaction in each group and after each dose was erythema. The incidence of erythema and induration peaked after the 1st dose in groups 1 and 2. Group 2 subjects experienced higher rates of erythema and induration compared to subjects in groups 1 and 3. Reports of tenderness were highest after the first dose in group 3 subjects. Overall, local reactions were most frequently reported on day 2.

Table 109. Study 6096A1-3002. Subjects with solicited local reactions by severity within 4 days after each vaccination.

	Safety Populations					
	Group 1 7 to < 12 months			Group 2 12 to < 24 months		Group 3 24 to < 72 months
Graded Local Reaction	Dose 1 N[a]=86 %	Dose 2 N[a]=86-87 %	Dose 3 N[a]=78-82 %	Dose 1 N[a]=108-110 %	Dose 2 N[a]=98-106 %	Dose 1 N[a]=147-149 %
Erythema						
Any	48.8	46.0	37.8	70.0	54.7	50.0
0.5 - 2.0 cm	41.9	40.2	31.3	55.5	44.7	37.4
2.5 - 7.0 cm	16.3	9.3	12.5	38.2	25.5	25.7
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0
Induration						
Any	36.0	32.2	25.0	44.5	41.0	36.9
0.5 - 2.0 cm	32.6	28.7	20.5	36.7	36.2	28.2
2.5 - 7.0 cm	11.6	14.0	11.3	24.8	12.1	20.3
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0
Tenderness						
Any	15.1	15.1	15.2	33.3	43.7	42.3
Interferes with limb movement	1.2	3.5	6.4	0.0	4.1	4.1

[a] = number of subjects reporting yes for at least 1 day or no for all days.
Source: 125324/0.2,m5.3.5.2, CSR-71057-report body.pdf, pages 53-55.(Tables 10-2 to 10-4).

The mean duration of local reactions ranged from 1.3 to 3.4 days across all groups and doses. Local reactions ranged from 1-9 days in duration among group 1 subjects, 1-14 days for group 2 subjects, and 1-9 days for group 3 subjects. The reactions with the longest duration occurred after the first dose in each study group.

9.1.4.3.3 Solicited Systemic Reactions Within 4 days of Vaccination

The most frequently reported systemic events were irritability in groups 1 and 2 and decreased appetite in group 3. The incidence of fever and irritability peaked after the 2nd dose in groups 1 and 2.

With the exception of 3 outliers, systemic events lasted between 1 and 9 days and averaged 1-5 days. Systemic reactions lasting > 10 days occurred in 2 subjects (one group 2 subject experienced decreased sleep for 23 days and irritability for 24 days after dose 2; a second group 1 subject experienced decreased sleep for 65 days after dose 1). The duration of the events occurring in three group 1 subjects after the 3rd dose was listed as unknown because the events were listed as ongoing at the final study visit.

Table 110. Percentage of subjects with solicited systemic adverse events within 4 days after each 13vPnC vaccination in Study 6096A1-3002.

	Safety Populations					
	Group 1 7 to < 12 months			Group 2 12 to < 24 months		Group 3 24 to < 72 months
Systemic Reaction	**Dose 1** N[a]=86-87 %	**Dose 2** N[a]=86-87 %	**Dose 3** N[a]=78-81 %	**Dose 1** N[a]=108 %	**Dose 2** N[a]=98-100 %	**Dose 1** N[a]=147-148 %
Fever[b]						
38.0°C ≤ x ≤ 39.0°C	3.4	8.1	5.1	3.7	5.1	0.7
39°C < x ≤ 40.0°C	1.2	2.3	1.3	0.9	0.0	0.7
> 40°C	0.0	0.0	0.0	0.0	0.0	0.0
Decreased appetite	19.5	17.2	17.5	22.2	25.5	16.3
Irritability	24.1	34.5	24.7	30.6	34.0	14.3
Increased sleep	9.2	9.3	2.6	13.0	10.1	11.6
Decreased sleep	24.1	18.4	15.0	19.4	20.4	6.8

[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: 125324/0.2,m5.3.5.2, CSR-71057-report body.pdf, pages 57-58.(Tables 10-5 to 10-7).

Table 111. Study 6096A1-3002, Subjects who received antipyretics within 4 days following any dose of 13vPnC vaccine to treat symptoms or to prevent symptoms.

	Use of Antipyretics to Treat Symptoms			Use of Antipyretics to Prevent Symptoms		
Dose number	**Group 1 n (%)**	**Group 2 n (%)**	**Group 3 n (%)**	**Group 1 n (%)**	**Group 2 n (%)**	**Group 3 n (%)**
1	N[b]=87 8 (9.2)	N=109 11 (10.1)	N=147 4 (2.7)	N=87 7 (8.0)	N=109 15 (13.8)	N=147 7 (4.8)
2	N=86 8 (9.3)	N=98 13 (13.3)	-	N=86 4 (4.7)	N=98 14 (14.3)	-
3	N=79 6 (7.6)	-	-	N=79 4 (5.1)	-	-

Source: 125324/0.2,m5.3.5.1, CSR-62926-report-body, pages 57-58 (Tables 10-5 to 10-7).

9.1.4.3.4 Unsolicited Adverse Events

Unsolicited adverse events were reported by 38/90 (42.2%) group 1 subjects after dose 1 and 2 combined and 28/89 (31.5%) group 1 subjects after dose 3. The most frequently reported adverse events in this group following dose 1 and 2 combined were pharyngitis (8.9%), diarrhea (6.7%), exanthema subitum (5.6%), rhinitis (5.6%), and nasopharyngitis (4.4%). After dose 2, the most frequently reported AEs were nasopharyngitis (7.9%), upper respiratory tract infection (6.7%), bronchitis (4.5%), pharyngitis (4.5%), respiratory tract infection (4.5%), and pyrexia (3.3%).

Among group 2 subjects, unsolicited AEs were reported by 62/112 (55.4%) for doses 1 and 2 combined. The most frequently reported AEs in this group following dose 1 and 2 combined were upper respiratory tract infection (14.3%), pharyngitis (12.5%), nasopharyngitis (10.7%), rhinitis (8.0%), bronchitis (8.0%), diarrhea (7.1%), gastroenteritis (3.6%), and laryngitis (3.6%).

Among group 3 subjects, unsolicited AEs were reported by 38/152 (25.0%) subjects after dose 1. The most frequently reported AEs in this group were pharyngitis (3.9%), nasopharyngitis (3.3%), upper respiratory tract infection (2.6%), and rhinitis (2.6%).

Selected unsolicited AEs occurring in 1-2% of subjects include the following:

- Group 1 doses 1 and 2: vomiting, (1.1%), bronchitis (2.2%), respiratory tract infection (2.2%), upper respiratory tract infection (2.2%), viral infection (2.2%), otitis media (1.1%), ear infection (1.1%), pneumonia (1.1%), febrile convulsion (1.1%), rash (1.1%), and gastroenteritis/gastrointestinal infection (2.2%).
- Group 1 dose 3: diarrhea (1.1%), pyrexia (1.1%), viral infection (2.2%), acute tonsillitis (1.1%), pneumonia (1.1%), rhinitis (1.1%), tonsillitis (1.1%), asthma (1.1%).
- Group 2 doses 1 and 2: vomiting (1.8%), pyrexia (1.8%), injection site erythema (0.9%), injection site pain (0.9%), exanthema subitum (1.8%), otitis media (1.8%), viral infection (1.8%), pneumonia (0.9%), asthma (1.8%), cough (0.9%), and rash (0.9%).
- Group 3 dose 1: vomiting (0.7%), pyrexia (0.7%), gastroenteritis (1.3%), acute tonsillitis (0.7%), bronchitis (0.7%), laryngitis (0.7%), respiratory tract infection (0.7%), tonsillitis (0.7%), syncope (0.7%), asthma (0.7%), dysphonia (0.7%), dermatitis (0.7%), rash (0.7%), and swelling face (0.7%).

Group 3 subject 3002-004-00325 had an episode of mild facial swelling at the post-dose 1 blood draw visit, one month after administration of dose 1.

Two group 1 subjects were reported to have experienced 3 “severe adverse events” after dose 1 and 2 combined; these events included a respiratory tract infection, thermal burn, and febrile convulsion. One group 1 subject experienced “severe” pneumonia after dose 3. One group 2 subject experienced severe stomatitis and pharyngitis after dose 1 and 2 combined. There were no severe adverse events experienced by any group 3 subject.

9.1.4.3.5 Serious Adverse Events

No subjects died during the course of this study and no subjects were withdrawn because of an adverse event. Overall, nine out of 354 subjects (2.5%) across all study groups experienced twelve SAEs. Line listings were provided, however no narratives were provided. No SAE was categorized by the study investigator as related to the study vaccine. No SAEs were reported after dose 1 in group 1 subjects. No subjects withdrew from the study because of a SAE.

In group 1, five out of 90 subjects (5.6%) experienced SAEs. Four subjects experienced 5 SAEs after dose 2, and one subject experienced 1 SAE after dose 3:

1. Beginning 101 days after dose 3, subject 002-000107 experienced a moderate gastrointestinal infection which required hospitalization and which resolved after 11 days.
2. Beginning 47 days after dose 2, subject 003-000220 experienced a severe thermal burn which required hospitalization and which resolved after 86 days.

3. Beginning 28 days after dose 2, subject 005-000403 experienced 3 days of mild diarrhea and a severe febrile convulsion for 1 day. The subject was hospitalized; the final outcome for both events was reported as resolved.
4. Beginning 27 days after dose 2, subject 005-000415 was admitted to the hospital with a one day history of fever and was diagnosed with mild exanthema subitum which resolved after 5 days. This subject also experienced a mild upper respiratory infection starting 13 days after dose 3 and a mild viral infection starting 36 days after dose 3. The viral URI, which required an ER visit, resolved after 10 days. The viral infection resolved after 3 days.
5. Beginning 9 days after dose 3, subject 008-000705 was hospitalized for severe pneumonia which resolved after 28 days. This subject also experienced (1) mild nasopharyngitis beginning 5 days after dose 3 which resolved after 5 days; (2) mild asthma beginning 9 days after dose 3,which was noted to be persistent at the time of the study follow-up; and (3) mild allergic dermatitis beginning 9 days after dose 2 and which resolved within 5 days.

In group 2, 2 out of 112 subjects (1.8%) experienced SAEs. Two subjects experienced 4 SAEs (3 SAEs after dose 1, and 1 SAE after dose 2):

1. Beginning 62 days after dose 1 and 9 days after dose 2, subject 001-000040 experienced fever, 2 days of mild vomiting and 8 days of moderate bilateral otitis media respectively. The subject required hospitalization and administration of concomitant medication. The final outcome for both of these is resolved.
2. Beginning 20 days after dose 1, subject 006-000530 experienced severe pharyngitis and severe stomatitis requiring hospitalization; both events resolved after 8 days.

In group 3, two out of 152 subjects (1.3%) experienced 2 SAEs:

1. Beginning 15 days after dose 1, subject 004-000304 experienced 7 days of moderate pharyngitis. Symptoms began 15 days after dose 1, and required hospitalization, concomitant medication, and an unscheduled clinic visit (with tests or procedures), and resolved after 7 days.
2. Beginning 27 days after dose 1, subject 004-000319 experienced 2 days of moderate dyspepsia. Symptoms began 27 days after dose 1, required hospitalization, concomitant medication, and an unscheduled clinic visit (with tests or procedures), and resolved after 2 days.

9.1.4.4 Summary and Conclusions

Study 3002 was an open-label, non-randomized, non-controlled study evaluating the safety and immunogenicity of three age-appropriate Prevnar 13 catch-up vaccination schedules for pneumococcal vaccine naïve infants 15 months through 5 years of age. The review of the safety data from this study raised no additional safety isues regarding the use of Prevnar 13 in children 7 months through 5 years of age with no prior pneumococcal vaccinations. The immunogenicity data from descriptive analyses suggest lower IgG GMCs for most serotypes compared to the GMCs achieved after a 4 dose infant and toddler immunization series (at 2, 4, 6, and 12-15 months) with Prevnar 13. For children 24 months through 5 years of age, the data suggest that the catch-up schedule may result in lower antibody concentrations for some serotypes compared to antibody concentrations following 3 doses of Prevnar 13 (given at 2, 4, and 6 months). It is not known whether the observation of lower GMCs is predictive of diminished effectiveness in preventing invasive disease in these older children. Functional OPA antibody responses were not assayed in this study.

9.1.4.4.1 Safety

No subjects died during the course of this study and no subjects were withdrawn because of an adverse event. Overall, nine out of 354 subjects (2.5%) across all study groups experienced twelve SAEs.

Solicited local reactions, which were collected for 4 days following each vaccination, were reported most frequently in Group 2 subjects. The most common solicited local reaction in each group was erythema. Rates of any and mild erythema and induration after dose 1 were similar in group 1 and 3 subjects but higher in group 2 subjects. However, rates of moderate erythema and induration after dose 1 were higher in group 3 compared to groups 2 and 1. Differences were not evaluated for

statistical significance. Tenderness occurred more frequently in the older age groups (groups 2 and 3) compared to group 1. Significant tenderness increased with each subsequent dose in group 1 and 2; after the first dose, significant tenderness was highest in the oldest age group (group 3).

The most frequently reported systemic event was irritability and decreased appetite. Mild and moderate fever peaked after dose 2 in group 1 and 2 subjects. There were no cases of fever > 40^{o}C. Rates of fever were lower than those observed in U.S. infant studies. Antipyretics within four days following each vaccination to treat or prevent symptoms related to vaccination were used by 5-9% in group 1, 10-14% in group 2, and 3-5% in group 3.

9.1.4.4.2 Immunogenicity

Overall, seroresponse rates ≥ 0.35µg/mL after the last vaccination ranged from 98-100% in group 1, 93-100% in group 2, and 93-100% in group 3. Responses were typically higher in groups 1 and 2 than in group 3.

Among group 1 subjects enrolled at 7 to < 12 months of age and administered 3 doses of Prevnar 13, at least 97.6% achieved an anti-pneumococcal antibody concentrations ≥ 0.35µg/mL to each of the vaccine serotypes one month after the last dose. GMCs for each vaccine serotype ranged from 1.9 to 8.0.

Among group 2 subjects enrolled at 12 to < 24 months of age and administered 2 doses of Prevnar 13, at least 92.7% achieved anti-pneumococcal antibody concentrations ≥ 0.35µg/mL to each of the vaccine serotypes one month after the last dose. GMCs for each vaccine serotype ranged from 1.9 to 6.5.

Among group 3 subjects enrolled at 24 to < 72 months of age and administered 1 dose of Prevnar 13, at least 88.1% achieved anti-pneumococcal antibody concentrations ≥ 0.35µg/mL to each of the vaccine serotypes one month after the last dose. GMCs for each vaccine serotype ranged from 1.4 to 6.0. The GMC to serotype 14 was particularly low in this group [2.24 (95% CI 1.71, 2.93)] compared to groups 1 and 2 [Group 1: 8.04 (95% CI 6.95, 9.30); Group 2: 6.45 (95% CI 5.48, 7.59).

9.2 Clinical Study Protocol # 6096A1-008

Clinical trials.gov registry identifier: NCT00366678

CSR # 73151: 4th dose analyses

Protocol Title: A Phase 3, Randomized, Active-Controlled, Double-blind,Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccination in France

Study -008 safety and immunogenicity results were in part used to support a 1-dose 13vPnC catch-up schedule in toddlers, who had received 3 prior PCV7 routine immunizations. A single 13vPnC dose would be given to toddlers considered 'unvaccinated' for the 6 new serotypes and incompletely vaccinated for the PCV7 serotypes. For the 7 common serotypes, a 13vPnC toddler dose would complete a routine 4-dose primary series. Study details pertinent to the toddler sequential PCV7/13vPnC regimen are presented in this review.

Study Design
This study was a randomized, double-blind, active-controlled trial in France. Infants received one of the following regimens: (a) four 13vPnC doses; (b) four PCV7 doses; or (c) a sequential PCV7 (doses 1-3)/13vPnC (dose 4). Vaccinations were administered at 2, 3, 4 and 12 months old. Study Period: October 2006 to November 2007.

Table 112. Study -008 Design

Study Group	Randomized subjects (N=613)	Vaccination Schedule				
		2 months old	3 months old	4 months old		12 months old
13v/13v	304	*13v*	*13v*	*13v*		*13v*
7v/7v	158	*7v*	*7v*	*7v*		***7v***
7v/13v	151	*7v*	*7v*	*7v*		***13v***

Objectives
The primary objective was to evaluate co-administration of DTaP-IPV-Hib (Pentavac; Sanofi Pasteur MSD) when given with 13vPnC. Included as an exploratory objective were comparisons of pneumococcal immune responses following a sequential 7v/13v schedule, four 13vPnC (13v/13v) doses, and four PCV7 (7v/7v) doses.

Endpoints
The exploratory endpoints for each pneumococcal serotype were the proportion of subjects achieving a serotype-specific IgG antibody concentration ≥0.35 µg/mL and the geometric mean IgG antibody concentration measured 1 month after the toddler dose. The proportion of toddlers achieving an OPA titer ≥ 1:8 to each non-PCV7 serotype and corresponding geometric mean OPA titers was assessed post-hoc.

Inclusion/Exclusion criteria
Eligibility criteria were the same as for U.S. pivotal immunogenicity study-004.

Concomitant vaccinations
DTaP-IPV-Hib (Pentavac; Sanofi Pasteur MSD). Permitted childhood vaccinations included BCG, hepatitis B, MMR, varicella and monovalent meningococcal C vaccines.

Safety Surveillance / Monitoring
Study participants were observed for immediate adverse reactions within 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 ≥ 38.0°C) occurring within 4 days after each vaccination were recorded daily in an electronic diary. Unsolicited

adverse events occurring within 30 days after each vaccination were collected at the next scheduled clinic visit. Newly diagnosed chronic medical conditions and serious adverse events (SAEs) reported during the study period and were obtained by a scripted telephone interview.

Immunogenicity Monitoring
Blood sampling occurred at 5 months, 12 months, and 13 months old.

Study Cohorts Analyzed
Safety population
All subjects who received at least 1 dose of study vaccine were included in the safety population. Study participant data were analyzed according to the vaccine or the planned sequence of vaccines received.

Evaluable immunogenicity population
Except for the age at the toddler dose (≥ 334 and ≤ 396 days) the criteria for the evaluable toddler immunogenicity population was the same as for U.S. pivotal immunogenicity study-004.

Results
Subject Disposition and Follow-up
The toddler safety population included 562 toddlers (13v/13v n= 273, 7v/13v n= 152, 7v/7v n=137). Prior to toddler vaccination, 51 of 611 vaccinated infants (13v/13v or 7v/13v n= 38, 7v/7v n=13) withdrew from the study due to parental request (n= 24), lost to follow-up (n=12), non-compliance with a scheduled visit (n=3) or a protocol violation (e.g., ineligibility criteria, receipt of non-study vaccines; n=8). Four toddlers who received 13vPnC and one PCV7 participant withdrew from the study due to parental request, non-compliance with a scheduled visit, protocol violation. One 13v/13v toddler withdrew for a reason listed as 'other'; additional details were not provided. During the study period, 4 participants (13v, 13v/13v, or 7v/13v n= 2, 7v/7v n=2) withdrew due to an adverse event [see section 12, other supportive safety studies].

Subject Demographics
Please see section 12, other supportive safety studies.

Immunogenicity Outcomes
Antibody responses following completion of a catch-up schedule: comparisons to control group post-dose 3 and 4 antibody responses
The applicant applies the following rationale for comparing *post-catch-up schedule completion* antibody responses to *post-dose 3* 13vPnC antibody responses

- In the NCKP clinical efficacy trial, the IPD primary endpoint was measured after the *3rd dose*
- For the 7 common serotypes, 13vPnC antibody responses were considered comparable to PCV7 antibody responses.

CBER considers comparisons of immune response after the 3rd and the 4th PnC dose as important analyses. Because children in the original PCV7 NCKP efficacy study received a fourth PCV7 dose, the trial design did not allow for an assessment of the durability of protection beyond 12 months of age in children who received only 3 doses. Consequently, IgG antibody responses following a 3rd dose are indicative of vaccine serotype protection from 6 months through 12 months of age; and post-dose 4 antibody responses are indicative of vaccine serotype protection beyond 12 months of age.

Study -008 between group comparisons

Antibody responses to 6 non-PCV7 serotypes following 7v/13 schedule completion: comparison to post-dose 3 control group responses

- *Comparison of 7v/13v, post-dose 4 vs. 13v/13v post-dose 3 IgG GMC*

A single 13vPnC dose given to 12 month old toddlers resulted in higher IgG GMCs to all non-PCV7 serotypes, compared to IgG GMCs following three 13vPnC doses given to infants.

Table 113. Study -008 Non-PCV7 serotype Geometric Mean Concentrations (µg/mL) of Pneumococcal IgG Antibodies Following Toddler and Infant 13vPnC vaccination (Evaluable Immunogenicity Populations)

	Post-dose 4		Post-dose 3	
study -008	**7v/13v**		**13v/13v**	
	n[a] = 109-113		n[a] = 238-244	
Serotype	**GMC[b]**	**(95% CI)[c]**	**GMC[b]**	**(95% CI)[c]**
Additional				
1	1.83	(1.5, 2.2)	1.21	(1.07, 1.38)
3	1.32	(1.1, 1.5)	1.25	(1.13, 1.37)
5	1.14	(1.0, 1.3)	0.93	(0.82, 1.06)
6A	2.6	(2.0, 3.4)	0.94	(0.82, 1.06)
7F	3.71	(3.2, 4.3)	1.93	(1.73, 2.15)
19A	5.33	(4.6, 6.2)	2.1	(1.87, 2.35)

[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] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.1,m5.3.5.1, CSR73151-report-body-toddler.pdf, pages 77-79 (Table 9-9); CSR67343-report-body-infant.pdf, page 64 (Table 9-6).

Antibody responses to each of 13 serotypes following 7v/13 schedule completion: comparison to post-dose 4 control group responses

- *Comparison of 7v/13v vs. 7v/7v, post-dose 4 IgG GMC*

13vPnC given as the 4th pneumococcal vaccination in infants receiving 3 PCV7 doses resulted in lower post-dose 4 IgG GMC for 6 of 7 common serotypes.

- *Comparison of 7v/13v vs. 13v/13v, post-dose 4 IgG GMC*

A 7v/13v schedule resulted in lower post-dose 4 IgG GMC for 4 of 7 common serotypes, and 5 of 6 non-PCV7 serotypes, compared to infants completing a 4-dose primary series with the same vaccine.

Table 114. Study -008 Geometric Mean Concentrations (µg/mL) of Pneumococcal IgG Antibodies Following the Toddler Dose (Evaluable Toddler Immunogenicity Population)

Study -008	Post-dose 4					
	13v/13v n[a]= 230-236		7v/13v n[a]= 108-113		7v/7v n[a]= 111-127	
Serotype	**GMC[b]**	**(95% CI) [c]**	**GMC[b]**	**(95% CI) [c]**	**GMC[b]**	**(95% CI) [c]**
PCV7						
4	4.20	(3.8, 4.7)	4.04	(3.4, 4.8)	4.85	(4.2, 5.6)
6B	8.99	(8.0, 10.1)	10.33	(8.2, 13.0)	9.63	(8.3, 11.2)
9V	2.59	(2.3, 2.8)	2.29	(2.0, 2.6)	3.24	(2.8, 3.7)
14	9.52	(8.5, 10.6)	7.81	(6.6, 9.3)	10.83	(9.4, 12.5)
18C	2.30	(2.1, 2.5)	2.43	(2.0, 2.9)	2.81	(2.5, 3.2)
19F	5.18	(4.5, 6.0)	3.73	(3.0, 4.6)	4.11	(3.4, 5.0)
23F	3.01	(2.7, 3.4)	3.12	(2.6, 3.7)	3.69	(3.1, 4.3)
Additional						
1	4.08	(3.7, 4.5)	1.83	(1.5, 2.2)		
3	0.99	(0.9, 1.1)	1.32	(1.1, 1.5)		
5	3.30	(3.0, 3.7)	1.14	(1.0, 1.3)		
6A	6.14	(5.5, 6.8)	2.60	(2.0, 3.4)		
7F	4.52	(4.1, 5.0)	3.71	(3.2, 4.3)		
19A	9.50	(8.5, 10.6)	5.33	(4.6, 6.2)		

[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] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.1,m5.3.5.1, CSR73151-report-body-toddler.pdf, pages 77-79 (Table 9-9).

Cross-study pneumococcal immune response comparisons by vaccination schedule (2, 3, 4 and 12 months old vs. 2, 4, 6 and 12-15 months old)

Comparisons of post-dose 4 OPA responses among study -008 7v/13v recipients, study -008 13v/13v recipients and study -004 13vPnC recipients:

After one 13vPnC toddler dose, OPA GMTs to each of 6 non-PCV7 serotypes were similar (i.e. within one titer dilution) among infants who had received PCV7 or 13vPnC at 2, 3 and 4 months old. Post-toddler OPA GMTs comparisons for 3 of 6 non-PCV7 serotypes were 1 titer dilution lower among infants who received 13vPnC at 2 ,3 and 4 months old than at 2, 4, and 6 months old.

Table 115. Studies -008 and 004. Post-toddler OPA GMTs to Pneumococcal non-PCV7 Serotypes

	Study 008 – Post-dose 4				Study 004 – Post-dose 4	
	13v/13v		7v/13v		13vPnC	
	n[a] =89-90		n[a] =89-90		n[a] =88-92	
Serotype	**GMT[b]**	**(95% CI)[c]**	**GMT[b]**	**(95% CI)[c]**	**GMT[b]**	**(95% CI)[c]**
Additional						
1	126	(100, 159)	**62**	(48, 79)	164	(114, 237)
3	345	(296, 403)	429	(347, 531)	380	(300, 482)
5	244	(200, 298)	**131**	(104, 166)	300	(229, 393)
6A	1347	(1144, 1586)	**891**	(695, 1144)	2242	(1707, 2945)
7F	8126	(6657, 9919)	17035	(14317, 20269)	11629	(9054, 14938)
19A	804	(616, 1050)	1072	(799, 1439)	1024	(774, 1355)

[a] n = Number of subjects with a determinate antibody concentration 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 concentrations.
Source: 125324/0.39, m1.11.3, Study 6096A1-008 additional data, page 17 (Table 1-7); 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 105 (Table 9-17).

Safety Outcomes

Immediate Reactions

Adverse reactions occurring within 30 minutes after vaccination were included among categories of any adverse events, but were not identified by time-to-onset of symptoms as an immediate reaction.

Solicited Local Reactions

The overall incidence of local reactions after the 4th vaccination was 71.3%, 78.0% and 81.9%, among the 7v/7v, 13v/13v and 7v/13v groups, respectively. Participants given a sequential 7v/13v regimen reported 13.7-19.2% more injection site tenderness than participants receiving four doses of the same vaccine.

Table 116. Study 6096A1-008. Percentage of subjects with solicited local adverse events, by severity within 4 days after the toddler dose

	13v/13v	7v/13v	7v/7v
Graded Local Reaction	**N[a]= 152-205** **%**	**N[a]= 73-105** **%**	**N[a]=86-108** **%**
Erythema			
Any	66.8	63.6	60.4
0.5 - 2.0 cm	60.0	60.0	54.7
2.5 - 7.0 cm	24.2	20.3	18.4
> 7.0 cm	0.7	0.0	0.0
Induration			
Any	53.5	59.8	57.6
0.5 - 2.0 cm	48.1	57.9	55.6
2.5 - 7.0 cm	19.5	20.7	15.9
> 7.0 cm	0.7	0.0	0.0
Tenderness			
Any	50.3	64.0	44.8
Interferes with limb movement	5.2	8.0	4.7

[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, CSR73151-report body.pdf, page 90 (Table 10-2).

Solicited Systemic Reactions
The overall incidence of systemic reactions after the 4th vaccination among the three groups ranged from 75.6% to 78.9%. Antipyretic treatment use was similar (54.0%-55.1%) among PCV7-immunized toddlers following a 13vPnC or PCV7 4th dose vaccination.

Table 117. Study 6096A1-008. Percentage of subjects with solicited system adverse events within 4 days after the toddler dose

	13v/13v	7v/13v	7v/7v
Graded Systemic Events	**N[a]= 153-201 %**	**N[a]= 73-105 %**	**N[a]= 88-114 %**
Fever			
38.0°C ≤ x ≤ 39.0°C	36.8	42.2	41.4
39°C < x ≤ 40.0°C	4.6	4.1	2.2
> 40°C	0.7	0.0	0.0
Decreased appetite [b]	29.3	31.3	34.4
Irritability [b]	50.6	50.5	46.5
Increased sleep [b]	21.5	23.5	23.9
Decreased sleep [b]	26.2	30.9	22.6
Prophylactic antipyretic use	38.7	40.0	44.4
Treatment antipyretic use	47.8	55.1	54.0

[a] Number of subjects reporting yes for at least 1 day or no for all days
[b] No other systemic event other than fever was graded.
Source: 125324/0.1,m5.3.5.1, CSR73151-report body.pdf, page 93 (Table 10-3).

Adverse Events
During the time period 28 to 42 days after the 4th vaccination, 38 (28.4%) subjects in the 7v/13v group, 75 (27.6%) subjects in the 13v/13v group, and 46 (30.7%) subjects in the 7v/7v group reported an adverse event.

Serious adverse event reports (through 1 month after the toddler vaccination) and safety related discontinuations are described in Section 12 [Other supportive safety studies].

Summary and Conclusions
In this study, 1-dose 13vPnC catch-up schedule was evaluated in toddlers who had received 3 prior PCV7 routine immunizations. Toddler participants were considered 'unvaccinated' for the 6 new serotypes and incompletely vaccinated for the PCV7 serotypes. For the 7 common serotypes, a 13vPnC toddler dose would complete a routine 4-dose primary series. Sequential 7v/13v resulted primarily in increased injection site tenderness, compared to toddlers given four doses of the same vaccine. Overall incidences of systemic reactions were similar (range 75.6% to 78.9%). OPA antibody responses to each of 6 new serotypes were comparable following completion of a 7v/13v or 13v/13v vaccination regimen given at 2-3-4 and 12 months old. when 13vPnC was given to toddlers previously immunized with PCV7 at 2, 3 and 4 months old, opsonophagocytic activity of antibodies to serotypes 1, 5, and 6A, were one dilution lower compared to corresponding OPA GMTs after four 13vPnC doses given at 2, 4, 6, and 12 to 15 months old.

9.3 Clinical Study Protocol # 6096A1-3011

Clinical trials.gov registry identifier: NCT00761631

CSR # 76155: Interim report for cohort 1 (Groups 1 and 2)

Protocol Title: Interim report: A phase 3, open-label trial evaluating the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine in healthy children aged 15 months to 17 years in the United States. Interim Report includes data from children < 5 years in groups 1 and 2.

This open-label study was designed to evaluate the safety and immunogenicity of 13vPnC when administered to healthy children aged 15 months through 17 years enrolled into 1 of 4 groups based on age (see table 118 below). Children 15 months through 23 months of age with ≥ 3 prior PCV7 doses were enrolled into group 1 and received 2 doses of 13vPnC at least 56 days apart. Children 24 months through 59 months of age with ≥ 3 prior PCV7 doses were enrolled into group 2 and received a single dose of 13vPnC. The dosing schedule for children 5 through 17 years of age enrolled into groups 3 and 4 was 1 dose of 13vPnC. Immune responses induced by 13vPnC, when measured one month after the last scheduled dose of 13vPnC were evaluated in each of the 4 groups.

This study evaluated the following: (1) 13vPnC safety as a 4th, 5th or 6th pneumococcal conjugate vaccination, (2) IgG antibody responses, particularly to the 6 additional serotypes, in children who previously received 3 or 4 PCV7 doses. In addition, the study assessed 13vPnC vaccinations to complete a catch-up schedule for PCV7 serotypes.

In accordance with CBER recommendations, the protocol was amended to enroll additional children (cohort 2) so that each of the four study groups would contain a total of 300 subjects for the safety evaluation. Group 1 (n=125) and group 2 (n=182) participants, enrolled prior to the protocol amendment, were designated cohort 1. Additional subjects enrolled after the protocol amendment were designated cohort 2. The sum total of the two cohorts is estimated to be 600 children (n=300 participants per study group).

This interim study report provides the immunogenicity results as well as partial safety data for subjects in cohort 1. Safety data are presented for subjects in cohort 1 through 1-month after the last 13vPnC vaccination. Six-month follow-up safety data for subjects in cohort 1, all cohort 2 safety data, and immunogenicity and safety results for groups 3 and 4 are anticipated in a future study report.

Table 118: Study design

Population	Vaccine	Dosing Schedule	Duration of subject participation
Group 1: Age > 15 mo to < 2 yrs with ≥ 3 prior PCV7 doses	13vPnC	2 doses ≥ 56 days apart	8 months
Group 2: Age ≥ 2 to < 5 yrs with ≥ 3 prior PCV7 doses	13vPnC	1 dose	6 months
Group 3: Age ≥ 5 to < 10 yrs with ≥ 1 prior PCV7 dose	13vPnC	1 dose	6 months
Group 4: Age ≥ 10 to < 18 yrs who never received a pneumococcal vaccine	13vPnC	1 dose	6 months

Clinical Reviewer Note: This study is viewed by CBER as a phase 2, exploratory study to collect descriptive data, as there is no formal hypothesis testing and no control group. In addition, because the 0.35µg/mL reference value is used primarily in the evaluation of immune responses in infants aged 7 months, evaluation of GMCs in study 3011 provides more meaningful information than seroresponse rates ≥ 0.35µg/mL. OPA data were not provided in the clinical study report for study 3011.

Study dates: 18-Nov-08 to 16-Jun-09 (Cohort 1)

Study Sites: Subjects in cohort 1 were enrolled from 32 sites in the United States.

Safety monitoring: Solicited events included injection site reactions (erythema, induration, and tenderness) and systemic events (decreased appetite, irritability, increased sleep, decreased sleep, hives (urticaria), fever (T ≥ 38.0°C). Temperature was measured using an age-appropriate method. Solicited events occurring within 7-days after each vaccination were recorded daily. Prophylactic or treatment antipyretic medication use was recorded during the same time period. Unsolicited adverse events were collected through one month after the last vaccination. SAEs were reported through 6 months after the last vaccination.

Laboratory: Early Phase Programs-Clinical Testing and Assay Development (EPP-CTAD) Wyeth conducted the pneumococcal IgG ELISAs and pneumococcal OPA assays.

Vaccine administration
13vPnC: Each 0.5ml dose contains 2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4ug saccharide for 6B individually conjugated to cross-reacting material 197 (CRM_{197}). The total concentration of CRM_{197} is ~32ug. The final formulation contains 5mM succinate buffer and 0.125 mg aluminum as AlPO4. The vaccine is formulated as a liquid and appears as a homogeneous, white suspension after shaking. Route: intramuscular (IM). Lot number: 7-5095-005A.

Immunogenicity Results

Population Enrolled/Analyzed

Subject Disposition
Approximately 284 subjects 15 through 59 months of age were included in the evaluable immunogenicity population. Approximately 71% of subjects in group 1 (aged 15 through 23 months) and 95% of subjects in group 2 (aged 24 through 59 months) received 4 prior doses of Prevnar. Demographic characteristics showed a higher percentage of males in group 2; a majority of subjects were White and non-Hispanic. A total of 120 subjects received non-study vaccinations.

Table 119. Study 6096A1-3011 Summary of Subject Disposition

	13vPnC Group 1 15 through23 months N=126		13vPnC Group 2 24 through 59 months N=181		Total N=307	
	n	%	n	%	n	%
Subjects consented[a]	126	100	181	100	307	100
Subjects randomized	126	100	181	100	307	100
Subjects vaccinated						
Dose 1	124	98.4	179	98.9	303	98.7
Dose 2	112	88.9	NA	NA	112	88.9
Completed	4	3.2	110	60.8	114	37.1
Unknown[b]	107	84.9	67	37.0	174	56.7
Withdrawn[c]	15	11.9	4	2.2	19	6.2
Reasons for withdrawal:						
Parent / legal guardian request	8	6.3	2	1.1	10	3.3
Lost to follow-up	2	1.6	2	1.1	4	1.3
Protocol violation	2	1.6	0	0	2	0.7
Other[c]	1	0.8	0	0	1	0.3
Failed to return	1	0.8	0	0	1	0.3
Investigator request	1	0.8	0	0	1	0.3

[a] These values are used as the denominators for percentages.

[b] Unknown completion status includes subjects whose 6-month follow-up viist had not occurred or whose 6-month completion form had not been filled out as of the data cutoff date for this report.
[c] Subject 3011-036-002314 was enrolled but, because a blood sample could not be taken, the child was withdrawn from the study and did not receive study vaccine.
Source: 125324/0.67,m5.3.5.1, CSR-76155-report body, pages 41-41 (Tables 8-2).

Table 120. Study 6096A1-3011 Number of Prior Prevnar Doses Received Before Study Enrollment

Number of Prior PCV7 Doses Received	13vPnC Group 1 15 through 23 months N=126		13vPnC Group 2 24 through 59 months N=181		Total N=307	
	n	%	n	%	n	%
0	0	0.0	1*	0.6	1*	0.3
3	37	29.4	8	4.4	45	14.7
4	89	70.6	172	95.0	261	85.0

* Subject 3011-014-000865 did have proof of prior vaccination with Prevnar, but was withdrawn from the study before receiving the study vaccination, and the numbe of prior Prevnar doses received by the subject was not entered in the CRF.

Table 121. Study 6096A1-3011 Summary of Immunogenicity Analysis Populations

	13vPnC Group 1 15 through 23 months N=126		13vPnC Group 2 24 through 59 months N=181		Total N=307	
	n	%	n	%	n	%
Randomized	126	100	181	100	307	100
All-available immunogenicity population	124	98.4	181	100	305	99.3
Subjects excluded from all-available immunogenicity population because of no assay result for any pneumococcal serotype or concomitant antigen	2	1.6	0	0	2	0.7
Evaluable immunogenicity population	109	86.5	175	96.7	284	92.5
Subjects excluded from the evaluable immunogenicity population[a]	17	13.5	6	3.3	23	7.5
No assay result for any pneumococcal serotype before or after vaccination	14	11.1	5	2.8	19	6.2
Did not receive all pneumococcal study vaccinations	12	9.5	2	1.1	14	4.6
Not in all-available immunogenicity population	2	1.6	0	0	2	0.7
Blood draw less than 1 day before the first vaccination	1	0.8	0	0	1	0.3
Not eligible for the study	0	0	1	0.6	1	0.3

[a] For group 1, assay result from blood sample obtained before the first vaccination and after the second vaccination; for group 2, assay result from blood sample obtained before and after vaccination. [b] Subjects may have been excluded for more than 1 reason.
Source: 125324/0.67,m5.3.5.1, CSR-76155-report body, page 54 (Tables 9-1).

Subject Demographics

Table 122. Study 6096A1-3011. Summary of Demographic Characteristics for Evaluable Immunogenicity Population

	13vPnC Group 1 15 through 23 months N=109		13vPnC Group 2 24 through 59 months N=175		Total N=284	
	n	%	n	%	n	%
Gender						
Male	51	46.8	104	59.4	155	54.6
Female	58	53.2	71	40.6	129	45.4
Race						
White	84	77.1	129	73.7	213	75
Black	16	14.7	29	16.6	45	15.8
Other	6	5.5	12	6.9	18	6.3
Asian	2	1.8	2	1.1	4	1.4
American Indian or Alaska Native	1	0.9	2	1.1	3	1.1
Native Hawaiian or other Pacific Islander	0	0	1	0.6	1	0.4
Ethnicity						
Non-Hispanic and Non-Latino	98	89.9	151	86.3	249	87.7
Hispanic or Latino	11	10.1	24	13.7	35	12.3
Age at dose 1	Months		Years			
Mean (SD)	18.0 (2.7)		3.1 (0.8)		NA	
Min, Max	15.1, 24.0		2.0, 5.0		NA	
Age at dose 2 (months)						
Mean (SD)	20.0 (2.7)		NA		NA	
Min, Max	17.0, 25.8		NA		NA	
Weight at enrollment (lbs)						
n	109		174		283	
Mean (SD)	11.6 (3.5)		15.5 (3.1)		14.0 (3.7)	
Min, Max	8.0, 44.0		10.1, 29.4		8.0, 44.0	

Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 52 (Table 8-11).

Nonstudy Concomitant Vaccinations

Table 123. Study 6096A1-3011. Number of Subjects Who Received Non-Study Vaccinations

	13vPnC Group 1 15 through 23 months (N=126)		13vPnC Group 2 24 through 59 months (N=181)		Total (N=307)	
Non-study vaccinations	**n**	**%**	**n**	**%**	**n**	**%**
Any	68	54	52	28.7	120	39.1
Pentacel	4	3.2	0	0.0	4	1.3
Haemophilus influenzae B vaccines	4	3.2	0	0.0	4	1.3
Act-Hib	1	0.8	0	0.0	1	0.3
Unspecified	3	2.4	0	0.0	3	1.0
Hepatit Vaccines	38	30.2	20	11.0	58	18.9
Havrix	3	2.4	0	0.0	3	1.0
Hepatitis A vaccine	34	27.0	20	11.0	54	17.6
Hepatitis B vaccine	2	1.6	1	0.6	3	1.0
Influenza Vaccines	16	12.7	28	15.5	44	14.3
Fluzone	4	3.2	14	7.7	18	5.9
Unspecified	12	9.5	14	7.7	26	8.5
Morbilli Vaccines	16	12.7	9	5	25	8.1
M-M-R II	2	1.6	0	0	2	0.7
Measles-mumps-rubella virus vaccine	14	11.1	9	5	23	7.5
Pertussis Vaccines	41	32.5	13	7.2	54	17.6
Prevnar	1	0.8	0	0	1	0.3
Poliomyelitis vaccines	2	1.6	9	5.0	11	3.6
Varicella virus vaccine, live	12	9.5	9	5	21	6.8

Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 139 (Table 15.9).

Immunogenicity Endpoints/Outcomes

Proportion of subjects achieving antibody levels ≥ 0.35µg/mL Before Vaccination
Pre-vaccination seroresponse rates were lower in group 2 subjects (24 through 59 months) compared to group 1 subjects (15 through 23 months) for the 7 common serotypes (particularly for serotypes 4, 14, and 18C); however, prevaccination seroresponse rates were higher in group 2 subjects than group 1 subjects for the 6 additional serotypes. Serotype 6A IgG antibody response is in part due to serotype 6B-induced cross-reacting antibody. Natural exposure to antigens that elicit non-functional antibodies is possible reason for high serotype 5 and 19A pre-vaccination responses.

Table 124. Study 6096A1-3011. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL Before Vaccination (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC Group 1 15 through 23 months				13vPnC Group 2 24 through 59 months			
Serotype	**N[a]**	**n[b]**	**%**	**95% CI[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7								
4	109	91	83.5	(75.2, 89.9)	172	67	39.0	(31.6, 46.7)
6B	109	109	100.0	(96.7, 100.0)	173	167	96.5	(92.6, 98.7)
9V	109	93	85.3	(77.3, 91.4)	174	126	72.4	(65.1, 78.9)
14	109	108	99.1	(95.0, 100.0)	175	137	78.3	(71.4, 84.2)
18C	109	82	75.2	(66.0, 83.0)	175	77	44.0	(36.5, 51.7)
19F	109	99	90.8	(83.8, 95.5)	170	134	78.8	(71.9, 84.7)
23F	109	97	89.0	(81.6, 94.2)	174	130	74.7	(67.6, 81.0)
Additional								
1	108	1	0.9	(0.0, 5.1)	166	21	12.7	(8.0, 18.7)
3	104	7	6.7	(2.7, 13.4)	169	49	29.0	(22.3, 36.5)
5	106	77	72.6	(63.1, 80.9)	167	139	83.2	(76.7, 88.6)
6A	107	86	80.4	(71.6, 87.4)	174	162	93.1	(88.3, 96.4)
7F	108	9	8.3	(3.9, 15.2)	171	43	25.1	(18.8, 32.3)
19A	109	106	97.2	(92.2, 99.4)	175	171	97.7	(94.3, 99.4)

[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. Assay result from blood sample obtained before vaccination 1 for all groups.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 57 (Table 9-2).

Proportion of subjects achieving antibody levels ≥ 1.00 µg/mL Before Vaccination

Table 125. Study 6096A1-3011. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 1.0 µg/mL Before Vaccination (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC Group 1 15 through 23 months Post-dose 2				13vPnC Group 2 24 through 59 months Post-dose 1			
Serotype	**N[a]**	**n[b]**	**%**	**95% CI[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7								
4	109	47	43.1	(33.7, 53.0)	172	14	8.1	(4.5, 13.3)
6B	109	98	89.9	(82.7, 94.9)	173	150	86.7	(80.7, 91.4)
9V	109	48	44.0	(34.5, 53.9)	174	59	33.9	(26.9, 41.5)
14	109	94	86.2	(78.3, 92.1)	175	74	42.3	(34.9, 50.0)
18C	109	38	34.9	(26.0, 44.6)	175	25	14.3	(9.5, 20.4)
19F	109	58	53.2	(43.4, 62.8)	170	83	48.8	(41.1, 56.6)
23F	109	60	55.0	(45.2, 64.6)	174	75	43.1	(35.6, 50.8)
Additional								
1	108	0	0.0	(0.0, 3.4)	166	9	5.4	(2.5, 10.0)
3	104	4	3.8	(1.1, 9.6)	169	37	21.9	(15.9, 28.9)
5	106	30	28.3	(20.0, 37.9)	167	88	52.7	(44.8, 60.5)
6A	107	53	49.5	(39.7, 59.4)	174	112	64.4	(56.8, 71.5)
7F	108	1	0.9	(0.0, 5.1)	171	17	9.9	(5.9, 15.4)
19A	109	75	68.8	(59.2, 77.3)	175	148	84.6	(78.4, 89.6)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥1.00 µg/mL for the given serotype. Assay result from blood sample obtained before vaccination 1 for all groups.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 59 (Table 9-4).

Proportion of subjects achieving antibody levels ≥ 0.35µg/mL One Month After the Last Vaccination
Among group 1 subjects (15 through 23 months), 94.5% to 100% of subjects achieved an anti-pneumococcal antibody concentration of 0.35µg/mL one month after the second vaccination; among group 2 subjects, 92% to 100% achieved an anti-pneumococcal antibody concentration of 0.35µg/mL one month after vaccination. The lowest seroresponse rate was to serotype 3, and the lower limit of the 95% CI for serotype 3 was 88% in group 1 and 87% in group 2. Although the proportion of subjects achieving an antibody concentration ≥ 0.35µg/mL was higher than those achieved by infants in study 004, the use of the ≥ 0.35µg/mL reference antibody level is not as meaningful of an endpoint in children beyond 7 months of age. Evaluation of GMCs shows that responses are similar to those achieved in study 004. OPA data were not provided from study 3011.

Table 126. Study 6096A1-3011. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After Vaccination (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC Group 1 15 through 23 months Post-dose 2				13vPnC Group 2 24 through 59 months Post-dose 1			
Serotype	**N[a]**	**n[b]**	**%**	**95% CI[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7								
4	109	107	98.2	(93.5, 99.8)	175	175	100.0	(97.9, 100.0)
6B	109	109	100.0	(96.7, 100.0)	173	173	100.0	(97.9, 100.0)
9V	109	109	100.0	(96.7, 100.0)	175	175	100.0	(97.9, 100.0)
14	109	109	100.0	(96.7, 100.0)	175	175	100.0	(97.9, 100.0)
18C	109	109	100.0	(96.7, 100.0)	175	175	100.0	(97.9, 100.0)
19F	109	109	100.0	(96.7, 100.0)	175	175	100.0	(97.9, 100.0)
23F	109	108	99.1	(95.0, 100.0)	175	175	100.0	(97.9, 100.0)
Additional								
1	109	109	100.0	(96.7, 100.0)	175	173	98.9	(95.9, 99.9)
3	109	103	94.5	(88.4, 98.0)	174	160	92.0	(86.9, 95.5)
5	109	109	100.0	(96.7, 100.0)	175	173	98.9	(95.9, 99.9)
6A	109	109	100.0	(96.7, 100.0)	173	173	100.0	(97.9, 100.0)
7F	109	109	100.0	(96.7, 100.0)	175	175	100.0	(97.9, 100.0)
19A	109	109	100.0	(96.7, 100.0)	175	175	100.0	(97.9, 100.0)

[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. Assay result from blood sample obtained before vaccination 1 for all groups.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 58 (Table 9-3).

Proportion of subjects achieving antibody levels ≥ 1.00 µg/mL One Month After the Last Vaccination
For the 7 common serotypes, 79-100% of group 1 subjects and 94-100% of group 2 subjects achieved an anti-pneumococcal antibody concentration ≥ 1.0 µg/mL one month after the last 13vPnC vaccination. Among the 6 additional serotypes, 51-100% of group 1 subjects and 55-100% of group 2 subjects achieved the ≥ 1.0 µg/mL reference value.

Table 127. Study 6096A1-3011. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 1.0 µg/mL After Vaccination (Evaluable Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC Group 1 15 through 23 months Post-dose 2				13vPnC Group 2 24 through 59 months Post-dose 1			
Serotype	**N[a]**	**n[b]**	**%**	**95% CI[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7								
4	109	88	80.7	(72.1, 87.7)	175	168	96.0	(91.9, 98.4)
6B	109	109	100.0	(96.7, 100.0)	173	173	100.0	(97.9, 100.0)
9V	109	97	89.0	(81.6, 94.2)	175	166	94.9	(90.5, 97.6)
14	109	109	100.0	(96.7, 100.0)	175	174	99.4	(96.9, 100.0)
18C	109	86	78.9	(70.0, 86.1)	175	165	94.3	(89.7, 97.2)
19F	109	105	96.3	(90.9, 99.0)	175	174	99.4	(96.9, 100.0)
23F	109	105	96.3	(90.9, 99.0)	175	171	97.7	(94.3, 99.4)
Additional								
1	109	109	100.0	(96.7, 100.0)	175	146	83.4	(77.1, 88.6)
3	109	56	51.4	(41.6, 61.1)	174	95	54.6	(46.9, 62.1)
5	109	107	98.2	(93.5, 99.8)	175	141	80.6	(73.9, 86.2)
6A	109	106	97.2	(92.2, 99.4)	173	171	98.8	(95.9, 99.9)
7F	109	109	100.0	(96.7, 100.0)	175	170	97.1	(93.5, 99.1)
19A	109	109	100.0	(96.7, 100.0)	175	175	100.0	(97.9, 100.0)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥1.00 µg/mL for the given serotype. Assay result from blood sample obtained after vaccination 2 for Group 1, after vaccination for Group 2.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 60 (Table 9-5).

Study 3011 Immunogenicity Comparisons to Study 004

Proportion of subjects achieving antibody levels ≥ 0.35 µg/mL After Vaccination – Compared to Post-dose 3 and Post-dose 4 Antibody Levels in Study 004

The tables below show seroresponse rates ≥ 0.35 µg/mL in study 3011 and in study 004 (post-dose 3 and post-dose 4). However, comparisons between seroresponse rates in studies 3011 and 004 were not a pre-specified study objective. The point estimates in both groups 1 and 2 of study 3011 were similar to or higher than the point estimates post-dose 3 in study 004. Compared to post-dose 4 in study 004, point estimates in group 1 were lower for serotypes 4 and 23F.

Table 128. Studies 6096A1-3011 and 6096A1-004. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After the Last Vaccination in Study 3011 and After Dose 3 in Study 004 (Evaluable Immunogenicity Population)

	Study 3011								Study 004							
	Group 1: 15 through 23 months with ≥ 3 prior PCV7 doses After 2 doses of 13vPnC				Group 2: 24 through 59 months with ≥ 3 prior PCV7 doses After 1 dose of 13vPnC				13vPnC After 3 doses of 13vPnC				PCV7 After 3 doses of PCV7			
Serotype	**N[a]**	**n[b]**	**%**	**95% CI[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7																
4	109	107	98.2	(93.5, 99.8)	175	175	100	(97.9, 100.0)	252	238	94.4	(90.9, 96.9)	251	246	98.0	(95.4, 99.4)
6B	109	109	100	(96.7, 100.0)	173	173	100	(97.9, 100.0)	252	220	87.3	(82.5, 91.1)	250	232	92.8	(88.9, 95.7)
9V	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	252	228	90.5	(86.2, 93.8)	252	248	98.4	(96.0, 99.6)
14	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	251	245	97.6	(94.9, 99.1)	252	245	97.2	(94.4, 98.9)
18C	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	252	244	96.8	(93.8, 98.6)	252	248	98.4	(96.0, 99.6)
19F	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	252	247	98.0	(95.4, 99.4)	251	245	97.6	(94.9, 99.1)
23F	109	108	99.1	(95.0, 100.0)	175	175	100	(97.9, 100.0)	252	228	90.5	(86.2, 93.8)	252	237	94.0	(90.4, 96.6)
Additional																
1	109	109	100	(96.7, 100.0)	175	173	98.9	(95.9, 99.9)	252	241	95.6	(92.3, 97.8)	248	4	1.6	(0.4, 4.1)
3	109	103	94.5	(88.4, 98.0)	174	160	92.0	(86.9, 95.5)	249	158	63.5	(57.1, 69.4)	241	11	4.6	(2.3, 8.0)
5	109	109	100	(96.7, 100.0)	175	173	98.9	(95.9, 99.9)	252	226	89.7	(85.2, 93.1)	197	61	31.0	(24.6, 37.9)
6A	109	109	100	(96.7, 100.0)	173	173	100	(97.9, 100.0)	252	242	96.0	(92.8, 98.1)	240	102	42.5	(36.2, 49.0)
7F	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	252	248	98.4	(96.0, 99.6)	248	7	2.8	(1.1, 5.7)
19A	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	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. Assay result from blood sample obtained before vaccination 1 for all groups.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 58 (Table 9-3); 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 74 (Table 9-3).

Table 129. Studies 6096A1-3011 and 6096A1-004. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL After the Last Vaccination in study 3011 and After Dose 4 in Study 004 (Evaluable Immunogenicity Population)

	Study 3011								Study 004							
	Group 1: 15 through 23 months with ≥ 3 prior PCV7 doses After 2 doses of 13vPnC				Group 2: 24 through 59 months with ≥ 3 prior PCV7 doses After 1 dose of 13vPnC				13vPnC After 4 doses of 13vPnC				PCV7 After 4 doses of PCV7			
Serotype	**N[a]**	**n[b]**	**%**	**95% CI[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7																
4	109	107	98.2	(93.5, 99.8)	175	175	100	(97.9, 100.0)	235	233	99.1	(97.0, 99.9)	223	223	100	(98.4,100.0)
6B	109	109	100	(96.7, 100.0)	173	173	100	(97.9, 100.0)	234	233	99.6	(97.6,100.0)	223	223	100	(98.4,100.0)
9V	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	234	232	99.1	(96.9, 99.9)	223	222	99.6	(97.5,100.0)
14	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	235	232	98.7	(96.3, 99.7)	223	221	99.1	(96.8, 99.9)
18C	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	236	233	98.7	(96.3, 99.7)	223	223	100	(98.4,100.0)
19F	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	235	235	100	(98.4,100.0)	223	220	98.7	(96.1, 99.7)
23F	109	108	99.1	(95.0, 100.0)	175	175	100	(97.9, 100.0)	234	233	99.6	(97.6,100.0)	222	222	100	(98.4,100.0)
Additional																
1	109	109	100	(96.7, 100.0)	175	173	98.9	(95.9, 99.9)	235	235	100	(98.4,100.0)	222	7	3.2	(1.3, 6.4)
3	109	103	94.5	(88.4, 98.0)	174	160	92.0	(86.9, 95.5)	232	210	90.5	(86.0, 94.0)	215	23	10.7	(6.9, 15.6)
5	109	109	100	(96.7, 100.0)	175	173	98.9	(95.9, 99.9)	235	234	99.6	(97.7,100.0)	198	137	69.2	(62.3, 75.5)
6A	109	109	100	(96.7, 100.0)	173	173	100	(97.9, 100.0)	235	235	100	(98.4,100.0)	221	196	88.7	(83.8, 92.5)
7F	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	235	234	99.6	(97.7,100.0)	223	13	5.8	(3.1, 9.8)
19A	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	236	236	100	(98.4,100.0)	211	209	99.1	(96.6, 99.9)

[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. Assay result from blood sample obtained before vaccination 1 for all groups.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 58 (Table 9-3); 125324/0.1, m5.3.5.1, CSR69238-report-body.pdf, pages 85-86 (Table 9-8).

Proportion of subjects achieving antibody levels ≥ 1.00 µg/mL After Vaccination

Sereresponse rates at ≥ 1.0 µg/mL were ≥ 51.4% in study 3011. Although comparisons to study 004 were not a pre-specified study objective, the tables below show both study 3011 and study 004 responses side-by-side. Compared to post-dose 3 responses in study 004, seroresponse rates in study 3011 similar to or higher in study 3011. Compared to post-dose 4 responses in both study groups from study 004, seroresponse rates in group 1 subjects in study 3011 were lower for serotypes 4 and 18C. Seroresponse rates in group 2 subjects in study 3011 were lower than Prevnar recipient responses in study 004 for serotypes 4, 18C, and 23F. Seroresponse rates in group 2 subjects in study 3011 were lower than Prevnar 13 recipients for serotypes 1 and 5.

Study 3011 group 2 subjects had higher seroresponse rates than group 1 subjects for serotypes 4, 9V, and 18C; group 1 subjects had higher seroresponse rates compared to group 2 subjects for serotypes 1 and 5.

Table 130. Study 6096A1-3011. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 1.0 µg/mL After Vaccination Compared to Post-dose 3 Responses from Study 004 (Evaluable Immunogenicity Population)

	Study 3011								Study 004							
	Group 1: 15 through 23 months with ≥ 3 prior PCV7 doses After 2 doses of 13vPnC				Group 2: 24 through 59 months with ≥ 3 prior PCV7 doses After 1 dose of 13vPnC				13vPnC After 3 doses of 13vPnC				PCV7 After 3 doses of PCV7			
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7																
4	109	88	80.7	(72.1, 87.7)	175	168	96	(91.9, 98.4)	252	170	67.5	(61.3, 73.2)	251	199	79.3	(73.7, 84.1)
6B	109	109	100	(96.7, 100.0)	173	173	100	(97.9, 100.0)	252	192	76.2	(70.4, 81.3)	250	200	80.0	(74.5, 84.8)
9V	109	97	89.0	(81.6, 94.2)	175	166	94.9	(90.5, 97.6)	252	121	48.0	(41.7, 54.4)	252	167	66.3	(60.1, 72.1)
14	109	109	100	(96.7, 100.0)	175	174	99.4	(96.9, 100.0)	251	237	94.4	(90.8, 96.9)	252	237	94.0	(90.4, 96.6)
18C	109	86	78.9	(70.0, 86.1)	175	165	94.3	(89.7, 97.2)	252	167	66.3	(60.1, 72.1)	252	202	80.2	(74.7, 84.9)
19F	109	105	96.3	(90.9, 99.0)	175	174	99.4	(96.9, 100.0)	252	203	80.6	(75.1, 85.3)	251	219	87.3	(82.5, 91.1)
23F	109	105	96.3	(90.9, 99.0)	175	171	97.7	(94.3, 99.4)	252	164	65.1	(58.8, 71.0)	252	191	75.8	(70.0, 80.9)
Additional																
1	109	109	100	(96.7, 100.0)	175	146	83.4	(77.1, 88.6)	252	200	79.4	(73.8, 84.2)	248	2	0.8	(0.1, 2.9)
3	109	56	51.4	(41.6, 61.1)	174	95	54.6	(46.9, 62.1)	249	54	21.7	(16.7, 27.3)	241	7	2.9	(1.2, 5.9)
5	109	107	98.2	(93.5, 99.8)	175	141	80.6	(73.9, 86.2)	252	162	64.3	(58.0, 70.2)	197	20	10.2	(6.3, 15.2)
6A	109	106	97.2	(92.2, 99.4)	173	171	98.8	(95.9, 99.9)	252	212	84.1	(79.0, 88.4)	240	33	13.8	(9.7, 18.8)
7F	109	109	100	(96.7, 100.0)	175	170	97.1	(93.5, 99.1)	252	225	89.3	(84.8, 92.8)	248	5	2.0	(0.7, 4.6)
19A	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	251	201	80.1	(74.6, 84.8)	238	107	45.0	(38.5, 51.5)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥1.00 µg/mL for the given serotype. Assay result from blood sample obtained after vaccination 2 for Group 1, after vaccination for Group 2.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 60 (Table 9-5); 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 240 (Table 15.21).

Table 131. Study 6096A1-3011. Proportion of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 1.0 µg/mL After Vaccination Compared to Post-dose 4 Responses in Study 004 (Evaluable Immunogenicity Population)

	Study 3011								Study 004							
	Group 1: 15 through 23 months with ≥ 3 prior PCV7 doses After 2 doses of 13vPnC				Group 2: 24 through 59 months with ≥ 3 prior PCV7 doses After 1 dose of 13vPnC				13vPnC After 4 doses of 13vPnC				PCV7 After 4 doses of PCV7			
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**	**N[a]**	**n[b]**	**%**	**(95% CI)[c]**
PCV7																
4	109	88	80.7	(72.1, 87.7)	175	168	96	(91.9, 98.4)	235	216	91.9	(87.7, 95.1)	223	220	98.7	(96.1, 99.7)
6B	109	109	100	(96.7, 100.0)	173	173	100	(97.9, 100.0)	234	228	97.4	(94.5, 99.1)	223	222	99.6	(97.5,100.0)
9V	109	97	89	(81.6, 94.2)	175	166	94.9	(90.5, 97.6)	234	210	89.7	(85.1, 93.3)	223	212	95.1	(91.3, 97.5)
14	109	109	100	(96.7, 100.0)	175	174	99.4	(96.9, 100.0)	235	227	96.6	(93.4, 98.5)	223	221	99.1	(96.8, 99.9)
18C	109	86	78.9	(70.0, 86.1)	175	165	94.3	(89.7, 97.2)	236	211	89.4	(84.8, 93.0)	223	216	96.9	(93.6, 98.7)
19F	109	105	96.3	(90.9, 99.0)	175	174	99.4	(96.9, 100.0)	235	230	97.9	(95.1, 99.3)	223	211	94.6	(90.8, 97.2)
23F	109	105	96.3	(90.9, 99.0)	175	171	97.7	(94.3, 99.4)	234	216	92.3	(88.1, 95.4)	222	220	99.1	(96.8, 99.9)
Additional																
1	109	109	100	(96.7, 100.0)	175	146	83.4	(77.1, 88.6)	235	226	96.2	(92.9, 98.2)	222	4	1.8	(0.5, 4.5)
3	109	56	51.4	(41.6, 61.1)	174	95	54.6	(46.9, 62.1)	232	104	44.8	(38.3, 51.5)	215	7	3.3	(1.3, 6.6)
5	109	107	98.2	(93.5, 99.8)	175	141	80.6	(73.9, 86.2)	235	219	93.2	(89.2, 96.1)	198	54	27.3	(21.2, 34.0)
6A	109	106	97.2	(92.2, 99.4)	173	171	98.8	(95.9, 99.9)	235	233	99.1	(97.0, 99.9)	221	160	72.4	(66.0, 78.2)
7F	109	109	100	(96.7, 100.0)	175	170	97.1	(93.5, 99.1)	235	226	96.2	(92.9, 98.2)	223	2	0.9	(0.1, 3.2)
19A	109	109	100	(96.7, 100.0)	175	175	100	(97.9, 100.0)	236	234	99.2	(97.0, 99.9)	211	198	93.8	(89.7, 96.7)

[a] N = number of subjects with a determinate IgG antibody concentration to the given serotype.
[b] n = Number of subjects with an antibody concentration ≥1.00 µg/mL for the given serotype. Assay result from blood sample obtained after vaccination 2 for Group 1, after vaccination for Group 2.
[c] Exact 2-sided confidence interval based on the observed proportion of subjects.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, page 60 (Table 9-5); 125324/0.1, m5.3.5.1, CSR69238-report-body.pdf, page 250 (Table 15.31).

Geometric Mean Concentrations (GMCs) at Baseline (Before 1st Dose of 13vPnC Vaccine) and After Last 13vPnC Vaccination

For the 7 common serotypes, baseline GMCs were similar between the two groups, while post-vaccination GMCs were typically higher in group 2 subjects. For the 6 additional serotypes, baseline GMCs were typically higher in Group 2 subjects; post-vaccination GMCs to serotypes 6A and 19A were higher among group 2 subjects.

Table 132. Study 6096A1-3011. Pneumococcal IgG GMCs (µg/mL) (Evaluable Immunogenicity Population)

		Before Vaccination			After Vaccination		
Serotype	**Group**	**n[a]**	**GMC[b]**	**(95% CI)[c]**	**n[a]**	**GMC[b]**	**(95% CI)[c]**
4	1	109	0.89	(0.73, 1.09)	109	2.14	(1.81, 2.53)
	2	172	0.25	(0.21, 0.29)	175	4.79	(4.14, 5.53)
6B	1	109	3.77	(3.13, 4.55)	109	15.40	(13.47, 17.61)
	2	173	3.10	(2.63, 3.67)	173	35.51	(30.75, 41.01)
9V	1	109	0.90	(0.76, 1.06)	109	2.03	(1.79, 2.30)
	2	174	0.64	(0.55, 0.75)	175	4.14	(3.62, 4.73)
14	1	109	2.72	(2.27, 3.26)	109	5.99	(5.16, 6.95)
	2	175	0.87	(0.73, 1.03)	175	13.53	(11.69, 15.66)
108C	1	109	0.70	(0.58, 0.85)	109	2.29	(1.94, 2.70)
	2	175	0.32	(0.27, 0.37)	175	3.64	(3.16, 4.18)
19F	1	109	1.22	(0.99, 1.51)	109	4.47	(3.74, 5.35)
	2	170	1.21	(0.96, 1.52)	175	10.12	(8.68, 11.80)
23F	1	109	1.21	(0.98, 1.50)	109	4.25	(3.61, 5.00)
	2	174	0.90	(0.75, 1.08)	175	6.74	(5.79, 7.85)
Additional							
1	1	108	0.04	(0.03, 0.05)	109	4.28	(3.74, 4.90)
	2	166	0.09	(0.07, 0.10)	175	2.43	(2.15, 2.75)
3	1	104	0.06	(0.04, 0.07)	109	1.11	(0.97, 1.28)
	2	169	0.22	(0.16, 0.30)	174	1.38	(1.17, 1.61)
5	1	106	0.56	(0.47, 0.67)	109	3.87	(3.40, 4.39)
	2	167	1.01	(0.86, 1.19)	175	2.13	(1.89, 2.41)
6A	1	107	0.89	(0.72, 1.09)	109	5.00	(4.26, 5.88)
	2	174	1.63	(1.38, 1.94)	173	12.96	(11.04, 15.21)
7F	1	108	0.04	(0.03, 0.05)	109	4.72	(4.23, 5.26)
	2	171	0.12	(0.10, 0.16)	175	4.22	(3.74, 4.77)
19A	1	109	1.98	(1.64, 2.38)	109	7.68	(6.78, 8.71)
	2	175	3.04	(2.58, 3.57)	175	14.18	(12.37, 16.25)

[a] GMC before the vaccination 1 for all groups.
[b] GMC after vaccination 2 for group 1; GMC after vaccination for group 2.
[c] n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
[d] Geometric mean concentrations (GMCs) were calculated using all subjects with available data at both before vaccination and after vaccination for the specified blood draw.
[e] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, pages 63-64 (Table 9-6).

GMCs at Baseline and After Last Vaccination in Study 3011 Compared to Post-dose 4 Antibody levels in Study 004

Baseline GMCs were lower in study 3011 than in study 004 for serotypes 4, 14, and 18C among group 2 subjects, for serotypes 3 and 5 among group 1 subjects, and for serotypes 1 and 7F among group 1 and 2 subjects. After the last vaccination, responses were lower in study 3011 than in study 004 for serotypes 4. 18C, 1, and 7F; responses were lower among group 1 subjects compared to study 004 for serotypes 9V, 14, 19F, 6A, and 19A.

For the 7 common serotypes, comparisons were made to study 004 Prevnar recipients because of the immunogenicity drift phenomenon.

Table 133. Pneumococcal IgG GMCs (µg/mL) Before and After Vaccination in Studies 3011 and 004 (Evaluable Immunogenicity Population)

		Study 3011						Study 004						
		Before 1st 13vPnC Vaccination			After Last 13vPnC Vaccination			Before 4th Vaccination				After 4th Vaccination		
Serotype	Group [a]	N[b]	GMC[c]	(95% CI)[d]	N[b]	GMC[c]	(95% CI)[d]	Group	N[b]	GMC[c]	(95% CI)[d]	N[b]	GMC[c]	(95% CI)[d]
4	1	109	0.89	(0.73, 1.09)	109	2.14	(1.81, 2.53)	13vPnC	229	0.35	(0.31, 0.39)	235	3.73	(3.28, 4.24)
	2	172	0.25	(0.21, 0.29)	175	4.79	(4.14, 5.53)	PCV7	208	0.51	(0.45, 0.57)	223	5.49	(4.91, 6.13)
6B	1	109	3.77	(3.13, 4.55)	109	15.40	(13.47, 17.61)	13vPnC	229	0.78	(0.69, 0.89)	234	11.53	(9.99, 13.30)
	2	173	3.10	(2.63, 3.67)	173	35.51	(30.75, 41.01)	PCV7	205	1.01	(0.88, 1.15)	223	15.63	(13.80, 17.69)
9V	1	109	0.90	(0.76, 1.06)	109	2.03	(1.79, 2.30)	13vPnC	227	0.39	(0.35, 0.43)	234	2.62	(2.34, 2.94)
	2	174	0.64	(0.55, 0.75)	175	4.14	(3.62, 4.73)	PCV7	206	0.53	(0.48, 0.59)	223	3.63	(3.25, 4.05)
14	1	109	2.72	(2.27, 3.26)	109	5.99	(5.16, 6.95)	13vPnC	228	1.89	(1.64, 2.17)	235	9.11	(7.95, 10.45)
	2	175	0.87	(0.73, 1.03)	175	13.53	(11.69, 15.66)	PCV7	206	2.49	(2.17, 2.85)	223	12.72	(11.22, 14.41)
18C	1	109	0.70	(0.58, 0.85)	109	2.29	(1.94, 2.70)	13vPnC	229	0.34	(0.30, 0.37)	236	3.20	(2.82, 3.64)
	2	175	0.32	(0.27, 0.37)	175	3.64	(3.16, 4.18)	PCV7	207	0.45	(0.41, 0.50)	223	4.70	(4.18, 5.28)
19F	1	109	1.22	(0.99, 1.51)	109	4.47	(3.74, 5.35)	13vPnC	229	0.73	(0.65, 0.82)	235	6.60	(5.85, 7.44)
	2	170	1.21	(0.96, 1.52)	175	10.12	(8.68, 11.80)	PCV7	205	0.65	(0.57, 0.74)	223	5.60	(4.87, 6.43)
23F	1	109	1.21	(0.98, 1.50)	109	4.25	(3.61, 5.00)	13vPnC	229	0.38	(0.33, 0.44)	234	5.07	(4.41, 5.83)
	2	174	0.90	(0.75, 1.08)	175	6.74	(5.79, 7.85)	PCV7	207	0.48	(0.42, 0.55)	222	7.84	(6.91, 8.90)
Additional														
1	1	108	0.04	(0.03, 0.05)	109	4.28	(3.74, 4.90)	13vPnC	229	0.64	(0.57, 0.72)	235	5.06	(4.43, 5.80)
	2	166	0.09	(0.07, 0.10)	175	2.43	(2.15, 2.75)	PCV7	205	0.03	(0.02, 0.03)	222	0.03	(0.03, 0.03)
3	1	104	0.06	(0.04, 0.07)	109	1.11	(0.97, 1.28)	13vPnC	224	0.15	(0.13, 0.17)	232	0.94	(0.83, 1.05)
	2	169	0.22	(0.16, 0.30)	174	1.38	(1.17, 1.61)	PCV7	198	0.05	(0.04, 0.06)	215	0.07	(0.05, 0.08)
5	1	106	0.56	(0.47, 0.67)	109	3.87	(3.40, 4.39)	13vPnC	228	0.77	(0.69, 0.86)	235	3.72	(3.31, 4.18)
	2	167	1.01	(0.86, 1.19)	175	2.13	(1.89, 2.41)	PCV7	188	0.44	(0.37, 0.51)	198	0.55	(0.47, 0.64)
6A	1	107	0.89	(0.72, 1.09)	109	5.00	(4.26, 5.88)	13vPnC	228	0.83	(0.75, 0.92)	235	8.20	(7.30, 9.20)
	2	174	1.63	(1.38, 1.94)	173	12.96	(11.04, 15.21)	PCV7	197	0.30	(0.26, 0.35)	221	1.87	(1.60, 2.19)
7F	1	108	0.04	(0.03, 0.05)	109	4.72	(4.23, 5.26)	13vPnC	228	0.83	(0.75, 0.93)	235	5.67	(5.01, 6.42)
	2	171	0.12	(0.10, 0.16)	175	4.22	(3.74, 4.77)	PCV7	204	0.04	(0.04, 0.05)	223	0.05	(0.04, 0.05)
19A	1	109	1.98	(1.64, 2.38)	109	7.68	(6.78, 8.71)	13vPnC	229	0.92	(0.81, 1.05)	236	8.55	(7.64, 9.56)
	2	175	3.04	(2.58, 3.57)	175	14.18	(12.37, 16.25)	PCV7	204	0.70	(0.61, 0.80)	211	3.54	(3.15, 3.98)

[a] Group 1 includes children 15 through 23 months of age with ≥ 3 prior Prevnar doses. Group 2 includes children 24 through 59 months of age with ≥ 3 prior Prevnar doses.
[b] n = Number of subjects with a determinate IgG antibody concentration to the given serotype.
[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data at both before vaccination and after vaccination for the specified blood draw.
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations, or the mean fold rise.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, pages 63-64 (Table 9-6); 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 112 (Table 9-19).

GMCs After Last Vaccination in Study 3011 Compared to Post-dose 3 Antibody levels in Study 004
GMCs after the last vaccination in study 3011 were higher for all serotypes compared to post-dose 3 GMCs in Prevnar 13 and Prevnar recipients in study 004.

Table 134. Studies 6096A1-3011 and 6096A1-004. Pneumococcal IgG GMCs (µg/mL) After the Last 13vPnC Vaccination in Study 3011 and After Dose 3 in Study 004.

		Study 3011			Study 004			
		After Last 13vPnC Vaccination			Post-dose 3			
Serotype	Group[a]	N[b]	GMC[c]	(95% CI)[d]	Group	N[b]	GMC[c]	(95% CI)[d]
4	1	109	2.14	(1.81, 2.53)	13vPnC	252	1.31	(1.19, 1.45)
	2	175	4.79	(4.14, 5.53)	PCV7	251	1.93	(1.75, 2.13)
6B	1	109	15.40	(13.47, 17.61)	13vPnC	252	2.10	(1.77, 2.49)
	2	173	35.51	(30.75, 41.01)	PCV7	250	3.14	(2.64, 3.74)
9V	1	109	2.03	(1.79, 2.30)	13vPnC	252	0.98	(0.89, 1.08)
	2	175	4.14	(3.62, 4.73)	PCV7	252	1.40	(1.27, 1.55)
14	1	109	5.99	(5.16, 6.95)	13vPnC	251	4.74	(4.18, 5.39)
	2	175	13.53	(11.69, 15.66)	PCV7	252	5.67	(5.02, 6.40)
18C	1	109	2.29	(1.94, 2.70)	13vPnC	252	1.37	(1.24, 1.52)
	2	175	3.64	(3.16, 4.18)	PCV7	252	1.79	(1.63, 1.96)
19F	1	109	4.47	(3.74, 5.35)	13vPnC	252	1.85	(1.69, 2.04)
	2	175	10.12	(8.68, 11.80)	PCV7	251	2.24	(2.01, 2.50)
23F	1	109	4.25	(3.61, 5.00)	13vPnC	252	1.33	(1.17, 1.51)
	2	175	6.74	(5.79, 7.85)	PCV7	252	1.90	(1.68, 2.15)
Additional								
1	1	109	4.28	(3.74, 4.90)	13vPnC	252	2.03	(1.78, 2.32)
	2	175	2.43	(2.15, 2.75)	PCV7	248	0.02	(0.02, 0.03)
3	1	109	1.11	(0.97, 1.28)	13vPnC	249	0.49	(0.43, 0.55)
	2	174	1.38	(1.17, 1.61)	PCV7	241	0.04	(0.03, 0.04)
5	1	109	3.87	(3.40, 4.39)	13vPnC	252	1.33	(1.18, 1.50)
	2	175	2.13	(1.89, 2.41)	PCV7	197	0.20	(0.16, 0.24)
6A	1	109	5.00	(4.26, 5.88)	13vPnC	252	2.19	(1.93, 2.48)
	2	173	12.96	(11.04, 15.21)	PCV7	240	0.25	(0.21, 0.29)
7F	1	109	4.72	(4.23, 5.26)	13vPnC	252	2.57	(2.28, 2.89)
	2	175	4.22	(3.74, 4.77)	PCV7	248	0.04	(0.03, 0.04)
19A	1	109	7.68	(6.78, 8.71)	13vPnC	251	2.07	(1.87, 2.30)
	2	175	14.18	(12.37, 16.25)	PCV7	238	0.89	(0.79, 0.99)

[a] Group 1 includes children 15 through 23 months of age with ≥ 3 prior Prevnar doses. Group 2 includes children 24 through 59 months of age with ≥ 3 prior Prevnar doses.
[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.67,m5.3.5.1, CSR76155-report body.pdf, pages 63-64 (Table 9-6); 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page 83 (Table 9-6).

Safety Results:
The cohort 1 all-available population consisted of 124 children aged 15 through 23 months of age and 179 children 24 through 59 months of age.
Cohort 1/study group 1 included children 15 through 23 months of age given 3 prior PCV7 doses [n=37 (29%)] or 4 prior PCV7 doses [n=89 (71%)]. Cohort 1 study group 2 included children 24 through 59 months of age given 3 prior PCV7 doses [n=8 (4%)] or 4 prior PCV7 doses [n=172 (95%)].

Safety outcomes
Depending on the PCV7 immunization history, 13vPnC administered to toddlers 15 through 23 months of age constituted a 4th, 5th or 6th pneumococcal vaccination. Among toddlers who had received 3 prior PCV7 doses, 13vPnC vaccinations resulted in more local reactogenicity. The incidence of injection site tenderness increased

from 53.1% post-13vPnC dose 1 to 76.0% post-13vPnC dose 2. Significant tenderness (interfering with limb movement) increased from 10.3% to 23.8%. Among toddlers who previously received 4 prior PCV7 doses, subsequent 13vPnC vaccinations increased irritability rates. The incidence of irritability was 57.3% after 13vPnC dose 1 and 65.1% after dose 2. Antipyretic treatment use and frequency of irritability followed the same trends.

Table 135. Study 3011. Percentage of Toddlers 15 Through 23 Months Old Reporting Solicited Reactions Within 7 Days Following 13vPnC Dose 1

Solicited Reaction	3 Prior PCV7 doses	4 Prior PCV7 doses
	N[a]= 28-33 %	N[a]= 62-79 %
Tenderness		
Any	53.1	50.0
Interferes with limb movement	10.3	6.3
Fever[b]		
Mild	10.7	18.8
Moderate	7.1	3.2
Severe	0	0
Decreased appetite	56.7	36.2
Irritability	66.7	57.3
Hives	0	1.6
Prophylactic Antipyretic use	54.8	38.4
Treatment Antipyretic use	41.4	42.1

[a] Number of subjects reporting yes for at least 1 day or no for all days.
[b] Fever gradings: mild (≥38°C but ≤39°C), moderate (>39°C but ≤40°C), and severe (> 40°C). No other systemic event other than fever was graded.

Table 136. Study 3011. Percentage of Toddlers 15 Through 23 Months Old Reporting Solicited Reactions Within 7 Days Following 13vPnC Dose 2

Solicited Reaction	3 Prior PCV7 doses N[a]= 21-26 %	4 Prior PCV7 doses N[a]= 47-66 %
Tenderness		
Any	76.0	50.0
Interferes with limb movement	23.8	2.1
Fever[b]		
Mild	14.3	14.3
Moderate	0	6.4
Severe	0	0
Decreased appetite	27.3	45.5
Irritability	65.2	65.1
Hives	4.8	2.1
Prophylactic Antipyretic use	43.5	47.4
Treatment Antipyretic use	45.5	43.9

[a] Number of subjects reporting yes for at least 1 day or no for all days.
[b] Fever gradings: mild (≥38°C but ≤39°C), moderate (>39°C but ≤40°C), and severe (> 40°C). No other systemic event other than fever was graded.

Children 24 through 59 months old received 13vPnC as a 5th or 6th pneumococcal vaccination. Compared to toddlers, the incidence of local reactions increased, but systemic reactions occurred less often.

Table 137. Study 3011. Percentage of Children 24 Through 59 Months Old Reporting Solicited Reactions Within 7 Days Following 13vPnC Dose 1

Solicited Reaction	3 or 4 Prior PCV7 doses
	N[a]= 132-151 %
Tenderness	
Any	62.8
Interferes with limb movement	10.4
Fever[b]	
Mild	5.3
Moderate	0.8
Severe	0.8
Decreased appetite	24.6
Irritability	40.7
Hives	0.8
Prophylactic Antipyretic use	19.4
Treatment Antipyretic use	21.4

[a] Number of subjects reporting yes for at least 1 day or no for all days.
[b] Fever gradings: mild (≥38°C but ≤39°C), moderate (>39°C but ≤40°C), and severe (> 40°C). No other systemic event other than fever was graded.

After 13vPnC dose 1, local reactions occurring among toddlers 15 months to 23 months old ranged from 62.5%-64.1%. The injection site tenderness rate was ~50% for toddlers who previously received 3 or 4 PCV7 doses. One incremental PCV7 dose and 13vPnC supplemental vaccination raised fever (T ≥ 38.0C) rates from 17.8% to 22.0%, whereas moderate fever (T39.1C-40.0C) decreased from 7.2% to 3.2%. Irritability reported after one 13vPnC dose ranged from 57.3% to 66.7%, depending on the PCV7 immunization history. After two supplemental 13vPnC doses, the incidence of irritability was 65% for all toddlers. Increased antipyretic treatment use and frequency of irritability followed the same trends. The percentage of children 16 to 23 months old experiencing at least one systemic adverse reaction was 77.3% to 84.3%.

Table 138. Study 3011. Percentage of Toddlers 15 months to 23 months old Reporting Solicited Reactions Within 7 Days Following 13vPnC Dose 1

Solicited Reaction	3 Prior PCV7 doses	4 Prior PCV7 doses
	N[a]= 28-33 %	N[a]= 62-79 %
Tenderness		
Any	53.1	50.0
Interferes with limb movement	10.3	6.3
Fever[b]		
Mild	10.7	18.8
Moderate	7.1	3.2
Severe	0	0
Decreased appetite	56.7	36.2
Irritability	66.7	57.3
Hives	0	1.6
Prophylactic Antipyretic use	54.8	38.4
Treatment Antipyretic use	41.4	42.1

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

[b] Fever gradings: mild (≥38°C but ≤39°C), moderate (>39°C but ≤40°C), and severe (> 40°C). No other systemic event other than fever was graded.

Table 139. Study 3011. Percentage of Toddlers 15 months to 23 months old Reporting Solicited Reactions Within 7 Days Following 13vPnC Dose 2

Solicited Reaction	3 Prior PCV7 doses N[a]= 21-26 %	4 Prior PCV7 doses N[a]= 47-66 %
Tenderness		
Any	76.0	50.0
Interferes with limb movement	23.8	2.1
Fever[b]		
Mild	14.3	14.3
Moderate	0	6.4
Severe	0	0
Decreased appetite	27.3	45.5
Irritability	65.2	65.1
Hives	4.8	2.1
Prophylactic Antipyretic use	43.5	47.4
Treatment Antipyretic use	45.5	43.9

[a] Number of subjects reporting yes for at least 1 day or no for all days.
[b] Fever gradings: mild (≥38°C but ≤39°C), moderate (>39°C but ≤40°C), and severe (> 40°C). No other systemic event other than fever was graded.

Children 24 through 59 months of age, who completed a PCV7 infant series, received 13vPnC as a 5th pneumococcal vaccination. After one 13vPnC supplemental dose, 50.7% of children reported at least one systemic adverse reaction. Fever (T ≥ 38.0C) occurred in 6.9% of participants, and <1% was 68%, which was ~ 1.3 times more frequent than among toddlers.

Table 140. Study 3011. Percentage of Children 24 through 59 months of age Reporting Solicited Reactions Within 7 Days Following 13vPnC Dose 1

Solicited Reaction	4 Prior PCV7 doses
	N[a]= 132-151 %
Tenderness	
Any	62.8
Interferes with limb movement	10.4
Fever[b]	
Mild	5.3
Moderate	0.8
Severe	0.8
Decreased appetite	24.6
Irritability	40.7
Hives	0.8
Prophylactic Antipyretic use	19.4
Treatment Antipyretic use	21.4

[a] Number of subjects reporting yes for at least 1 day or no for all days.
[b] Fever gradings: mild (≥38°C but ≤39°C), moderate (>39°C but ≤40°C), and severe (> 40°C). No other systemic event other than fever was graded.

Summary and Conclusions

The safety and immunogenicity of a 13vPnC supplemental dose(s) was evaluated in PCV7-immunized children. Depending on the PCV7 immunization history, 13vPnC vaccination constituted a 4th, 5th or 6th pneumococcal vaccination. Two 13vPnC doses were given to toddlers 15 to 23 months of age. The frequency of local reactions (3 prior PCV7 doses) and irritability (4 prior PCV7 doses) increased after the 2nd 13vPnC dose, compared to respective reactions reported after the 1st 13vPnC dose. Relative to toddlers, the ~1.3 times more post-vaccination local reactions occurred in children 24 through 59 months of age, but systemic reaction were reported less often. Local and systemic reaction rates after 13vPnC supplemental vaccinations were consistent with peak corresponding rates for infant vaccines.

Post-vaccination 13vPnC immunogenicity data among toddlers (3 or 4 prior PCV7 doses) were reported as a combined group. Pneumococcal IgG and OPA toddler antibody responses were not assessed after the 1st 13vPnC dose. Following the 2nd toddler 13vPnC dose, IgG antibody responses to the 6 additional (non-PCV7) serotypes were higher relative to U.S. pivotal immunogenicity post-dose 3 infant responses. Among children ≥ 2 years to <5 years old, non-PCV7 IgG antibody responses were higher after one 13vPnC dose, relative to post-dose 3 infant 13vPnC responses. 13vPnC supplemental regimens resulted in lower antibody responses for certain non-PCV7 serotypes, compared to four routine infant 13vPnC vaccinations. It is not known whether the observation of lower GMCs is predictive of diminished effectiveness in preventing invasive disease in these older children.

10.0 Other Supportive Studies

10.1 Clinical Study Protocol # 6096A1-003

Clinical trials.gov identifier: NCT00205803

CSR # 62926: Infant series, toddler dose, and 6-month safety follow-up analyses.

Protocol Title: A phase 1/2, 2-Stage Randomized, Double-blind Trial of Safety, Tolerability, and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) in Healthy Infants.

10.1.1 Objective/Rationale

This was the first clinical evaluation of 13vPnC in infants. The study aimed to evaluate the safety and immunogenicity of 13vPnC compared to PCV7. Immune responses to antigens contained in DTaP-HBV-IPV (Pediarix) and PRP-T (ActHib) were assessed in a descriptive manner. Progression to stage 2 required a review of stage 1 safety and post-dose 3 IgG antibody levels to the 7 common pneumococcal serotypes. The initiation of a phase 3 study would be supported by an acceptable 13vPnC safety profile and preliminary evidence of non-interference to concomitantly administered childhood vaccines and immunogenicity following 13vPnC vaccination.

10.1.1.1 Stage 1 Objectives

The primary objective in stage 1 was to evaluate the safety of 13vPnC when administered to infants at 2, 4, and 6 months of age. The secondary objective was to assess post-dose 3 immune responses to the seven common PCV7 serotypes in infants receiving 13vPnC. The exploratory objective was to evaluate post-dose 3 immune responses to the additional 6 new non-PCV7 serotypes in infants receiving 13vPnC.

10.1.1.2 Stage 2 Objectives

Primary objectives:

1. To evaluate the safety of 13vPnC in infants receiving 13vPnC at 2, 4, and 6 months of age.
2. To compare seroresponse rates to the 7 common serotypes in infants who received 3 doses of 13vPnC with infants receiving 3 doses of PCV7.

Secondary objectives:

1. To evaluate the immune response to the serotypes in 13vPnC among subjects in each study group after 3 and 4 doses of study vaccine
2. To evaluate the safety of 13vPnC after the 4th dose, and (3) to evaluate the immune response to concomitantly administered DTaP, IPV, HBV, and Hib conjugate vaccines. The exploratory objective was to assess the proportion of subjects with opsonophagocytic antibody (OPA) to the 13 serotypes in 13vPnC.

10.1.2 Design Overview

This was a phase 1/2, parallel-group, 2-stage, randomized (1:1), active-controlled, double-blind, multicenter study. With approval from the data monitoring committee, the study could proceed to stage 2 based on safety and immunogenicity analyses performed after the last subject completed stage I.

Table 141: Study 003 Stage 1 Design

Population planned: n=40	Vaccine	Dosing Schedule	Concomitant Vaccines
n= 20	13vPnC	2, 4, and 6 months	DTaP-HBV-IPV (Pediarix) and PRP-T (ActHIB) at 2, 4, and 6 months
n= 20	PCV7 (Prevnar)		

Source: 125324/0.1,m5.3.5.1, CSR62926-protocol-amend.pdf

Table 142: Study 003 Stage 2 Design

Population planned:	Vaccine	Dosing Schedule	Concomitant Vaccines
Stage 1 subjects continuing into Stage 2	13vPnC	12-15 months	PRP-T (ActHIB) at 12-15 months
	PCV7		
192 additional subjects enrolled into Stage 2	**Vaccine**	**Dosing Schedule**	**Concomitant Vaccines**
n= 96	13vPnC	2, 4, 6, and 12-15 months	DTaP-HBV-IPV (Pediarix) at 2. 4. and 6 months; PRP-T (ActHIB) at 2, 4, 6, and 12-15 months
n= 96	PCV7 (Prevnar)		

Source: 125324/0.1,m5.3.5.1, CSR62926-protocol-amend.pdf

10.1.3 Protocol

10.1.3.1 Population

10.1.3.1.1 Study Period
The study period was September 2004 to August 2007.

10.1.3.1.2 Study sites and recruitment
Study 6096A1-003 was conducted at 19 sites in the United States.

10.1.3.1.3 Inclusion Criteria
Study 003 contained each inclusion criterion specified in study 004 and further limited eligibility to infants born at ≥ 36 weeks gestational age.

10.1.3.1.4 Exclusion Criteria
Study 003 exclusion criteria were similar to those used in study 004. However, study 003 did not include the following exclusion criteria: direct descendants of study site personnel; previous vaccination with hepatitis A, measles, mumps, rubella, or varicella vaccines; contraindication to vaccination with hepatitis A, measles, mumps, rubella, or varicella vaccines; and history of culture proven invasive disease caused by H. influenzae type b (Hib); or confirmed measles, mumps, rubella, or varicella infection.

10.1.3.1.5 Criteria for Temporarily Delaying Vaccine Administration
The criteria for temporarily delaying vaccine administration were identical to those in study 004.

10.1.3.1.6 Criteria for Withdrawal of a Subject From the Study
The criteria for withdrawal of a subject from the study were identical to those in study 004.

10.1.3.2 Concomitant medications
Antipyretic medications were permitted to prevent or treat symptoms related to study vaccination, and this information was collected on days 1 to 15 after vaccination.

10.1.3.3 Products mandated by the protocol
Children received the following study vaccines as per protocol.

13vPnC: Each 0.5ml dose contains 2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4ug saccharide for 6B individually conjugated to CRM_{197}. The total concentration of CRM_{197} is 29ug. The final formulation contains 5mM succinate buffer and 0.125 mg elemental aluminum as AlPO4. The vaccine is formulated as a liquid, appears as a homogeneous, white suspension after shaking, and is supplied in single-dose syringes. Route: IM; Lt thigh. Lot number: 7-5064-001A.

PCV7 [Prevnar; WLVP]: Each 0.5 ml dose includes 2 ug of saccharide from pneumococcal serotypes 4, 9V, 14, 18C, 19F, 23F, and 4 ug for serotype 6B. The total concentration of CRM_{197} carrier protein is 20ug CRM_{197} carrier protein. The final formulation contains 0.125mg of elemental aluminum as $AlPO_4$ adjuvant. This formulation is the same as the marketed product, Prevnar, but was filled in development facilities rather than commercial Prevnar lines. The vaccine is formulated as a white, liquid suspension and is supplied in single-dose syringes. Route: IM; Lt thigh. Lot number: 7-5029-008A.

DTaP-HBV-IPV [Pediarix; GSK]: Each 0.5ml dose includes 25 limits of flocculation (Lf) of diphtheria toxoid, 10 Lf of tetanus toxoid, 3 pertussis antigens (PT 25 µg, FHA 25 µg, PRN 8 µg), 10 µg of HBsAg, 40 D-antigen Units (DU) of type 1 Poliovirus (Mahoney), 8 DU of type 2 Poliovirus (MEF-1), 32 DU of type 3 Poliovirus (Saukett), 4.5 mg NaCl, and aluminum adjuvant (not more than 0.85 mg by assay). Each dose also contains ≤ 100 µg residual formaldehyde and ≤ 100 µg polysorbate 80. Neomycin sulfate and polymyxin B may also be present at ≤ 0.05ng and ≤ 0.01 ng respectively per dose. The vaccine appears as a turbid, white liquid suspension (after shaking vigorously), and it is packaged in single-dose vials. Route: IM; Rt thigh. Lot number: AC21B065AA.

PRP-T [ActHIB; Sanofi Pasteur SA]: Each 0.5ml dose contains 10ug purified capsular polysaccharide (PRP) conjugated to 24 ug of inactivated tetanus toxoid and 8.5% sucrose. The vaccine is a lyophilized preparation and packaged in a single dose vial. When reconstituted with saline, the vaccine is a clear, colorless liquid. Route: IM; Rt thigh (1½ to 2 inches apart from Pediarix site). Lot numbers: UE764AA, UE767AA, UE784AA, UE785AA, UE836AA, UE840AA, UE845AA, UE846AA, UE849AA, UE853AA, UE854AA, UE856AA, UE859AA, UE862AA, UE922AA, and UE962AE.

Permitted vaccines included HBV vaccine at birth. No other vaccines were to be administered concomitantly with the study vaccine.

10.1.3.4 Endpoints

Safety is the primary comparison of interest for stage I of the study, while the primary comparisons of interest for stage II of the study include both safety and immunogenicity.

10.1.3.4.1 Primary Immunogenicity Endpoints

The primary immunogenicity endpoint during stage II of the study includes the proportion of subjects achieving a post-dose 3 IgG antibody concentration ≥ 0.35 µg/mL to the 7 common pneumococcal serotypes.

10.1.3.4.2 Secondary Immunogenicity Endpoints

Stage 1:

1. Post-dose 3 GMCs to the 7 common pneumococcal serotypes.
2. Proportion of subjects achieving a post-dose 3 IgG antibody concentration of ≥ 0.15 and ≥ 0.5 µg/mL to each of the 7 common pneumococcal serotypes.

Stage 2:

1. Proportion of subjects achieving a post-dose 3 IgG antibody concentration ≥ 0.35 to the 6 new serotypes contained in 13vPnC.
2. Post-dose 3 GMCs to each of the 13 pneumococcal serotypes.
3. Proportion of subjects achieving a post-dose 3 IgG antibody concentration ≥ 0.15 and ≥ 0.50 µg/mL to each of the 13 pneumococcal serotypes.

10.1.3.4.3 Primary Safety Endpoint

Primary assessments during stage I and II include comparisons of safety between the two study groups after administration of 3 study vaccine doses to healthy infants and toddlers. During stage II, safety comparisons will also be made after administration of study dose 4. The primary endpoints for these safety comparisons include incidence rates for solicited local injection site reactions, solicited systemic events including fever ≥ 38^{o}C, and unsolicited AEs.

Solicited local reactions collected included erythema, induration/swelling, and tenderness at the site of the pneumococcal conjugate injection. Solicited systemic events collected included fever, decreased appetite, decreased sleep, increased sleep, and irritability. Unsolicited adverse events collected include symptoms requiring treatment, a clinic or ER visit, hospitalization, or life-threatening events during the subject's participation in the trial.

10.1.3.4.4 Stage 2 Exploratory Immunogenicity Endpoints

1. Proportion of subjects achieving a post-dose 4 IgG antibody concentration ≥ 0.15, ≥ 0.35, and ≥ 0.5 µg/mL to each of the 13 serotypes
2. Post-dose 4 GMCs to each of the 13 pneumococcal serotypes
3. Post-dose 3 geometric mean titers (GMTs) to each of the 13 pneumococcal serotypes
4. Proportion of subjects achieving an OPA titer ≥ 1:8 to the 13 serotypes
5. Post-dose 3 GMCs to diphtheria, tetanus, PRP, polio types 1-3, HBV, and pertussis
6. Proportion of subjects achieving the following prespecified antibody concentrations/titers against concomitant antigens

Table 143: Study 003, Pre-specified antibody concentrations/titers against concomitant antigens

Antibody	Post-dose 3 Endpoint
Anti-diphtheria toxoid	≥ 0.01 and ≥ 0.1 International Units (IU)/mL
Anti-tetanus toxoid	≥ 0.01 and ≥ 0.1 IU/mL
Pertussis (PT, FHA. PRN)	≥ the level (EU/mL) achieved by 95% of PCV7 subjects*
PRP	≥ 0.15 and ≥ 1.0 µg/mL
Anti-Hepatitis B surface antigen	≥ 10 mIU/mL
Polio type 1, 2, and 3	≥ 1:8 neutralizing titers

* Antibody level achieved by 95% of PCV7 subjects against each pertussis antigen were used as the comparison level between the two vaccine groups: 82 EU/mL for FHA, 43 EU/mL for PT, and 18 EU/mL for Pertactin (r69K).
Source: 125324/0.1,m5.3.5.1, CSR62926-report-body.pdf

10.1.3.5 Surveillance

10.1.3.5.1 Immunogenicity Monitoring

- Blood samples were obtained for immunogenicity analyses at the first study visit prior to the first vaccination (at 42-98 days of age), one month post-dose 3 (21-42 days after dose 3), at visit 5 prior to dose 4 (12-15 months of age), and one month post-dose 4 (21-42 days after dose 4).
- In a random subset of 60 subjects, post-dose 3 functional antibody responses to the 13vPnC serotypes were assessed by OPA. Post-dose 4 OPA analyses for serotypes 5, 6A, and 19A were performed post-hoc. These 3 serotypes were selected because higher than expected IgG antibody levels were observed for each serotype following PCV7 vaccination.
- Post-dose 3 blood samples from a random subset of 80 subjects was also analyzed for antibodies to concomitantly administered Hib conjugate, diphtheria, tetanus, pertussis, HBV, and inactivated polio vaccines.
- Any 13vPnC group subject with an antibody level < 0.15 µg/mL to 3 or more Prevnar serotypes, did not receive any additional doses of investigational product. Instead, these subjects received 1 dose of Prevnar at ~ 8 to 10 months of age and 1 dose of Prevnar at 12-15 months of age. Any subject with a PRP antibody titer < 1.0 µg/mL did not continue to receive investigational product; instead, these subjects received one dose of ActHIB at 8 to 10 months of age and one booster dose of ActHIB at 12-15 months of age. The two Prevnar or ActHIB doses were to be given at least 8 weeks apart (≥ 56 days).

Table 144: Study 6096A1-003 Serological Assays for Pneumococcal and Concomitant Vaccine Antigens

Antigen	Assay	Units	Blood Sample Obtained	Laboratory
13 pneumococcal serotypes	ELISA IgG Antibodies	µg/mL	Pre-dose 1 & 4, post-dose 3 & 4	EPP-CTAD†, Wyeth, Pearl River, NY
	OPA	titers	Post-dose 3	EPP-CTAD†, Wyeth, Pearl River, NY
Diphtheria toxoid	ELISA IgG Antibodies	IU/mL	Post-dose 3	b(4)
Tetanus toxoid	ELISA IgG Antibodies	IU/mL	Post-dose 3	b(4)
Pertussis (PT, FHA. PRN)	ELISA IgG Antibodies	EU/mL	Post-dose 3	b(4)
Polyribosylribitol phosphate (PRP)	ELISA IgG Antibodies	µg/mL	Post-dose 3	b(4)
Hepatitis B surface antigen	FDA approved in vitro diagnostic kit	mIU/mL	Post-dose 3	----------(b)(4)----------
Polio types 1, 2, and 3	In vitro plaque neutralization assay	Neutralizing antibody titers	Post-dose 3	----------(b)(4)----------

† Early Phase Programs – Clinical Testing and Assay Development (EPP-CTAD)
----------b(4)----------

Source: 125324/0.1,m5.3.5.1, CSR62926-report-body.pdf

10.1.3.5.2 Safety Surveillance / Monitoring

- Subjects were observed for 30 minutes following each vaccination for immediate reactions.
- Table 145 presents the number of days which solicited events were recorded by parents with the use of a memory aid.

Table 145: Safety Monitoring in Study 003

	Number of Days After Vaccination of Data Collection	
Prospectively Collected Data	**Stage I**	**Stage II**
Rectal Temperature	8 days†	5 days
Injection site reactions‡	15 days	8 days
Systemic Events Other than Fever*	15 days	15 days

† Temperature also measured any time a fever was suspected during days 1 to 15 after vaccination and if a fever develop, daily until resolution (i.e. temperature < 38°C for 1 day).
‡ The parent(s) / legal guardian(s) measured the size of erythema or induration with a caliper (1 to 14, and > 14 caliper unites) in whole number increments. Measurements were rounded up to the nearest whole number. Measurements were converted into centimeters (1 caliper unit = 0.5 cm) when entered into the clinical database.
* Includes use of antipyretic medication to prevent or treat symptoms related to vaccination.
Source: 125324/0.1,m5.3.5.1, CSR62926-protocol-amend.pdf

- Grading scales for solicited adverse events:
  - Erythema and induration: mild (0.5 - 2 cm), moderate (2.5 – 7 cm), severe (> 7 cm)
  - Tenderness: any (present); significant (interfered with limb movement)
  - Fever grading scale: mild (≥ 38°C), moderate (> 39°C), and severe (> 40°C)
  - No grading scale for decreased appetite, irritability, increased sleep, and decreased sleep.
- Erythema or induration at the injection site > 7 cm required an unscheduled visit for an assessment.
- During stage I, AEs occurring from the 1st to the post-third dose visit were collected. During stage II, AEs occurring from the 1st to the post-dose 3 visit, and from the 4th dose visit to the post-dose 4 visit were collected. Serious AEs (SAEs) were collected from study start to the final blood draw in both study stages. They were also collected at the 6-month safety telephone call in stage II of the study.
- Parents/legal guardians were reminded on day 3 to 4 and day 7 to 10 to complete their worksheets. Stage II, parents/legal guardians received an additional contact phone on day 16 to 18.
- In stage I, parents mailed memory aids back to study sites for data collection. Because of the delayed return of diaries by some parents during stage I, the protocol was revised so that diary data were

transcribed to paper case report forms (CRFs) by telephone during stage II. A diary card was considered collected if at least 1 value was recorded for any event for at least 1 day. A completed diary card had all expected data for all days with no missing data. Uncollected diary cards were considered not completed.

- Parents/legal guardians were contacted by telephone 6-months after the last vaccination regarding unexpected physician visits, emergency room visits, hospitalizations, or other SAEs since the last study visit. This includes rescue subjects who had insufficient post-dose 3 concentrations of either anti-PRP or IgG to ≥ 3 Prevnar serotypes at the end of stage I.
- Medical history and physical examination performed before each vaccination, and at the 7-month and 13- to 16-month visits.
- AEs categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

10.1.3.6 Statistical considerations

Statistical analyses were based on plan outlined in version 2 of the statistical analysis plan (SAP) for the study, dated May 19-2005. The stage II interim analysis was the primary analysis for the study. An internal Data Monitoring Committee (DMC) was established to monitor individual assay results after the 3rd dose and to perform an interim analysis for stage 1 of the study. In addition, an interim analysis post-dose 3 was performed by the study statistician when immunogenicity results were available for all subjects in stage 1 and 2. No adjustments for covariates and no adjustments for multiple comparisons were made in the immunogenicity analyses. Nonmissing values were not excluded from analysis except when comparing 2 or more variables at more than 1 time point for the same subject; in such cases, nonmissing values were dropped as the procedure required all values to be available. No analyses of subgroups were performed.

Blinding

To maintain the blind upon availability of assay data, the data were loaded into the database with scrambled subject identifiers and were not viewable to study team members. The database remained blinded for both interim analyses; but the statisticians who performed the interim analyses were provided with the unblinded treatment assignment codes and packaging assignment codes. A nonstudy statistician performed the first interim analysis at the end of stage I. After completion of the 6-month telephone follow-up contact in stage II, the study statistician performed the second interim analysis (i.e. the primary analysis); this was conducted after the medical monitor provided a list of protocol violations that excluded subjects from the evaluable populations. For subjects who met rescue criteria, the database was unblinded for the 6-month telephone follow-up contact.

10.1.3.6.1 Sample Size/Statistical Power

The sample size for stage I and the combined sample size for stages I and II were not based on statistical considerations. This study was not designed to test non-inferiority.

Stage 1:

In stage I, after accounting for dropouts, the study planned to enroll approximately 48 healthy infants between 6 and 14 weeks of age at approximately 8 sites in the US in order to ensure 20 evaluable subjects per group. The applicant states that a sample size of 20 subjects per group in Stage I:

- Allows the study to detect 35% to 40% decreases in the proportion of subjects achieving a pneumococcal IgG antibody concentration of ≥ 0.15 µg/mL, if the response rates in the PCV7 group range from 98% to 95% respectively; and
- Allows a 95% chance to detect any event that occurs with a frequency of at least 14%.

Stage 2:

In stage II, the subjects who received the infant series in stage I were to receive a 4th dose at 12 to 15 months of age concomitantly with ActHIB. Stage I subjects would proceed to stage II without needed to be re-enrolled. In addition, 192 new subjects (96 in each group) were planned to be enrolled at approximately 18 sites in the US to receive the full infant series and the toddler dose. Stage II of the study aimed to ensure 100 subjects per group, after accounting for dropouts. Although the study was not designed to formally test study

hypotheses, the applicant determined the following detectable differences and power for the comparisons of interest (assuming a sample size of 100 subjects per group and a 2-sided, type I error of 0.05):

- There is at least 80% power to detect a difference of 13.2% to 20.3% between groups in any local reactions or systemic events, if the reaction occurs at a frequency of 5% to 35% respectively.
- There is at least 84% power to declare non-inferiority for 5 of the 7 serotypes (4, 9V, 14, 18C, and 19F), with respect to the proportion of subjects achieving an antibody concentration ≥ 0.35 µg/mL, assuming a non-inferiority criterion of -0.10 and no difference in the true proportion between the groups.
- There is at least 90% power to declare non-inferiority for each serotype individually and greater than 85% power for all 7 serotypes in PCV7, with respect to the GMR assuming a 2-fold non-inferiority criterion and no difference in the true GMCs between the groups (i.e. GMR = 1.0).
- There is at least 82% power to declare non-inferiority with respect to the proportion of subjects achieving an antibody concentrations to concomitant vaccine antigens of at least a pre-specified level, assuming a non-inferiority criterion of -0.10 and no difference in the true proportion between the groups. The pre-specified levels were 0.15 µg/mL for PRP, 0.1 IU/mL for diphtheria and tetanus, 10MIU/mL for hepatitis B, and titers of 1:8 for polio type 1, 2, and 3. See section 1.3 of the SAP dated May 18, 2005 for additional details.

10.1.3.6.2 Study Cohorts Analyzed

For stage I and stage II post-dose 3 immunogenicity analyses, immunogenicity populations included an evaluable and an all-available post-dose 3 population. For post-dose 4 immunogenicity analyses in stage II, only an all-available population was used. Primary analyses were based on the evaluable immunogenicity populations. To be included in the all available immunogenicity population, subjects must have had at least 1 valid and determinate assay result related to the proposed analysis. To be included in the evaluable immunogenicity population, subjects must have met the following requirements:

- Received the vaccine to which they were randomly assigned
- Had blood drawn within protocol-specified timeframes
- Had valid and determinate assay results for the proposed analysis
- Had no other protocol violations

For safety analyses, a safety population was created for each dose and for each stage of the study. Populations used for Stage II analyses included subjects from stage I in their definition. Data from subjects who received at least 1 dose of study vaccine were included in the infant series safety analysis population; data from subjects who received the toddler dose were included in the toddler dose safety analysis population. Subjects discontinued from study participation were not replaced.

Protocol deviations that were determined by the medical monitor (before unblinding) to considerably affect clinical observations or immune response were considered major protocol violations. These violations resulted in a subject's exclusion from the evaluable and/or the all-available immunogenicity populations. Minor protocol deviations were not discussed in the study report, as they were determined to have no affect on the safety of the study subjects or the conduct or conclusions of the study.

10.1.3.6.3 Statistical Analyses

Immunogenicity analyses:

Proportions of subjects achieving an antibody concentration greater than or equal to any observed value was graphically displayed using reverse cumulative distribution curves (RCDCs). Proportions of subjects achieving anti-pneumococcal IgG antibody concentrations ≥ 0.15 µg/mL, ≥ 0.35 µg/mL, and ≥ 0.50 µg/mL were summarized by vaccine group with exact, 2-sided, 95% confidence intervals (CIs) on the difference in proportions (13vPnC-PCV7). Within each group and for each serotype and sampling point, GMCs were calculated with 2-sided, 95% CIs; to assess differences between the two groups, 2-sided, 95% CIs for the ratio (13vPnC:PCV7) were calculated.

For the seven common PCV7 serotypes, non-inferiority was declared in stage 2 if the lower bound of the 95% CI for the GMR was > 0.5 (2-fold criterion). For the additional 6-serotypes in the 13vPnC vaccine, statistical superiority was declared in stage II if the lower bound of the 95% CI for the GMR was > 1.

Similar statistical procedures were used for evaluation of the concomitant vaccine components and the OPA titers (i.e. GMCs, GMTs, or % of subjects achieving predefined levels were calculated along with corresponding 2-sided, 95% CIs).

Safety analyses:
Subjects were analyzed according to the vaccine received. The difference in proportions between the 13vPnC and PCV7 groups for stage 2 were tested using the 2-sided Fischer exact test; no CIs were calculated. SAEs were summarized for stage I and for the entire study.

Interim analyses:
Two interim analyses were planned. The first interim analysis was planned at the end of stage I. The second interim analysis was planned after all subjects completed their 7-month post-dose 3 visit, after assay data became available, and after the database was considered clean. The second interim analysis was considered the primary analysis, and all alpha was spent for this analysis. Data collected subsequent to the second interim analysis and their associated analyses were exploratory. A final analysis was performed after the post-dose 4 six-month follow-up visit, when all data had been collected.

Immunogenicity and safety were assessed by the internal monitoring committee (IMC) at the end of stage I, after all data from the initial 48 subjects in stage I were available.

Rescue Criteria (apply to 13vPnC subjects only):
The IMC also reviewed each subject's immune responses as they became available to determine if they met immunologic rescue criteria. Rescue criteria, which determined the need for additional vaccinations for subjects who received 13vPnC, included the following: (a) the post-dose 3 anti-PRP response was < 1.0 µg/mL or if (b) the post-dose 3 anti-pneumococcal IgG response for 3 or more Prevnar serotypes was < 0.35 µg/mL; if either occurred, the subject's random assignment was reviewed, and the investigator was notified of subjects assigned to the 13vPnC group so they would be withdrawn and given an additional dose of Hib, Prevnar, or both. If a subject was assigned to the PCV7 group or did not meet rescue criteria, the investigator was notified that the subject could proceed into stage 2.

Stopping criteria:
Based on analyses performed at the end of stage I, if any of the following criteria were met, the study was not to proceed into stage II, in order to allow further review of stage I findings:

- Three or more subjects in the 13vPnC group did not have pneumococcal IgG antibody concentrations ≥ 0.15 µg/mL for 3 or more of the seven PCV7 serotypes.
- Two or more subjects in the 13vPnC group developed severe local reactions after any of the 3 vaccinations.
- Two or more subjects in the 13vPnC group developed severe fevers beginning on days 1, 2, and 3 after any of the 3 vaccinations, without any identifiable signs or symptoms of infection.

10.1.4 Results

10.1.4.1 Populations Enrolled/Analyzed
A total of 249 subjects were enrolled into this study; 122 subjects were randomized to the 13vPnC group and 127 to the PCV7 group. The all-available infant series population consisted of 244 subjects (118 in the 13vPnC group and 126 in the PCV7 group); 4 subjects in the 13vPnC group and 1 subject in the PCV7 group were excluded because of no valid and determinate assay results. The evaluable infant series population consisted of 202 subjects (94 in the 13vPnC group and 108 in the PCV7 group); 28 subjects in the 13vPnC group and 19 in the PCV7 group were excluded. The reasons for these exclusions are included in Table 147.

During Stage I, 48 subjects were enrolled and randomized in a 1:1 ratio to either the 13vPnC group (24 subjects) or the PCV7 group (24 subjects). Thirty-eight infants (14 13vPnC subjects and 24 PCV7 subjects) from stage I of the study were able to proceed into stage II; these subjects were given a fourth dose of 13vPnC or PCV7 at 12 to 15 months of age. In stage II of the study, an additional 201 subjects were enrolled and randomized in a 1:1 ratio to receive either 13vPnC vaccine (98 subjects) or PCV7 (103 subjects) at 2, 4, 6, and 12 to 15 months of age.

The safety analysis population for each dose consisted of the following:

- Dose 1: 247 subjects – 121 in the 13vPnC group and 126 in the PCV7 group.
- Dose 2: 235 subjects – 113 in the 13vPnC group and 122 in the PCV7 group.
- Dose 3: 228 subjects – 109 in the 13vPnC group and 119 in the PCV7 group.
- Dose 4: 189 subjects – 86 in the 13vPnC group and 103 in the PCV7 group.

One subject (subject 003-009-000361) in the 13vPnC who received PCV7 instead of 13vPnC at the 3rd dose was excluded from the summaries of AEs in the infant series.

10.1.4.1.1 Subject Disposition and Follow-up

Stage I infant series (dose 1 to post-dose 3 blood draw):
All 48 enrolled subjects (24 per group) completed the 3 infant series doses during stage I. Eight out of 24 subjects (33.3%) in each group met the Hib rescue criteria. Two subjects (8.3%) in the 13vPnC group and 1 subject (4.2%) in the PCV7 group met the Prevnar rescue criteria. The 10 subjects in the 13vPnC group who met either rescue criteria were withdrawn from the study at the end of stage I. The 8 subjects in the 13vPnC group who met the Hib rescue criteria received an additional dose of Hib vaccine; and the 2 subjects in the 13vPnC group who met the Prevnar rescue criteria received an additional dose of Prevnar. Subjects in the PCV7 group who met rescue criteria continued in the study as they were receiving standard of care.

At the end of stage I, the DMC reviewed data from the first interim analysis. There were no subjects who experienced severe local reactions or severe fevers, and no 13vPnC recipient failed to achieve serotype-specific IgG antibody concentrations ≥ 0.15µg/mL for three or more Prevnar serotypes. Therefore, none of the stopping criteria were met and the DMC allowed the study to proceed to stage II.

Stage II infant series:
One subject in each group was not vaccinated following randomization during the stage II infant series because of parent/legal guardian request. Therefore, during stage II alone, 97 subjects in the 13vPnC group and 102 subjects in the PCV7 group were vaccinated. In stage I and II combined, a total of 249 subjects were enrolled; 122 subjects were randomized to the 13vPnC group and 127 subjects were randomized to the PCV7 group). A total of 247 subjects were vaccinated: 121 subjects in the 13vPnC group and 126 subjects in the PCV7 group. Twenty-nine subjects (11.6%) were withdrawn during the infant series, so that a total of 220 subjects (104 subjects in the 13vPnC group and 116 subjects in the PCV7 group) completed the 3-dose infant series. No subjects were withdrawn because of an AE.

Table 146: Study 6096A1-003 Summary of Subject Disposition for the Infant Series (Stage I and II)

	13vPnC N=122		PCV7 N=127		Total N=249	
	n	%	n	%	n	%
Randomized	122	100.0	127	100.0	249	100.0
Vaccinated						
Dose 1	121	99.2	126	99.2	247	99.2
Dose 2	115	99.4	122	96.1	237	99.5
Dose 3	110▼	90.2	118	92.9	228	91.6
Completed	104	85.2	116	91.3	220	88.4
Withdrawn	18	14.8	11	8.7	29	11.6
Reasons for withdrawal:						
Lost to follow-up	10	8.2	4	3.1	14	5.6
Parent / legal guardian request	2	1.6	5	3.9	7	2.8
Investigator request for noncompliance	3	2.5	1	0.8	4	1.6
Protocol violation†	1	0.8	0	0.0	1	0.4
Other‡	2	1.6	1	0.8	3	1.2
Evaluable immunogenicity population	94	77.0	108	85.0	202	81.1
Subjects excluded from Evaluable Population	28	23.0	19	15.0	47	18.9
Received PCV7 instead of 13vPnC at dose 3	1	0.8	0	0.0	1	0.4
Subjects withdrew and didn't receive all study conjugate vaccinations or concomitant vaccinations	11	9.0	9	7.1	21	8.4
Post-dose 3 blood draw > 42 days after 3rd dose	8	6.5	5	3.9	14	5.6
Did not have post-dose 3 blood draw	7	5.7	4	3.1	11	4.4
Received HBIG at birth	1	0.8	0	0.0	1	0.4
Received concomitant influenza vaccine	0	0.0	1	0.8	1	0.4
All-available immunogenicity population	118	96.7	126	99.2	244	98.0
Subjects excluded because had no assay result for any serotype	4	3.3	1	0.8	5	2.0

Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 46, 59, 161, and 162.
† Subject received hepatitis B immune globulin (HBIG) at birth.
‡ These 3 subjects were withdrawn because they lost their Kaiser Insurance and could no longer be seen at the Kaiser clinic, where the study was being conducted.
▼ Includes one subject who received PCV7 instead of 13vPnC at the 3rd dose.

Table 147: Study 6096A1-003, Summary of Subject Disposition for Dose 4 and 6-month follow-up (Stage II)

	13vPnC		PCV7		Total	
	n	%	n	%	n	%
Subjects enrolled and randomized	122	100.0	127	100.0	249	100.0
Completed infant series	104	85.2	116	91.3	220	88.4
Withdraw after completion of infant series	18	14.8	13	10.2	31	12.4
Reasons for withdrawal:						
Other[†]	10	8.2	4	3.1	14	5.6
Investigator request[‡]	3	2.5	2	1.6	5	2.0
Parent / legal guardian request	1	0.8	4	3.1	5	2.0
Lost to follow-up	2	1.6	1	0.8	3	1.2
Adverse event	1	0.8	1	0.8	2	0.8
Protocol violation[*]	1	0.8	1	0.8	2	0.8
Vaccinated toddler dose	86	70.5	103	81.1	189	75.9
Completed toddler dose	84	68.9	100	78.7	184	73.9
Withdrawn after toddler dose	4	3.3	3	2.4	5	2.0
Reason for withdrawal:						
Lost to follow-up	2	1.6	2	1.6	6	2.4
Completed study	80	65.6	98	77.2	178	71.5
Entered 6-month follow-up	90	73.8	106	83.5	196	78.7
Completed 6-month follow-up	82	67.2	99	78.0	181	72.7
Evaluable immunogenicity population	N/A	N/A	N/A	N/A	N/A	N/A
All-available immunogenicity population	85	69.7	102	80.3	187	75.1

Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 48 and 49 (Table 8-3 and 8-4)
[†] Includes ten 13vPnC subjects withdrawn because they met either Hib or Prevnar rescue criteria, 3 PCV7 subjects withdrawn because of lost medical insurance and inability to be seen at the Kaiser clinic, and 1 PCV7 subject withdrawn because eligibility criteria were no longer met following a febrile seizure after dose 3.
[‡] The investigator requested withdrawal of 5 subjects because of noncompliance.
[*] One subject in the 13vPnC received a nonstudy vaccine and 1 subject in the PCV7 group received the 12-month vaccinations outside of the protocol-defined window.

10.1.4.1.2 Subject Demographics

Table 148 provides a summary of subject demographics for the evaluable infant immunogenicity population. The PCV7 group had slightly more males, slightly less females, and slightly less Hispanics compared to the 13vPnC study group. All other demographic characteristics were similar between the two groups.

Table 148: Study 6096A1-003 Demographic characteristics of evaluable infant immunogenicity population

	13vPnC		PCV7		Total	
	n	%	n	%	n	%
Sex						
Male	46	48.9	59	54.6	105	52.0
Female	48	51.1	49	45.4	97	48.0
Race						
Black	22	23.4	27	25.0	49	24.3
Hispanic	7	7.4	3	2.8	10	5.0
Asian	1	1.1	0	0.0	1	0.5
Other	6	6.4	9	8.3	15	7.4
White	58	61.7	69	63.9	127	62.9
Age at first vaccination (weeks)						
Mean (SD)	9.2 (1.5)		9.1 (1.2)		9.2 (1.3)	
Median	9.0		9.1		9.1	
Range	6.1 – 13.8		6.0 – 12.1		6.0 – 13.8	

Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 61.

10.1.4.2 Immunogenicity Endpoints/Outcomes

10.1.4.2.1 Post-dose 3 Pneumococcal Serotype Immunogenicity Outcomes

Eight of 24 subjects (33.3%) in each group met Hib rescue criteria. Two of 24 (8.5%) 13vPnC recipients met the pneumococcal rescue criteria compared to 1 of 24 (4.2%) PCV7 recipients. Subjects in the 13vPnC group who met either rescue criteria were withdrawn.

Proportion of subjects achieving a post-dose 3 pneumococcal IgG antibody concentration ≥ 0.35µg/mL and an OPA titer ≥ 1:8:
For the 7 common serotypes, the IgG seroresponse rate ≥ 0.35µg/mL for each serotype was similar between the 13vPnC and PCV7, with overlapping 95% confidence intervals. Except for 19F, the percentage of participants achieving an OPA titer ≥ 1:8 was at least 92%.

IgG seroresponse rates for the 6 additional serotypes were at least 96.8% in the 13vPnC group. The OPA seroresponse rate for serotype 19A, serotype 3, and serotype 1 was 77.3%, 80.0%, and 83.3% respectively in the 13vPnC group. The OPA response for the three remaining non-PCV7 serotypes in the 13vPnC group was at least 96%.

6B/6A cross-reactivity:
Inclusion of serotype 6A in the 13vPnC vaccine increased the IgG antibody response to this serotype from 36/106 (34.0%) to 90/93 (96.8%). Inclusion also resulted in a similar increase in the proportion of subjects achieving an anti-6A OPA titer ≥ 1:8 from 14/29 (48.3%) to 24/25 (96.0%). The increases in IgG antibody response rate and OPA response rate indicate that most of the cross-reactive anti-6A antibodies induced by serotype 6B are functional.

19F/19A cross-reactivity:
Inclusion of serotype 19A in the 13vPnC vaccine increased the IgG antibody response to this serotype from 94.4% to 100%, and it increased the OPA response from 3/24 (12.5%) to 17/22 (77.3%). Although serotype 19F induced a significant cross-reactive IgG antibody response to 19A among PCV7 subjects, the IgG response (94.4%) did not correlate with high functional antibody response (12.5%).

Table 149. Study 6096A1-003. 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	94	91	96.8	(91.0, 99.3)	107	106	99.1	(94.9, 100.0)	-2.3	(-8.1, 2.3)
6B	94	83	88.3	(80.0, 94.0)	107	95	88.8	(81.2, 94.1)	-0.5	(-9.9, 8.7)
9V	94	91	96.8	(91.0, 99.3)	108	107	99.1	(94.6, 100.0)	-2.3	(-8.1, 2.3)
14	94	92	97.9	(92.5, 99.7)	107	104	97.2	(92.0, 99.4)	0.7	(-5.0, 6.2)
18C	94	91	96.8	(91.0, 99.3)	106	105	99.1	(94.9, 100.0)	-2.3	(-8.2, 2.4)
19F	94	92	97.9	(92.5, 99.7)	106	103	97.2	(92.0, 99.4)	0.7	(-4.8, 6.3)
23F	94	89	94.7	(88.0, 98.3)	108	103	95.4	(89.5, 98.5)	-0.7	(-7.8, 5.9)
Additional										
1	94	92	97.9	(92.5, 99.7)	108	27	25.0	(17.2, 34.3)	72.8	(63.3, 81.1)
3	94	93	98.9	(94.2, 100.0)	107	15	14.0	(8.1, 22.1)	84.9	(76.7, 91.1)
5	93	93	100.0	(96.1, 100.0)	107	45	42.1	(32.6, 52.0)	57.9	(48.0, 67.2)
6A	93	90	96.8	(90.9, 99.3)	106	36	34.0	(25.0, 43.8)	62.8	(52.3, 72.2)
7F	94	93	98.9	(94.2, 100.0)	105	7	6.7	(2.7, 13.3)	92.3	(85.3, 96.5)
19A	94	94	100.0	(96.2, 100.0)	107	101	94.4	(88.2, 97.9)	5.6	(1.2, 11.9)

[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) expressed as a percentage.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC - PCV7, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 63 (Table 9-3).

Table 150. Study 6096A1-003. Comparison of Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ 1:8 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	30	29	96.7	(82.8, 99.9)	33	33	100.0	(89.4, 100.0)
6B	27	25	92.6	(75.7, 99.1)	30	28	93.3	(77.9, 99.2)
9V	27	27	100.0	(87.2, 100.0)	27	27	100.0	(87.2, 100.0)
14	27	27	100.0	(87.2, 100.0)	30	30	100.0	(88.4, 100.0)
18C	27	27	100.0	(87.2, 100.0)	30	29	96.7	(82.8, 99.9)
19F	25	21	84.0	(63.9, 95.5)	25	20	80.0	(59.3, 93.2)
23F	27	25	92.6	(75.7, 99.1)	26	26	100.0	(86.8, 100.0)
Additional								
1	30	25	83.3	(65.3, 94.4)	32	2	6.3	(0.8, 20.8)
3	25	20	80.0	(59.3, 93.2)	29	1	3.5	(0.1, 17.8)
5	30	30	100.0	(88.4, 100.0)	33	2	6.1	(0.7, 20.2)
6A	25	24	96.0	(79.7, 99.9)	29	14	48.3	(29.5, 67.5)
7F	22	22	100.0	(84.6, 100.0)	24	5	20.8	(7.1, 42.2)
19A	22	17	77.3	(54.6, 92.2)	24	3	12.5	(2.7, 32.4)

[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, CSR62926-report body.pdf, page 70 (Table 9-6).

Post-dose 3 IgG Geometric Mean Concentrations (GMCs) and OPA Geometric Mean Titers (GMTs):
Table 151 presents post-dose 3 GMC values achieved by subjects in the evaluable infant immunogenicity population. Results in the all-available population were similar. For each of the 7 common serotypes, GMCs were lower in the 13vPnC group compared to the PCV7 group. In particular, post-dose 3 GMCs were noticeabley lower in the 13vPnC group compared to the PCV7 group for serotypes 4, 18C, and 23F. Subjects in the 13vPnC group achieved a lower OPA GMTs for serotypes 4 and 23F and a higher OPA GMT for serotype 19F compared to the PCV7 group. The OPA GMTs for the remaining common serotypes were similar between the two study groups.

PCV7 subjects did produce some antibodies to the six non-PCV7 serotypes, especially with regards to serotypes 19A, 5, and 6A. Inclusion of 6A and 19A in the 13vPnC vaccine increased IgG GMCs by 9.4 fold (from 0.25µg/mL to 2.36µg/mL) for 6A and by 1.7 fold (from 1.12µg/mL to 1.93µg/mL) for 19A. Inclusion of 6A and 19A increased OPA GMTs by 32.3 fold (from 28.4 to 916.5) for 6A and by 7.2% (from 5.3 to 38.7) for 19A. Therefore inclusion of 6A and 19A resulted in larger increases in OPA GMTs compared to the increases in IgG GMCs.

Table 151. Study 6096A1-003. Comparison of 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	94	1.81	(1.54, 2.13)	107	2.40	(2.01, 2.87)	0.76	(0.59, 0.96)
6B	94	2.74	(2.02, 3.71)	107	2.86	(2.09, 3.91)	0.96	(0.62, 1.48)
9V	94	1.52	(1.29, 1.78)	108	1.78	(1.55, 2.05)	0.85	(0.69, 1.05)
14	94	4.24	(3.44, 5.23)	107	5.19	(4.13, 6.52)	0.82	(0.60, 1.11)
18C	94	1.53	(1.30, 1.80)	106	2.46	(2.08, 2.91)	0.62	(0.49, 0.79)
19F	94	2.21	(1.87, 2.61)	106	2.58	(2.17, 3.08)	0.86	(0.67, 1.09)
23F	94	1.39	(1.15, 1.67)	108	1.81	(1.51, 2.19)	0.77	(0.59, 1.00)
Additional								
1	94	2.57	(2.14, 3.08)	108	0.06	(0.05, 0.09)	39.78	(27.47, 57.63)
3	94	1.40	(1.20, 1.62)	107	0.09	(0.07, 0.11)	15.56	(11.63, 20.81)
5	93	2.41	(2.07, 2.80)	107	0.28	(0.22, 0.34)	8.67	(6.65, 11.29)
6A	93	2.36	(1.89, 2.94)	106	0.25	(0.20, 0.30)	9.60	(7.07, 13.04)
7F	94	1.85	(1.62, 2.11)	105	0.07	(0.06, 0.08)	26.78	(20.97, 34.22)
19A	94	1.93	(1.64, 2.27)	107	1.12	(0.96, 1.32)	1.71	(1.36, 2.16)

[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] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC to PCV7
[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).
Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 67 (Table 9-5).

Table 152. Study 6096A1-003. Comparison of Pneumococcal OPA GMTs After Dose 3 of the Infant Series (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]
PCV7						
4	30	456.1	(280.6, 741.4)	33	618.5	(427.2, 895.5)
6B	27	696.7	(312.3, 1554.4)	30	615.9	(316.5, 1198.6)
9V	27	2328.5	(1210.3, 4479.8)	27	1584.3	(887.1, 2829.4)
14	27	1896.2	(1111.5, 3234.9)	30	1742.2	(1188.3, 2554.2)
18C	27	612.8	(349.4, 1074.8)	30	615.9	(390.5, 971.4)
19F	25	54.2	(29.5, 99.6)	25	41.1	(21.6, 78.2)
23F	27	525.3	(260.0, 1061.2)	26	970.8	(612.1, 1539.7)
Additional						
1	30	45.3	(25.8, 79.5)	32	4.7	(3.6, 6.1)
3	25	11.5	(8.1, 16.3)	29	4.1	(3.9, 4.3)
5	30	250.2	(159.8, 391.6)	33	5.4	(3.5, 8.1)
6A	25	916.5	(500.4, 1678.6)	29	28.4	(12.4, 65.2)
7F	22	2113.6	(1348.1, 3313.5)	24	9.2	(4.5, 19.0)
19A	22	38.7	(18.2, 82.2)	24	5.3	(3.8, 7.5)

[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] 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 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, CSR62926-report body.pdf, page 71 (Table 9-7).

10.1.4.2.2 Pre- and Post-dose 4 Pneumococcal Serotype Immunogenicity Outcomes
(All available Population Only)

Opsonophagocytic activity of antibodies to serotypes 6A and 19A were assessed post-hoc due to apparent cross-reactivity observed after three completed PCV7 vaccinations.

Pre and post-dose 4 IgG GMCs and OPA GMTs:
With the exception of serotype 3, post-dose 4 GMCs were higher than post-dose 3 GMCs for all serotypes in both treatment groups. The GMC for serotype 5 increased from 0.28 µg/mL (95% CI 0.23, 0.35) post-dose 3 to 0.40 µg/mL (95% CDI 0.31, 0.50) pre-dose 4, to 0.56 (95% CI 0.45, 0.70) one month post-dose 4.

Compared to the PCV7 group, post-dose 4 GMCs were lower in the 13vPnC group for 6 of the 7 common serotypes. Post-dose 4 GMCs were 0.3, 0.25, 0.37, and 0.3 times lower in the 13vPnC group compared to the PCV7 group for serotypes 4, 14, 18C, and 23F respectively. The response to type 19F after dose 4 was 0.6 times higher in the 13vPnC group compared to the PCV7 group. GMCs in the 13vPnC group for the remaining common serotypes (types 6B and 9V) were 7% lower compared to the PCV7 group. IgG GmCs pre-dose 4 followed the same trends as post-dose 4 IgG antibody response

For the 6 additional serotypes, there was some antibody production among PCV7 subjects in response to serotypes 5, 6A, and 19A. Inclusion of 6A and 19A in the 13vPnC vaccine increased IgG GMCs by 4.8% (from 1.68 µg/mL to 80.6 µg/mL) for 6A and by 2.0% (from 2.82 µg/mL to 5.60 µg/mL) for 19A. Inclusion of 6A and 19A in the 13vPnC vaccine increased OPA GMCs by 3.6% (from 599.9 to 2147.58) for 6A and by 21.9% (from 36.62 to 802.2) for 19A. Thus, inclusion of 6A and 19A resulted in larger increases in OPA GMTs compared to IgG GMCs.

Table 153. Study 6096A1-003. Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 4 (Evaluable Toddler Immunogenicity Population)

	Vaccine Group As Randomized											
	13vPnC						PCV7					
	Pre-Vaccination			Post-Vaccination			Pre-vaccination			Post-Vaccination		
Serotype	N[a]	GMC[b]	(95% CI)[c]	N[a]	GMC[b]	(95% CI)	N[a]	GMC[b]	(95% CI)[c]	N[a]	GMC[b]	(95% CI)[c]
PCV7												
4	83	0.33	(0.28, 0.40)	78	2.86	(2.31, 3.55)	100	0.48	(0.41, 0.56)	94	4.09	(3.34, 5.00)
6B	82	0.84	(0.69, 1.03)	78	11.03	(8.78, 13.86)	98	0.95	(0.77, 1.18)	93	11.85	(9.63, 14.56)
9V	83	0.43	(0.37, 0.51)	78	2.55	(2.15, 3.02)	100	0.43	(0.37, 0.50)	94	2.75	(2.37, 3.18)
14	83	1.59	(1.27, 2.00)	78	7.68	(6.08, 9.70)	100	2.00	(1.66, 2.41)	93	10.24	(8.23, 12.74)
18C	83	0.25	(0.22, 0.30)	78	2.57	(2.08, 3.18)	100	0.40	(0.34, 0.46)	94	4.08	(3.42, 4.87)
19F	82	0.81	(0.66, 1.00)	78	6.34	(5.06, 7.94)	100	0.60	(0.49, 0.72)	93	3.97	(3.26, 4.85)
23F	83	0.29	(0.24, 0.36)	78	3.36	(2.70, 4.18)	100	0.38	(0.31, 0.47)	93	4.79	(3.86, 5.94)
Additional												
1	83	0.68	(0.56, 0.82)	78	3.44	(2.79, 4.23)	90	0.04	(0.03, 0.04)	91	0.03	(0.03, 0.04)
3	83	0.27	(0.23, 0.32)	78	1.11	(0.94, 1.33)	98	0.09	(0.07, 0.12)	92	0.10	(0.08, 0.12)
5	83	1.01	(0.87, 1.18)	78	3.92	(3.27, 4.69)	92	0.40	(0.31, 0.50)	78	0.56	(0.45, 0.70)
6A	82	0.81	(0.68, 0.96)	78	8.06	(6.60, 9.85)	96	0.27	(0.22, 0.33)	92	1.68	(1.27, 2.21)
7F	83	0.58	(0.50, 0.67)	78	2.67	(2.26, 3.16)	91	0.04	(0.03, 0.05)	85	0.05	(0.04, 0.06)
19A	83	0.85	(0.67, 1.09)	78	5.60	(4.60, 6.83)	100	0.64	(0.52, 0.79)	93	2.82	(2.32, 3.41)

[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] Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 80 (Table 9-11).

Table 154. Study 6096A1-003. Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 4 (Evaluable Toddler 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	78	2.86	(2.31, 3.55)	94	4.09	(3.34, 5.00)	0.70	(0.52, 0.94)
6B	78	11.03	(8.78, 13.86)	93	11.85	(9.63, 14.56)	0.93	(0.69, 1.26)
9V	78	2.55	(2.15, 3.02)	94	2.75	(2.37, 3.18)	0.93	(0.74, 1.16)
14	78	7.68	(6.08, 9.70)	93	10.24	(8.23, 12.74)	0.75	(0.55, 1.03)
18C	78	2.57	(2.08, 3.18)	94	4.08	(3.42, 4.87)	0.63	(0.48, 0.83)
19F	78	6.34	(5.06, 7.94)	93	3.97	(3.26, 4.85)	1.59	(1.18, 2.15)
23F	78	3.36	(2.70, 4.18)	93	4.79	(3.86, 5.94)	0.70	(0.52, 0.95)
Additional								
1	78	3.44	(2.79, 4.23)	91	0.03	(0.03, 0.04)	101.48	(77.24, 133.32)
3	78	1.11	(0.94, 1.33)	92	0.10	(0.08, 0.12)	11.25	(8.37, 15.11)
5	78	3.92	(3.27, 4.69)	78	0.56	(0.45, 0.70)	6.98	(5.26, 9.27)
6A	78	8.06	(6.60, 9.85)	92	1.68	(1.27, 2.21)	4.81	(3.39, 6.83)
7F	78	2.67	(2.26, 3.16)	85	0.05	(0.04, 0.06)	54.62	(41.23, 72.37)
19A	78	5.60	(4.60, 6.83)	93	2.82	(2.32, 3.41)	1.99	(1.51, 2.62)

[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] Confidence intervals (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.
[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).
Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 81 (Table 9-12).

Table 155: Post-dose 4 Geometric Mean OPA Titers and Treatment Comparisons for Pneumococcal Serotypes in Study 6096A1-003 (All-Available Toddler Immunogenicity Population)

	Vaccine Group (as Randomized)					
	13vPnC			PCV7		
Serotype	N[a]	GMT[b]	(95% CI[c])	N[a]	GMT[b]	(95% CI[c])
6A	73	2147.58	(1630.73, 2828.23)	70	599.9	(375.83, 957.54)
19A	71	802.24	(633.92, 1015.24)	72	36.62	(21.09, 63.59)

[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 CI based on the Student t distribution for the mean logarithm of the titers.
[d] Ratio of GMTs; 13vPnC to PCV7.
[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).
Source: 125324/0.1,m5.3.5.1, CSR-62926-opa-addendum, page 11 (Table 3-2).

Post-dose 4 serotype-specific anti-pneumococcal OPA antibody titers ≥ 1:8:
Consistent with post-dose 3 responses to the 6 additional serotypes, subjects who received 4 doses of PCV7 achieved cross-reactivity with regards to functional antibody production against serotypes 6A and 19A.

Table 156: Number (%) of Subjects Achieving Post-dose 4 serotype-specific OPA antibody titer ≥ 1:8 and Treatment Comparisons in Study 6096A1-003 (All-Available Toddler Immunogenicity Population)

	Vaccine Group (as Randomized)							
	13vPnC				PCV7			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
6A	73	73	100	(95.1, 100.0)	70	63	90	(80.5, 95.9)
19A	71	71	100	(94.9, 100.0)	72	37	51.4	(39.3, 63.3)

[a] N = number of subjects with a determinate posttoddler dose 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 (CI) based upon the observed proportion of subjects.
[d] Difference in proportions, expressed as a percentage.
[e] Exact 2-sided CI for the difference in proportions, 13vPnC – PCV7, expressed as a percentage.
Source: 125324/0.1,m5.3.5.1, CSR-62926-opa-addendum, page 8 (Table 3-1).

10.1.4.2.3 Concomitant Vaccine Immunogenicity Results

The immunogenicity for all vaccine antigens contained in DTaP-HBV-IPV and Hib vaccines was assessed one month post-dose 3 as an exploratory endpoint. The proportion of subjects in the 13vPnC group achieving the pre-specified endpoint for pertussis toxoid (PT) was lower compared to the PCV7 group (89.2% versus 95.6%). Whereas a higher proportion of 13vPnC subjects achieved the pre-specified 0.15µg/mL and 1.0µg/mL PRP endpoints compared to the PCV7 group. The proportion of subjects achieving all other concomitant antigen endpoints was similar.

Table 157. Study 6096A1-003. Comparison of Subjects Achieving a Pre-specified antibody Concentration for Concomitant Vaccine Antigens After Dose 3 (Evaluable Infant Immunogenicity Population)

		Vaccine Group As Randomized									
		13vPnC				PCV7					
Concomitant Vaccine Antigen	Comparison level	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]	Differ-ence[d]	(95% CI)[e]
Hib (PRP)	≥ 0.15 µg/mL	84	75	89.3	(80.6, 95.0)	87	75	86.2	(77.2, 92.7)	3.1	(-7.2, 13.7)
	≥ 1.0 µg/mL	84	59	70.2	(59.3, 79.7)	87	55	63.2	(52.2, 73.3)	7.0	(-7.3, 21.1)
Diphtheria	≥ 0.1 IU/mL	38	38	100.0	(90.8, 100.0)	48	48	100.0	(92.6, 100.0)	0.0	(-9.4, 7.7)
	≥ 0.1 IU/mL	38	38	100.0	(90.8, 100.0)	48	48	100.0	(92.6, 100.0)	0.0	(-9.4, 7.7)
Tetanus											
	≥ 0.01 IU/mL	38	38	100.0	(90.8, 100.0)	48	48	100.0	(92.6, 100.0)	0.0	(-9.4, 7.7)
	≥ 0.1 IU/mL	38	38	100.0	(90.8, 100.0)	48	48	100.0	(92.6, 100.0)	0.0	(-9.4, 7.7)
Polio											
Type 1	≥ 1:8	61	61	100.0	(94.1, 100.0)	64	64	100.0	(94.4, 100.0)	0.0	(-6.0, 5.7)
Type 2	≥ 1:8	61	60	98.4	(91.2, 100.0)	64	64	100.0	(94.4, 100.0)	-1.6	(-8.8, 4.2)
Type 3	≥ 1:8	61	60	98.4	(91.2, 100.0)	63	63	100.0	(94.3, 100.0)	-1.6	(-8.8, 4.2)
Hepatitis B	≥10 mIU/mL	38	38	100.0	(90.8, 100.0)	48	48	100.0	(92.6, 100.0)	0.0	(-9.4, 7.7)
Pertussis											
FHA	≥ 40.5 EU/mL	65	61	93.9	(85.0, 98.3)	68	65	95.6	(87.6, 99.1)	-1.7	(-11.0, 7.0)
PT	≥ 16.5 EU/mL	65	58	89.2	(79.1, 95.6)	68	65	95.6	(87.6, 99.1)	-6.4	(-17.0, 3.2)
PRN	≥ 26 EU/mL	65	63	96.9	(89.3, 99.6)	68	65	95.6	(87.6, 99.1)	1.3	(-6.8, 9.7)

[a] N = number of subjects with a determinate postinfant series antibody concentration to the given concomitant antigen.
[b] n = Number of subjects with an antibody concentration ≥ prespecified level for the given concomitant antigen.
[c] Exact 2–sided confidence interval based upon the observed proportion of subjects.
[d] Difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[e] Exact 2–sided confidence interval for the difference in proportions, 13vPnC – PCV7, expressed as a percentage.
[f] Comparison level = the level that 95% of the subjects in the PCV7 group achieve.
Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 74 (Table 9-8).

Table 158. Study 6096A1-003. Comparison of Concomitant Vaccine Antigen GMCs After Dose 3 (Evaluable Infant Immunogenicity Population)

		Vaccine Group As Randomized							
		13vPnC N[a]=103			PCV7 N[a]=114				
Concomitant Vaccine Antigen	Units	N[b]	GMC[c]	(95% CI)[d]	N[b]	GMC[c]	(95% CI)[d]	Ratio[e]	(95% CI)[f]
Hib (PRP)	µg/mL	84	1.99	(1.34, 2.97)	87	1.64	(1.09, 2.47)	1.21	(0.69, 2.14)
Diphtheria	IU/mL	38	0.86	(0.65, 1.14)	48	1.04	(0.80, 1.34)	0.83	(0.57, 1.21)
Tetanus	IU/mL	38	0.93	(0.72, 1.22)	48	0.97	(0.73, 1.28)	0.97	(0.66, 1.42)
Polio									
Type 1	NA titer[g]	61	483.72	(352.52, 663.75)	64	479.79	(361.79, 636.26)	1.01	(0.66, 1.53)
Type 2	NA titer	61	368.26	(250.75, 540.84)	64	403.45	(294.90, 551.96)	0.91	(0.56, 1.49)
Type 3	NA titer	61	914.01	(638.80, 1307.80)	63	812.75	(577.32, 1144.18)	1.12	(0.69, 1.84)
Hepatitis B	mIU/mL	38	1257.74	(904.77, 1748.42)	48	1300.01	(976.91, 1729.99)	0.97	(0.63, 1.48)
Pertussis									
FHA	EU/mL	65	207.85	(178.72, 241.74)	68	225.12	(191.97, 264.01)	0.92	(0.74, 1.15)
PT	EU/mL	65	98.68	(82.89, 117.49)	68	96.58	(86.45, 107.89)	1.02	(0.83, 1.25)
PRN	EU/mL	65	141.23	(113.02, 176.48)	68	135.51	(107.13, 171.41)	1.04	(0.76, 1.44)

[a] N = Number of subjects with a postinfant series blood sample.
[b] n = Number of subjects with a determinate antibody concentration for the specified concomitant antigen.
[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
[d] Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations.
[e] Ratio of GMCs; 13vPnC to PCV7.
[f] 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).
[g] NA titer – Neutralizing antibody titer.
Source: 125324/0.1,m5.3.5.1, CSR62926-report body.pdf, page 75 (Table 9-9).

10.1.4.3 Safety Outcomes

10.1.4.3.1 Immediate Reactions

Although immediate reactions were collected and reported along with other unsolicited adverse events, these events could not be idenitifed from the data submitted to the BLA. The specific time-to-onset of symptoms was not recorded, therefore reactions that occurred within 30 minutes of vaccination could not be identified.

10.1.4.3.2 Solicited Local Reactions

Table 159 presents the incidence of solicited local adverse events at the 13vPnC and PCV7 sites occurring within 15 days following each of doses 1 through 3 and within 8 days following dose 4. The most common solicited local reaction after each of the first 3 doses was tenderness. The most common local reaction after dose 4 was erythema in the 13vPnC group. Any tenderness was reported in 22.4 - 34.5% of 13vPnC subjects, and tenderness interfering with limb movement was reported in 1.8 - 8.4% of 13vPnC subjects. A staitically significantly lower number of subjects in the 13vPnC group experienced significant tenderness interfering with limb movement after the second dose (1.8%) compared to the Prevnar group (8.5%). There were no severe cases of induration or erythema. The frequency of all solicited local reactions peaked after dose 1.

Table 159: Solicited Local Reactions Occurring Within 15 days after Doses 1, 2, and 3 and Within 8 days after Dose 4 in Study 6096A1-003.

	Actual Treatment Group																			
	13vPnC								PCV7											
	N[a]				%				N[b]				%				p-value[c]			
	Dose				Dose				Dose				Dose				Dose			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Tenderness																				
Any	41	31	26	19	34.5	28.2	24.3	22.4	54	43	30	30	43.5	36.4	25.6	29.7	0.1	0.2	0.9	0.32
Significant[d]	10	2	5	2	8.4	1.8	4.7	2.4	7	10	7	4	5.6	8.5	6.0	4.0	0.46	0.03	0.8	0.69
Induration																				
Any	26	18	18	16	21.8	16.4	16.8	18.8	24	23	22	17	19.4	19.5	18.8	17.0	0.6	0.6	0.7	0.85
0.5 - 2.0 cm	24	18	18	16	20.2	16.4	16.8	18.8	22	20	20	17	17.9	17.1	17.2	17.0	0.7	>0.99	>0.99	0.85
2.5 - 7.0 cm	4	4	0	2	3.4	3.6	0.0	2.4	3	4	5	3	2.4	3.4	4.3	3.0	0.7	>0.99	0.06	>0.99
> 7.0 cm	0	0	0	0	0.0	0.0	0.0	0.0	0	0	0	0	0.0	0.0	0.0	0.0	>0.99	>0.99	>0.99	>0.99
Erythema																				
Any	25	18	19	21	21.0	16.2	17.8	24.7	24	21	23	19	19.4	17.8	19.7	19.0	0.7	0.9	0.7	0.37
0.5 - 2.0 cm	24	15	17	21	20.2	13.6	16.0	24.7	24	20	21	16	19.4	17.1	18.1	16.2	>0.99	0.6	0.7	0.20
2.5 - 7.0 cm	3	3	1	3	2.5	2.8	0.9	3.5	0	0	3	5	0.0	0.0	2.6	5.1	0.1	0.1	0.6	0.73
> 7.0 cm	0	0	0	0	0.0	0.0	0.0	0.0	0	0	0	0	0.0	0.0	0.0	0.0	>0.99	>0.99	>0.99	>0.99

***** Number of 13vPnC subjects with known values: Dose 1: 119; Dose 2: 108-111; Dose 3: 106-107; Dose 4: 85.
Number of PCV7 subjects with known values: Dose 1: 123-124; Dose 2: 117-118; Dose 3: 116-117; Dose 4: 99-101.
[a] Number of subjects with known values.
[b] Number of subjects with the given characteristic.
[c] Two (2)-sided Fisher Exact test. p-values are not corrected for multiple comparisons.
[d] Significant = present and interfered with limb movement.
Source: 125324/0.1,m5.3.5.1, CSR-62926-report-body, pages 91-93 and 98 (Tables 10-3 to 10-5 and 10-9).

Among subjects who received the first three doses of 13vPnC vaccine, tenderness reactions ranged from 1-5 days in duration; induration reactions ranged from 1-12 days in duration; and erythema reactions ranged 1-5 days duration following any of the infant series doses. The mean duration of local reactions after the first three doses ranged from 1.4 to 2.9 for all solicited local reactions. Following the 4th dose, tenderness and erythema reactions ranged from 1-9 days in duration; induration reactions ranged from 1-12 days in duration. The mean duration of local reactions after dose 4 ranged from 1.9 to 3.4.

10.1.4.3.3 Solicited Systemic Reactions

Table 160 presents the incidence of solicited systemic adverse events occurring within 15 days following each of doses 1 through 4 of 13vPnC and PCV7. Irritability was the most frequently reported solicited systemic adverse event. The incidence of mild and moderate fever and decreased sleep peaked after dose 2. The incidence of decreased appetite, increased sleep and irritability peaked after dose 1. 13vPnC group subjects were statistically significantly less likely to have increased sleep reported after the fourth dose (p=0.033).

Table 160: Solicited Local Reactions Occurring Within 15 days after Doses 1, 2, 3, and 4 in Study 6096A1-003.

	Actual Treatment Group																			
	13vPnC								PCV7											
	N[a]				%				n[b]				%				p-value[c]			
	Dose				Dose				Dose				Dose				Dose			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Fever[d]																				
38.0°C ≤ x ≤ 39.0°C	19	22	20	11	16.7	21.6	20.0	14.1	20	28	23	12	16.5	24.6	20.4	12.8	>.99	0.631	>.99	0.825
39°C < x ≤ 40.0°C	3	4	2	2	2.7	3.9	2.0	2.6	1	4	1	0	0.8	3.5	0.9	0.0	0.355	>.99	0.603	0.201
> 40°C	0	0	0	0	0.0	0.0	0.0	0.0	0	0	0	0	0.0	0.0	0.0	0.0	>.99	>.99	>.99	>.99
Decreased appetite	36	25	29	19	30.5	22.7	27.1	22.4	39	27	36	22	31.5	22.9	30.8	21.8	0.89	>.99	0.559	>.99
Decreased sleep	22	27	23	11	18.6	24.5	21.5	13.1	22	23	22	15	17.7	19.5	18.8	14.9	0.869	0.424	0.621	0.833
Increased sleep	67	47	37	24	56.3	42.3	34.6	27.9	67	55	48	44	54.0	46.6	41.0	43.6	0.797	0.595	0.338	0.033
Irritability	79	69	55	33	66.9	62.7	51.4	38.8	88	67	63	48	71.0	56.8	53.8	47.5	0.578	0.418	0.789	0.24

***** Number of 13vPnC subjects with known values: Dose 1: 113-119; Dose 2: 102-111; Dose 3: 100-107; Dose 4: 76-86.
Number of PCV7 subjects with known values: Dose 1: 121-124; Dose 2: 113-118; Dose 3: 113-117; Dose 4: 94-101.

[a] Number of subjects with known values.

[b] Number of subjects with the given characteristic.

[c] Two (2)-sided Fisher Exact test. p-values are not corrected for multiple comparisons.

[d] 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: 125324/0.1,m5.3.5.1, CSR-62926-report-body, pages 101-103 and 108 (Tables 10-11 to 10-13 and 10-17).

Among subjects who received four doses of 13vPnC vaccine, mild fevers ranged from 1-6 days in duration, moderate fevers lasted for 1 day, and all other solicited systemic events other than fever ranged from 1-22 days in duration. The mean duration was 1.1 to 1.8 days for mild fever. The mean duration for all other systemic events other than fever was 2.8 to 5.7 days.

Antipyretic Use:
13vPnC group subjects were statistically significantly less likely to have been given antipyretic medication after the fourth dose to prevent vaccine-related symptoms compared to PCV7 group subjects (p=0.008).

Table 161. Study 6096A1-003, Number of subjects who received antipyretics to treat symptoms or to prevent symptoms within 15 days following doses 1-3 and within 8 days following dose 4 of 13vPnC or PCV7.

	Use of Antipyretics to Treat Symptoms		Use of Antipyretics to Prevent Symptoms	
Dose number	13vPnC n (%)	PCV7 n (%)	13vPnC n (%)	PCV7 n (%)
1	N[a]=94 42 (44.7)	N=101 35 (34.7)	N=95 28 (29.5)	N=101 34 (33.7)
2	N=86 42 (48.8)	N=96 48 (50.0)	N=86 30 (34.9)	N=96 31 (32.3)
3	N=84 36 (42.9)	N=94 45 (47.9)	N=83 30 (36.1)	N=93 40 (43.0)
4	N=85 25 (29.4)	N=101 28 (27.7)	N=85 15 (17.6)*	N=102 36 (35.3)*

[a] Number of subjects reporting yes for at least 1 day or no for all days
* p=0.008 (two-sided Fisher Exact test). p-values are not corrected for multiple comparisons.
Source: 125324/0.1,m5.3.5.1, CSR-62926-report-body, pages 101-103 and 108 (Tables 10-11 to 10-13 and 10-17).

10.1.4.3.4 Unsolicited Adverse Events

Unsolicited adverse events were reported by 104/120 (86.7%) subjects in the 13vPnC group and 110/126 (87.3%) subjects in the PCV7 group following doses 1, 2, or 3. There were no statistically significant differences between the two vaccine groups in the rates of any AEs reported in subjects following the first three doses. The most frequently reported adverse events during the infant series were upper respiratory tract infections (13vPnC: 47.5%, PCV7: 51.6%), otitis media (13vPnC: 33.3%, PCV7: 29.4%), bronchioloitis (13vPnC: 13.3%, PCV7: 12.7%), and conjunctivitis (13vPnC: 10.8%, PCV7: 12.7%). Four subjects in the 13vPnC group and zero subjects in the PCV7 group reported immune system disorders (p=0.055). Three of these events may have been attributable to seasonal allergy, a drug exposure and a chemical exposure. Oral candidiasis was reported more frequently in the 13vPnC group (8/120, 6.7%) than in the PCV7 group (2/126, 1.6%) (p=0.055). However, there was no difference between the two vaccine groups in the frequency of all candida infections (oral candidiasis, candidiasis, skin candida, and candida nappy rash, 13vPnC: 18/120, 15.0%; PCV7: 17/126, 13.5%).

Unsolicited adverse events were reported by 30/86 (34.9%) subjects in the 13vPnC group and 51/103 (49.5%) subjects in the PCV7 group within 30 days after the fourth dose. Following the 4th dose, the most frequently reported adverse events were upper respiratory tract infections (13vPnC: 9.3%, PCV7: 9.7%), rhinorrhoea (13vPnC: 3.5%, PCV7: 2.9%), and croup infections (13vPnC: 3.5%, PCV7: 1.0%). Otitis media was reported in a statistically significantly lower proportion of subjects in the 13vPnC group (1.2%) compared to the PCV7 group (9.7%).

Unsolicited adverse events occurring in at least 1% of 13vPnC subjects and in more 13vPnC subjects compared to PCV7 subjects include the following:

- Following doses 1-3 (n_{13vPnC}=120, n_{PCV7}=126): otitis media (33.3%, 29.4%), bronchitis (13.3%, 12.7%), rhinorrhea (9.2%, 6.3%), (8.3%, 4.8%), canidida nappy rash (6.7%, 5.6%), gastroenteritis (6.7%, 4.0%), oral candidiasis (6.7%, 1.6%), gastroenteritis viral (3.3%, 2.4%), decreased appetite (3.3%, 2.4%), umbilical hernia (3.3%, 1.6%), pharyngitis (3.3%, 0.8%), asthma (2.5%, 1.6%),

bronchial hyperreactivity (2.5%, 1.6%), seborrhoeic dermatitis (2.5%, 1.6%), respiratory syncytial virus bronchioloitis (2.5%, 1.6%), viral rash (2.5%, 1.6%), dacryostenosis congenital (2.5%, 1.6%), teething (1.7%, 1.6%), insomnia (1.7%, 1.6%), rash macular (1.7%, 0.8%), food intolerance (1.7%, 0.8%), granuloma (1.7%, 0.0%), xerosis (1.7%, 0.0%), acrodermatitis (1.7%, 0.0%), body tinea (1.7%, 0.0%), fall (1.7%, 0.0%), leukocytosis (1.7%, 0.0%), and rhinitis allergic (1.7%, 0.0%).

- Dose 4 safety population (n_{13vPnC}=86, n_{PCV7}=103): middle ear effusion (1.2%, 0.0%), constipation (1.2%, 0.0%), stomatitis (1.2%, 0.0%), candida nappy rash (1.2%, 0.0%), conjunctivitis viral (1.2%, 0.0%), croup infections (3.5%, 1.0%), nasopharyngitis (1.2%, 1.0%), pharyngitis streptococcal (1.2%, 0.0%), respiratory tract infection viral (1.2%, 0.0%), sinusitis (1.2%, 0.0%), tonsillitis (1.2%, 0.0%), viral pharyngitis (1.2%, 1.0%), viral upper respiratory tract infection (1.2%, 0.0%), arthropod bite (2.3%, 1.9%), cardiac murmur (1.2%, 0.0%), weight gain poor (1.2%, 0.0%), penile adhesion (1.2%, 1.0%), asthma (1.2%, 0.0%), cough (1.2%, 1.0%), rhinorrhoea (3.5%, 2.9%), status asthmaticus (1.2%, 0.0%), dermatitis (0.2%, 0.0%), dermatitis allergic (1.2%, 0.0%), dermatitis diaper (1.2%, 1.0%), eczema (1.2%, 0.0%), and urticaria (1.2%, 0.0%).

10.1.4.3.5 Serious Adverse Events

No subjects died during the course of the study. Table 162 presents a list of SAEs reported during the study period. There were no statistically significant differences in the incidence of SAEs between the vaccine groups.

Table 162: Study 6096A1-003, Summary of SAEs Occurring Doses 1-3.

	Actual Treatment Group					
	13vPnC N = 120			PCV7 N = 126		
System Organ Class / Preferred Term	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Any event	9	7.5	23	9	7.1	13
Blood and lymphatic system disorders	2	1.7	2	0	0.0	0
Leukocytosis	1	0.8	1	0	0.0	0
Lymphadenitis	1	0.8	1	0	0.0	0
Congenital, familial and genetic disorders	1	0.8	1	0	0.0	0
Arnold-chiari malformation	1	0.8	1	0	0.0	0
Gastrointestinal disorders	1	0.8	1	0	0.0	0
Vomiting	1	0.8	1	0	0.0	0
General disorders and administration site conditions	2	1.7	3	1	0.8	1
Pyrexia	1	0.8	1	1	0.8	1
Irritability	1	0.8	2	0	0.0	0
Infections and infestations	7	5.8	9	8	6.3	10
Bronchiolitis	3	2.5	3	3	2.4	3
Gastroenteritis	1	0.8	1	1	0.8	1
Otitis media	2	1.7	2	0	0.0	0
Pneumonia	0	0.0	0	2	1.6	2
Respiratory syncytial virus bronchiolitis	1	0.8	1	1	0.8	1
Cystitis	1	0.8	1	0	0.0	0
Meningitis pneumococcal	0	0.0	0	1	0.8	1
Staphylococcal skin infection	1	0.8	1	0	0.0	0
Urinary tract infection	0	0.0	0	1	0.8	1
Viral diarrhea	0	0.0	0	1	0.8	1
Metabolism and nutrition disorders	2	1.7	4	2	1.6	2
Dehydration	2	1.7	3	2	1.6	2
Hypoglycaemia	1	0.8	1	0	0.0	0
Nervous system disorders	2	1.7	3	0	0.0	0
Febrile convulsion	1	0.8	1	0	0.0	0
Sensory integrative dysfunction	1	0.8	1	0	0.0	0
Tethered cord syndrome	1	0.8	1	0	0.0	0

[a] The number of subjects reporting at least 1 event of the type specified. For "Any Event" it represents the number of subjects reporting at least 1 event of any kind.
[b] The total number of events of the type specified. Subjects can be represented more than once. For "Any Event" it represents the total number of events.
[c] Two (2)-sided Fisher Exact test.
Note: Subject 000361 received vaccine other than that to which he was randomized at dose 3; therefore he is not counted in any treatment group.
Source: 125324/0.1,m5.3.5.1, CSR-62926-report-body, pages 133-134 (Tables 10-30).

Table 163: Summary of SAEs Occurring Within 1 Month After Dose 4 in Study 6096A1-003

	Actual Treatment Group					
	13vPnC N = 86			PCV7 N = 103		
System Organ Class / Preferred Term	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Any event	1	1.2	3	0	0.0	0
Infections and infestations	1	1.2	2	0	0.0	0
Conjunctivitis viral	1	1.2	1	0	0.0	0
Respiratory tract infection viral	1	1.2	1	0	0.0	0
Respiratory, thoracic and mediastinal disorders	1	1.2	1	0	0.0	0
Status asthmaticus	1	1.2	1	0	0.0	0

[a] The number of subjects reporting at least 1 event of the type specified. For "Any Event" it represents the number of subjects reporting at least 1 event of any kind.
[b] The total number of events of the type specified. Subjects can be represented more than once. For "Any Event" it represents the total number of events.
[c] Two (2)-sided Fisher Exact test.
Note: Relationship to study treatment was assessed by the investigator.
Source: 125324/0.1,m5.3.5.1, CSR-62926-report-body, pages 135 (Tables 10-31).

Table 164 presents a line list of all SAEs occurring after dose 1-3 in study 003.

Table 164: Study 6096A1-003, Listing of SAEs Occurring After Vaccination in Study 6096A1-003

Site-Subject Number	Vaccine Group	Dose	Preferred Term (MedDRA)	Time to Onset (Days)[a]	Duration (Days)	Severity[b]
Doses 1-3						
004-000140	13vPnC	3	Bilateral Otitis Media	37	20	MO
		3	Dehydration	37	3	SE
		3	Vomiting	37	3	SE
005-000188	13vPnC	3	Chairi I malformation	127	-	SE
		3	Dehydration	91	6	SE
		3	Dehydration	125	4	SE
		3	Gastroenteritis	91	6	SE
		3	Hypoglycemia	91	6	MO
		3	Irritability	125	-	MO
		3	Irritability	125	-	SE
		3	Otitis media	125	4	MO
		3	Sensory integration disorder	125	-	MO
		3	Tethered cord syndrome	127	-	MO
006-000219	13vPnC	2	Bronchiolitis	56	37	MO
006-000224	13vPnC	3	Bronchiolitis	17	22	SE
006-000240	13vPnC	1	Fever unknown origin	15	3	SE
		1	Leukocytosis	15	3	SE
009-000343	13vPnC	3	Febrile seizure	193	1	MO
009-000358	13vPnC	3	Bronchiolitis	21	8	MO
		3	Cystitis	246	15	MO
		3	Lymphadenitis	251	10	MO
106-000843	13vPnC	3	Bronchiolitis RSV	7	3	MO
206-000914	13vPnC	3	Staphylococcal infection (Hand)	100	15	SE
001-000004	PCV7	3	Pneumococcal meningitis	57	18	LT
004-000141	PCV7	2	Right upper & left lower lobe pneumonia	42	23	MO
		2	Urinary tract infection	42	5	MO
005-000198	PCV7	3	Dehydration	79	3	SE
		3	Gastroenteritis	79	3	SE
		3	Rotaviral diarrhea	78	9	SE
006-000218	PCV7	2	Pneumonia right middle lobe	61	6	MO
006-000242	PCV7	1	Dehydration	23	3	MI
		1	Febrile illness (fever)	23	3	MI
007-000253	PCV7	2	Bronchiolitis	9	3	MO
106-000841	PCV7	3	Bronchiolitis	28	3	SE
206-000919	PCV7	3	Bronchiolitis	101	22	MI
206-000921	PCV7	1	RSV Positive Bronchiolitis	26	60	SE
Dose 4						
106-000843	13vPnC	4	Status asthmaticus	9	3	SE
		4	Viral conjunctivitis	9	3	MI
		4	Viral respiratory infection	9	3	MI
6-month follow-up						
006-000226	13vPnC	4	Bronchiolitis	134	15	SE
		4	Viral URI	134	15	MO
		4	Status asthmaticus	140	2	SE
006-000240	13vPnC	4	Complex febrile seizure	32	1	SE
		4	Fever of unknown origin	32	1	SE
006-000243	13vPnC	4	Asthma exacerbation	34	15	SE
		4	RSV positive bronchiolitis	148	6	SE
		4	Status asthmaticus	148	6	SE
206-000904	13vPnC	4	Seizure	103	2	SE
106-000855	PCV7	4	Asthma exacerbation	122	11	SE

RSV = Respiratory syncytial virus

[a] Days since most recent vaccine dose.
[b] Event severity of mild (MI), moderate (MO), severe (SE), or life-threatening (LT) was assessed by the investigator.
Source: 125324/0.1,m5.3.5.1, CSR-62926-report-body, pages 129-132 (Tables 10-27 to 10-29)).

10.1.4.3.6 Clinical Case narratives

Clinical case narratives are provided for two subjects who AEs resulting in withdrawal from the study.

Subject 6096A1-003-009-000004

Fifty-seven days after the 3rd PCV7 vaccination, this male infant was brought to an outpatient clinic with a history of fever, irritability, lethargy, and vomiting for 2 days. On exam, the infant had a temperature of 104°F and was noted to have a stiff neck and bulging anterior fontanelle. Lumbar pucture was consistent with a bacterial meningitis; the infant was hospitalized and started on empiric intravenous antibiotic treatment. Blood and CSF cultures both grew penicillin-susceptible *Streptococcus pneumoniae*. The CDC performed serotyping on the isolate and determined it to be serotype 33F. The infant was discharged on approximately hospital day 9 and continued IV antibiotics for about 10 more days. Follow-up testing performed approximately two months later revealed profound hearing loss in the right ear (hearing screening at birth had been normal). The adverse event is persistent due to persistent sequelae of sensorineural hearing loss. The infant was withdrawn from the study because he met culture confirmed invasive pneumococcal disease exclusion criterion.

Subject 6096A1-003-009-000343

Approximately 6 months after the 3rd 13vPnC vaccination 3, this infant developed fever and seizure-like activity witness by his grandparents. He was diagnosed with a febrile seizure and was not admitted. The cause of the fever was suspected to be from a viral illness, although a subsequent urine culture grew E. coli. The infant has recovered from this event. The subject was withdrawn approximately two months after this event because the infant met the significant neurological disorder exclusion criterion.

10.1.4.4 Summary and Conclusions

Study 6096A1-003 was a Phase 1/2 safety and immunogenicity trial in U.S. infants. A preliminary assessment of immune responses to concomitant childhood vaccination was included in the study design.

10.1.4.4.1 Safety

Overall, the rates of solicited local and systemic adverse events in the 13vPnC group were similar to adverse events in the Prevnar group. There was no imbalance in rates of serious adverse events between the 13vPnC and PCV7 groups. No subjects died during the course of the study. One subject was diagnosed with bacterial meningitis 57 days after the 3rd dose of PCV7 due to *S. pneumoniae* serotype 33F (a non-vaccine serotype).

10.1.4.4.2 Immunogenicity

Study 6096A1-003 was a hypothesis generating study for planning a phase 3 confirmatory immunogenicity trial.

13vPnC post-vaccination immune responses:
Following 13vPnC dose 3, IgG seroresponse rates for the 7 common serotypes were similar to corresponding responses following PCV7 vaccination. The 95% confidence intervals for each seroresponse were overlapping. IgG GMCs to serotypes 4,18C, and 23F were lower among 13vPnC recipients compared to PCV7 recipients. OPA GMT analyses showed that for each serotype functional antibody was present (OPA $\geq$1:8) after 13vPnC vaccination; and,the OPA GMTs among the two vaccine groups were similar (i.e., within one titer dilution) for each serotype. Post-dose 3 IgG seroresponse rates for the 6 additional serotypes were at least 96.8% in the 13vPnC group. After administration of 13vPnC, there is a high IgG polysaccharide-binding antibody response to serotype 6A and to serotype 19A, and the antibodies produced are functional for both serotypes. With the exception of serotype 3, post-dose 4 GMCs were higher than post-dose 3 GMCs for all serotypes in both treatment groups. Relative to the PCV7 group, post-dose 4 GMCs were lower in the 13vPnC group for 6 of the 7 common serotypes.

Post-vaccination immune responses to the 6 additional serotypes among Prevnar recipients:
Anti-6A IgG antibody responses post-PCV7 vaccinations were higher than expected, which is in part due to cross-reactivity with serotype 6B. Following PCV7 vaccination, increases in anti-19A IgG antibodies represented non-functional antibody production. OPA titers remained low. Serotype 5 IgG and OPA antibody responses followed the same trend as 19A. The anti-serotype 5 GMC value was noted to increase gradually at each blood draw. The GMCs for serotype 5 were 0.28 (95% CI 0.22, 0.34) one month post-dose 3, 0.40 (95% CI 0.31, 0.50) just before the 4th dose (at ~ 12-15 months of age), and 0.56 (95% CI 0.45, 0.70) one month after the fourth dose. This phenomenon, therefore, seems to suggest that the anti-serotype 5 antibody production may not be related to vaccination.

Concomitant Vaccinations:
ubjects in the 13vPnC group had lower seroresponse rates to pertussis toxin, but GMCs were similar between the two groups. Similar immune responses were observed between the two vaccine groups for all other vaccine antigens contained in DTaP-HBV-IPV and PRP-T vaccines.

13vPnC safety, measurable opsonophagocytic activity to 13 serotypes following 13vPnC vaccination, and a dose-response following the 4th 13vPnC vaccination support the vaccination schedule used for phase 3 infant studies.

10.2 Clinical Study Protocol # 6096A1-006

Clinical trials.gov registry identifier: NCT00366340

CSR #69237 (infant) and 74361 (toddler and 6-month safety follow-up)

Protocol Title: A phase 3, randomized, active-controlled, double-blind trial evaluating the safety, tolerability, and immunologic non-inferiority of a 13-valent Pneumococcal Conjugate (PnC) Vaccine compared to a 7-valent PnC vaccine in healthy infants given in a 2-, 3-, 4-, and 11- to 12-month schedule with routine pediatric vaccinations in Germany.

10.2.1 Objective/Rationale

The study was designed to meet the following objectives:

Primary objectives:

1. To demonstrate that the immune responses to the 7 common pneumococcal conjugates induced by 13vPnC are noninferior to the immune responses induced by PCV7, when measured 1 month after the third dose.
2. To demonstrate that the immune responses to the 6 additional pneumococcal conjugates induced by 13vPnC are noninferior to the lowest immune response elicited by a pneumococcal serotype contained in PCV7, when measured 1 month after the third dose.
3. To demonstrate that the immune responses induced by Infanrix hexa given with 13vPnC are noninferior to the immune responses induced by Infanrix hexa given with PCV7 when measured 1 month after the third dose. Responses to the following antigens in Infanrix hexa were assessed: hepatitis B, Hib, and diphtheria.

Safety objective:

To evaluate the acceptability of the safety profile of the 13vPnC, as measured by the incidence of local injection site reactions, systemic events, and adverse events (AEs).

Secondary objectives:

1. To assess the pneumococcal immune response induced by 13vPnC relative to the immune response induced by PCV7, when measured 1 month after the toddler dose.
2. To assess the immune responses induced by Infanrix hexa, given with 13vPnC, relative to the immune responses induced by Infanrix hexa, given with PCV7, when measured 1 month after the toddler dose. Responses to the following antigens in Infanrix hexa were assessed: hepatitis B, Hib, and diphtheria.
3. To assess the immune responses induced by Infanrix hexa given with 13vPnC relative to the immune responses induced by Infanrix hexa, given with PCV7, at alternative cutoff levels, when measured 1 month after the third dose and 1 month after the toddler dose. Responses to the following antigens in Infanrix hexa were assessed: diphtheria and Hib.

Exploratory objective:

To assess the level of 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 (100 subjects/group).

10.2.2 Design Overview

Table 165. Study 006 design: Phase 3, parallel-group, randomized, active-controlled, double-blind, multi-center study

Population n= 600 (Planned enrollment)	Vaccine	Dosing Schedule	Concomitant Vaccines	Blood Draws
n= 300	13vPnC	2, 3, 4, and 11-12 mo	DTaP-HBV-IPV-PRP-T (Infanrix hexa) at 2, 3, 4, and 11-12 mo	1 mo post-dose 3 Pre-dose 4 1 mo post-dose 4
n= 300	PCV7 (Prevnar)			

10.2.3 Protocol

10.2.3.1 Population

10.2.3.1.1 Study Period
The study period was from October 19, 2006 to April 23, 2008. August 13, 2007 was the date of last infant series blood draw and the end of the infant series phase of the study.

10.2.3.1.2 Study sites and recruitment
Study 6096A1-006 was conducted at 56 sites in Germany.

10.2.3.1.3 Inclusion Criteria
The protocol specified time frame for age at enrollment ranged from 56 to 112 days in study 006, whereas in study 004, it ranged from 42 to 98 days. All other inclusion criteria in study 006 were identical to those in study 004.

10.2.3.1.4 Exclusion Criteria
Measles, Mumps, Rubella, Varicella, and Hepatitis A vaccines were not vaccines mandated or permitted in study 006. Therefore, prior receipt of any of these vaccines was not an exclusion criterion. A contraindication to vaccination with measles, mumps, rubella, varicella, and/or Hepatitis A vaccine, and a history of confirmed measles, mumps, rubella, or varicella infection were also not exclusion criteria in study 006. Because subjects were to receive 4 doses of hepatitis B vaccine in study 006, previous vaccination with hepatitis B vaccine was considered an exclusion criterion. All other exclusion criteria in study 006 were identical to those in study 004.

10.2.3.1.5 Criteria for Temporarily Delaying Vaccine Administration
The criteria for temporarily delaying vaccine administration were identical to those in study 004.

10.2.3.1.6 Criteria for Withdrawal of a Subject From the Study
The criteria for withdrawal of a subject from study 006 were identical to those in study 004.

10.2.3.2 Concomitant medications
Concomitant medications permitted during the study period in study 006 were identical to those allowed in study 004.

10.2.3.3 Vaccine administration
Children received the following study vaccines as per protocol.

13vPnC: Each 0.5ml dose contains 2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4ug saccharide for 6B individually conjugated to cross-reacting material 197 (CRM_{197}). The total concentration of CRM_{197} is 29ug. The final formulation contains 5mM succinate buffer and 0.125 mg aluminum as AlPO4. The vaccine is formulated as a liquid and appears as a

homogeneous, white suspension after shaking. The vaccine was filled in containers that were identical to those containing PCV7. Route: intramuscular (IM), anterolateral left thigh. Lot number: 7-5093-003A.

PCV7 [Prevnar; WLVP]: Each 0.5 ml dose includes 2 ug of saccharide from pneumococcal serotypes 4, 9V, 14, 18C, 19F, 23F; 4 ug serotype 6B, 20ug CRM_{197} carrier protein, and 0.125mg of aluminum as $AlPO_4$ adjuvant. The vaccine is formulated as a white, liquid suspension, and packaged in single-dose vials. Route: IM, anterolateral left thigh. Lot number: 7-5092-005A.

DTaP-HBV-IPV-PRP-T [Infanrix hexa; GSK]: This vaccine is not licensed in the U.S. Each 0.5 mL dose contains 30 IU of diphtheria toxoid, 40 IU tetanus toxoid, 3 pertussis antigens (PT 25 µg, FHA 25 µg, PRN 8 µg), 10 µg HBsAg, and 10 µg of purified polyribosyl-ribitol-phosphate (PRP) capsular polysaccharide of H. influenzae type b (Hib) conjugated to 20-40 µg tetanus toxoid (PRP-T), adsorbed on aluminunm oxide hydrated (0.95 µg). It also contains 40 D-antigen units (DUs) of inactivated poliovirus type 1 (Mahoney strain), 8 DUs inactivated poliovirus type 2 (MEF-1 strain), and 32 DUs of inactivated poliovirus type 3 (Saukett strain). The final vaccine contains the excipients lactose, NaCl, $Al(OH)^3$, $AlPO_4$, phenoxyethanol, and water for injections. The vaccine also contains the following residues: medium 199 stabilizer, KCl, polysorbate 20 and 80, formaldehydre, glycine, NaPO4 dibasic dehydrate, KPO4 monobasic, neomycin sulfate and polymyxin B sulfate. The manufacture of this product includes exposure to bovine derived materials. Route: IM, anterolateral right thigh. Lot number: A21CA193A.

Permitted vaccines: As in study 004, influenza and rotavirus vaccinations were permitted during the study period. Influenza vaccine could be given from 7 days post-dose 3 until 14 days before dose 4 and from 7 days post-dose 4. Rotavirus vaccine could be given concomitantly with study vaccines after the European Commission granted marketing authorization and based on recommendations made by STIKO (ständige Impfkommission – German Advisory Committee on Immunization). Because MMR and varicella vaccines were not mandated by the study protocol, MMR and varicella vaccines were permitted after the blood draw at the post-dose 4 follow-up visit (at 12-13 months of age. The study report indicates that on clinical review of the data, MMR and varicella vaccines given after the post-dose 3 visit but 28 days before the dose 4 visit were also permitted, as the applicant did not consider this to affect the clinical observations or the immune responses.

10.2.3.4 Endpoints

10.2.3.4.1 Primary Immunogenicity Endpoints

Primary immunogenicity endpoints included the following:

1. Proportion of subjects with pneumococcal serotype-specific IgG antibody concentrations ≥ 0.35 µg/mL 1 month after 3rd dose.
2. Proportion of subjects with anti-diphtheria ELISA antibody concentrations ≥ 0.1 IU/mL 1 month after 3rd dose.
3. Proportion of subjects with anti-hepatitis B antibody concentrations ≥ 10.0 mIU/mL 1 month after 3rd dose.
4. Proportion of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL 1 month after 3rd dose.

10.2.3.4.2 Secondary Immunogenicity Endpoints

Secondary immunogenicity endpoints included the following:

1. Proportion of subjects with a pneumococcal serotype-specific IgG antibody concentration ≥ 0.35 µg/mL 1 month after toddler dose.
2. Proportion of subjects achieving a pneumococcal serotype-specific IgG antibody concentration ≥ 1.0 µg/mL at 1 month post-dose #3 and #4.
3. Pneumococcal serotype-specific IgG GMC at 1 month post-dose #3 and before dose #4.
4. If any pneumococcal serotype failed non-inferiority at the 0.35µg/mL level after the dose 3, then an additional 0.15µg/mL level would be examined.
5. For Infanrix hexa concomitant antigens, the proportion of subjects achieving an alternative cutoff level of ≥ 1.0 µg/mL for anti-PRP antibody and an alternative cutoff level of ≥ 0.01IU/mL for anti-diphtheria ELISA antibody at one month post-dose #3.

10.2.3.4.3 Safety Endpoint

The safety endpoints were the incidence rates of unsolicited adverse events, serious adverse events, and solicited local reactions, and systemic events. With one exception, solicited local and systemic adverse events were identical to those listed in study 004; urticaria was not a solicited systemic adverse event in study 004. Solicited AEs were prospectively collected for four days after each vaccination.

10.2.3.4.4 Exploratory Immunogenicity Endpoint

Proportion of subjects achieving a serotype-specific OPA antibody titer ≥ 1:8 measured 1 month after the 3rd dose and 1 month after the 4th dose, in a subset of 100 subjects per vaccine group

10.2.3.5 Surveillance

10.2.3.5.1 Immunogenicity Monitoring

Blood samples were obtained for immunogenicity analyses one month (28-42 days) after the third dose (~ 5 months of age), prior to the fourth dose (~ 11-12 months of age), and one month (28-42 days) after the fourth dose (~ 12-13 months of age) for all subjects. Pneumococcal assays performed on these blood samples included ELISA for serotype-specific anticapsular IgG antibodies for the 13 pneumococcal serotypes and serum OPAs in the immunogenicity subset for the 13 serotypes after dose 3 and for select serotypes after dose 4. Concomitant vaccine antigen assays performed on these samples included total anti-PRP IgG antibody levels, anti-diphtheria toxoid IgG antibody levels, and anti-HBsAg IgG antibody levels were measured.

10.2.3.5.2 Safety Surveillance / Monitoring

With a few exceptions, safety monitoring in study 006 was identical to the monitoring conducted in study 004. Safety monitoring described in the protocol for study 006 differed from that of study 004 in 4 rather than 7 days of monitoring for solicited adverse events, no inclusion of urticaria as a solicited local AE, and no requirement for unscheduled visits to evaluate subjects with suspected rashes for urticaria.

Table 166: Study 6096A1-006, Study Flowchart

Visit No.	1	2	3	4	5	6	7
Visit ID	2-Month Visit	3-Month Visit	4-Month Visit	5-Month Visit	11-12-Month Visit	12-13 Month Visit	17-18 Month Visit
Study Interval	Vaccine dose 1	Vaccine dose 2	Vaccine dose 3	Post-infant series	Vaccine dose 4	Post-toddler dose	6-Month Follow-up
Visit Window	56-112 days of age	28-42 days after visit 1	28-42 days after visit 2	28-42 days after visit 3	335-395 days of age	28-42 days after visit 5	165-210 days after last study vaccine
Informed consent	X						
Review inclusion/ exclusion/delay criteria	X						
Medical Hx/PE	X						
Core rectal temp	X	X	X		X		
Randomization	X						
Study vaccination & 30 minute observation	X	X	X		X		
Infanrix hexa vaccination	X	X	X		X		
Confirm continued eligibility		X	X	X	X	X	
AE collection	⟷ X ⟶				⟷ X ⟶		
SAE collection	⟷ X ⟶						
Obtain 5 mL blood sample				X	X (before 4th dose)	X	
Assess acute reactions	Day 1 to 4*	Day 1 to 4	Day 1 to 4		Day 1 to 4		
Use of antipyretic medication	Day 1 to 4	Day 1 to 4	Day 1 to 4		Day 1 to 4		
Telephone call							X

*Day of vaccination is considered day 1.

Source: 125324/0.2,m5.3.5.1, CSR69237-protocol-amend.pdf

10.2.3.6 Statistical considerations

This is a double blind study. Unblinding occurred at analysis of the infant series data for the purposes of regulatory submission. Eligible subjects were prospectively randomized in a 1:1 allocation into 1 of 2 treatment groups using -----b(4)---------- system. A block randomization scheme was used for each site separately. Subjects who discontinued from the study after randomization were not to be replaced.

The random subset of 200 subjects for the OPA assays was selected once study enrollment was complete. Subjects were randomly ordered, and then the first 100 subjects in each vaccine group were selected. Additional subjects, if needed, were to be selected from the vaccine group of the subject they were replacing for the infant series and the toddler dose separately.

10.2.3.6.1 Sample Size/Statistical Power

Sample size estimation was based on the proportion of responders in each vaccine group for pneumococcal serotypes and Infanrix hexa concomitant vaccine antigens from study D139-P500 and D140-P001. For hepatitis B, the EMEA guidance document for Infanrix hexa was used. Study 006 planned to enroll 300 subjects per group in order to achieve 270 evaluable subjects per group, assuming a dropout rate of 10%. This sample size was estimated to provide at least 90% overall power to ascertain non-inferiority for all 16 antigen comparisons using a 2-sided, type I error rate of 0.05 and a non-inferiority criterion of -0.10.

10.2.3.6.2 Study Cohorts Analyzed

Study 006 included the same four immunogenicity analysis populations defined in study 004: evaluable infant, all-available infant, evaluable toddler, and all-available toddler. The evaluable immunogenicity population inclusion criteria in study 006 only differed from the corresponding study 004 criteria in that study 004 subjects had to be ≥ 55 and ≤ 113 days of age on the first day of vaccination and ≥ 334 and ≤ 396 days of age at the toddler dose. Also, in study 006, if no important differences were noted between the evaluable toddler and all-available toddler immunogenicity populations, a single all-available toddler immunogenicity analysis was to be performed. As in study 004, there were 5 safety populations; a separate population for each dose and an infant series safety population. Immunogenicity analyses were based on subjects' randomized treatment assignment.

10.2.3.6.3 Statistical Analyses

Immunogenicity analyses:

For each primary endpoint, the non-inferiority criterion for each antigen was as follows: lower limit of the 2-sided 95% confidence interval is > -0.10 for the difference in proportions (13vPnC-PCV7). Although anti-pneumococcal geometric mean concentrations were not a primary endpoint in this study, non-inferiority of 13vPnC relative to PCV7 based on GMCs was assessed using a 2-fold non-inferiority criterion (lower limit of the CI for the ratio > 0.5).

Safety analyses:

The safety analyses in study 006 were identical to those described in study 004.

Interim analyses:

A primary analysis was performed after all subjects completed their post-dose 3 visit, their assay data had become available, and the database was considered clean. All Type I error was to be spent for this analysis. Data collected following the primary analysis are secondary and/or exploratory. Analyses of the toddler data and the 6 month follow-up data were to be performed after all data for the specific visit had been collected.

10.2.3.7 Changes in the Study Protocol (Protocol Amendments) and in the Planned Analyses

No amendments to the original protocol and no changes to the planned analyses were made. For determination of subject inclusion in the evaluable immunogenicity population, the following deviations from protocol specified windows were allowed: a 1 day deviation for age at enrollment and age at the

toddler dose was permitted and blood draws 1 day before and 14 days after the protocol-specified timings were permitted. These deviations were allowed because the protocol did not provide directions to investigators on how to calculate age or timings

OPA data were reviewed before analyses were performed, and the applicant noted that results across the different serotypes were not comparable. Therefore, additional analyses were performed for both proportions of subjects achieving OPA titers ≥ 1:8 and for GMTs, directly comparing serotype-specific responses in each study group. The SAP implied that OPA results for the 6 additional serotypes in the 13vPnC group would be compared to the lowest OPA response among the 7 common serotypes in the PCV7 group.

10.2.4 Results

10.2.4.1 Populations Enrolled/Analyzed

A total of 604 subjects were enrolled/randomized into this study at 56 sites in Germany; 301 subjects were randomized to the 13vPnC group and 303 subjects to the PCV7 group. There were 564 subjects in the evaluable infant immunogenicity population, 547 subjects in the evaluable toddler immunogenicity population, 584 subjects in the infant all-available immunogenicity population, and 578 in the toddler all-available immunogenicity population. The all-available infant series safety population included a total of 603 subjects who received at least one dose of a pneumococcal conjugate vaccine.

10.2.4.1.1 Subject Disposition and Follow-up

A total of 587 infants (294 13vPnC subjects and 293 PCV7 subjects) completed the infant series; 574 infants (289 13vPnC subjects and 285 PCV7 subjects) completed the toddler dose, and 569 (287 13vPnC subjects and 282 PCV7 subjects) completed the study. A total of 588 subjects (293 in the 13vPnC group and 295 in the PCV7 group) entered the 6-month follow-up, and 578 subjects (288 13vPnC subjects and 290 PCV7 subjects) completed the 6-month follow-up.

Table 167. Study 6096A1-006 Summary of Analysis Populations

	13vPnC N=301		PCV7 N=303		Total N=604	
	n	%	n	%	n	%
Randomized	301	100.0	303	100.0	604	100.0
Vaccinated						
Dose 1	300	99.7	303	99.3	603	99.8
Dose 2	296	98.3	297	98.0	593	98.2
Dose 3	294	97.7	293	96.7	587	97.2
Dose 4	290	96.3	287	94.7	577	95.5
Completed infant series	294	97.7	293	96.7	587	97.2
Withdrawn during infant series	8	2.7	10	3.3	18	3.0
Reasons for withdrawal:						
Protocol violation	3	1.0	4	1.3	7	1.2
Parent/legal guardian request	3	1.0	3	1.0	6	1.0
Adverse event	0	0.0	2	0.7	2	0.3
Lost to follow-up	1	0.3	1	0.3	2	0.3
Failed to return	1	0.3	0	0.0	1	0.2
Withdrawn after infant series	4	1.3	6	2.0	10	1.7
Reasons for withdrawal:						
Protocol violation	2	0.7	2	0.7	4	0.7
Parent/legal guardian request	1	0.3	1	0.3	2	0.3
Failed to return	1	0.3	1	0.3	2	0.3
Lost to follow-up	0	0.0	1	0.3	1	0.2
Adverse event	0	0.0	1	0.3	1	0.2
Completed toddler dose	289	96.0	285	94.1	574	95.0
Withdrawn during toddler dose	1	0.3	1	0.3	2	0.3
Reason for withdrawal						
Parent/legal guardian request	0	0.0	1	0.3	1	0.2
Failed to return	1	0.3	0	0.0	1	0.2
Withdrawn after toddler dose	2	07	3	1.0	5	0.8
Reason for withdrawal						
Lost to follow-up	2	0.7	2	0.7	4	0.7
Protocol violation	0	0.0	1	0.3	1	0.2
Completed study	287	95.3	282	93.1	569	94.2
Entered 6-month follow-up[a]	293	97.3	295	97.4	588	97.4
Completed 6-month follow-up[b]	288	95.7	290	95.7	578	95.7

[a] An attempt was made to contact all subjects 6-months after the last vaccination, regardless of whether they received all protocol-specified vaccinations.
[b] Completion of the 6-month follow up indicates subjects were reached by phone and provided the requested information.
Source: 125324/0.2,m5.3.5.1, CSR69237-report body-infant.pdf, page 41 (Table 8-2); CSR74361-report-body-toddler.pdf page 41 (Table 8-1); and CSR74361-follow-up-addendum.pdf page 6 (Table 3-1).

Table 168. Study 6096A1-006 Summary of Immunogenicity Analysis Populations

	13vPnC N=301		PCV7 N=303		Total N=604	
	n	%	n	%	n	%
Randomized	301	100.0	303	100.0	604	100.0
All-available infant immunogenicity population	292	97.0	292	96.4	584	96.7
Subjects excluded from all-available infant immunogenicity population because no postinfant assay result for any pneumococcal serotype or concomitant antigen	10	3.3	11	3.6	21	3.5
Evaluable infant immunogenicity population	285	94.7	279	92.1	564	93.4
Subjects excluded from the evaluable infant immunogenicity population[a]	17	5.6	24	7.9	41	6.8
All-available toddler immunogenicity population	290	96.3	288	98.3	578	95.7
Subjects excluded from all-available toddler immunogenicity population because no pre- or posttoddler pneumococcal serotype or concomitant antigen assay result	4	1.3	5	1.7	9	1.5
Evaluable toddler immunogenicity population	279	92.7	268	91.5	547	90.6
Subjects excluded from the evaluable toddler immunogenicity population[a]	15	5.0	25	8.5	40	6.6

[a] Subjects may have been excluded for more than 1 reason.
Source: 125324/0.2,m5.3.5.1, CSR69237-report body.pdf, page 53 (Table 9-1); CSR74361-report-body.pdf page 51 (Table 9-1)

10.2.4.1.2 Subject Demographics

Subject 006-00481, was pre-randomized to the 13vPNC group after verbal consent, but the consent form was never signed and the subject was not vaccinated; this subject is not included in the results for this study.

Table 169. Study 6096A1-006, Summary of Demographic Characteristics for All Subjects by Randomized Vaccine Group

	13vPnC N=301		PCV7 N=303		Total N=604	
	n	%	n	%	n	%
Gender						
Male	150	49.8	176	58.1	327	54.1
Female	151	50.2	127	41.9	279	46.2
Race						
White	291	96.7	292	96.4	585	96.9
Other	6	2.0	7	2.3	13	2.2
Asian	3	1.0	3	1.0	6	1.0
Black or African American	1	0.3	1	0.3	2	0.3
Ethnicity						
Non-Hispanic and Non-Latino	300	99.7	301	99.3	603	99.8
Hispanic or Latino	0	0.0	2	0.7	2	0.3
Unknown	1	0.3	0	0.0	1	0.2

Source: 125324/0.2,m5.3.5.1, CSR69237-report body.pdf, page 49 (Table 8-8).
Subject 006-012-000461 did not provide ethnicity.

10.2.4.2 Nonstudy Concomitant Vaccinations

Five subjects received nonstudy vaccines during the infant series. One 13vPnC group subject received pneumococcal conjugate vaccine and two subjects in each study group received a rotavirus vaccine. Between the post-dose 3 blood draw and the toddler dose visit, 18 subjects received nonstudy vaccines; six were excluded from the evaluable immunogenicity population because the protocol violation was likely to affect immune responses; this included three subjects who received PnC +/- Infanrix hexa and 3 subjects who received MMRV within 14 days of the toddler dose. During the toddler dose visit and the 6-month follow-up period, 244 (81.1%) 13vPnC subjects and 230 (75.9%) PCV7 subjects received a nonstudy vaccine. Most of the nonstudy vaccinations were MMR, meningococcal vaccine, and varicella

vaccine. A total of 8 of these subjects were excluded from the evaluable toddler immunogenicity population.

10.2.4.3 Immunogenicity Endpoints/Outcomes

10.2.4.3.1 Post-dose 3 Pneumococcal Serotype Immunogenicity Outcomes

Post-dose 3 Seroresponse Rates: Primary Immunogenicity Analysis

Serotype 6B failed to meet the pre-specified primary objective of demonstrating noninferior immune responses within a -10% non-inferiority criterion.

Table 170. Study 6096A1-006. 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	285	280	98.2	(96.0, 99.4)	279	274	98.2	(95.9, 99.4)	0.0	(-2.5, 2.6)
6B	284	220	77.5	(72.2, 82.2)	278	242	87.1	(82.5, 90.8)	-9.6	(-16.0, -3.3)
9V	285	281	98.6	(96.4, 99.6)	279	269	96.4	(93.5, 98.3)	2.2	(-0.4, 5.2)
14	284	281	98.9	(96.9, 99.8)	279	272	97.5	(94.9, 99.0)	1.5	(-0.9, 4.1)
18C	285	277	97.2	(94.5, 98.8)	277	273	98.6	(96.3, 99.6)	-1.4	(-4.2, 1.2)
19F	284	272	95.8	(92.7, 97.8)	277	266	96.0	(93.0, 98.0)	-0.3	(-3.8, 3.3)
23F	284	252	88.7	(84.5, 92.2)	277	248	89.5	(85.3, 92.9)	-0.8	(-6.0, 4.5)
Additional										
1	285	274	96.1	(93.2, 98.1)	‡				9.1	(4.5, 13.9)
3	282	277	98.2	(95.9, 99.4)	‡				11.2	(7.0, 15.8)
5	284	264	93.0	(89.3, 95.6)	‡				5.9	(0.8, 11.1)
6A	283	260	91.9	(88.1, 94.8)	‡				4.8	(-0.3, 10.1)
7F	285	281	98.6	(96.4, 99.6)	‡				11.5	(7.4, 16.1)
19A	285	283	99.3	(97.5, 99.9)	‡				12.2	(8.3, 16.8)

[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.
[‡] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 6B [87.1% (95% CI 82.5, 90.8)].
Source: 125324/0.2, m5.3.5.1, CSR69237-report body-infant.pdf, page 58 (Table 9-3).

Data for the 6 additional pneumococcal serotypes: **Post dose 3 IgG Seroresponse Rates ≥ 0.35 ug/mL**

Table 171 shows the actual response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 170 because the PCV7 reference value (serotype 6B) was used to calculate the difference in proportions.

Table 171. Study 6096A1-006, 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	285	280	98.2	(96.0, 99.4)	279	274	98.2	(95.9, 99.4)	0.0	(-2.5, 2.6)
6B	284	220	77.5	(72.2, 82.2)	278	242	87.1	(82.5, 90.8)	-9.6	(-16.0, -3.3)
9V	285	281	98.6	(96.4, 99.6)	279	269	96.4	(93.5, 98.3)	2.2	(-0.4, 5.2)
14	284	281	98.9	(96.9, 99.8)	279	272	97.5	(94.9, 99.0)	1.5	(-0.9, 4.1)
18C	285	277	97.2	(94.5, 98.8)	277	273	98.6	(96.3, 99.6)	-1.4	(-4.2, 1.2)
19F	284	272	95.8	(92.7, 97.8)	277	266	96.0	(93.0, 98.0)	-0.3	(-3.8, 3.3)
23F	284	252	88.7	(84.5, 92.2)	277	248	89.5	(85.3, 92.9)	-0.8	(-6.0, 4.5)
Additional										
1	285	274	96.1	(93.2, 98.1)	277	4	1.4	(0.4, 3.7)	9.1	(4.5, 13.9)
3	282	277	98.2	(95.9, 99.4)	272	17	6.3	(3.7, 9.8)	11.2	(7.0, 15.8)
5	284	264	93.0	(89.3, 95.6)	244	77	31.6	(25.8, 37.8)	5.9	(0.8, 11.1)
6A	283	260	91.9	(88.1, 94.8)	272	86	31.6	(26.1, 37.5)	4.8	(-0.3, 10.1)
7F	285	281	98.6	(96.4, 99.6)	276	11	4.0	(2.0, 7.0)	11.5	(7.4, 16.1)
19A	285	283	99.3	(97.5, 99.9)	269	213	79.2	(73.8, 83.9)	12.2	(8.3, 16.8)

[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 PCV7 serotypes, the reference value is the corresponding proportion in the PCV7 group. 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: 125324/0.2,m5.3.5.1, CSR69237-report body.pdf, page 55-56 and 58 (Table 9-2 and 9-3).

Post dose 3 Pneumococcal IgG Geometric Mean Concentrations

Table 172. Study 6096A1-006, Comparison of 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	285	2.18	(1.98, 2.40)	279	2.99	(2.68, 3.33)	0.73	(0.63, 0.84)
6B	284	0.98	(0.84, 1.14)	278	1.49	(1.27, 1.75)	0.65	(0.52, 0.82)
9V	285	1.65	(1.51, 1.80)	279	1.96	(1.77, 2.17)	0.84	(0.74, 0.96)
14	284	4.14	(3.68, 4.66)	279	4.61	(4.07, 5.23)	0.90	(0.76, 1.07)
18C	285	1.94	(1.76, 2.14)	277	2.25	(2.04, 2.49)	0.86	(0.75, 0.99)
19F	284	1.73	(1.56, 1.92)	277	2.86	(2.53, 3.24)	0.60	(0.51, 0.71)
23F	284	1.26	(1.11, 1.43)	277	1.44	(1.25, 1.65)	0.88	(0.73, 1.06)
Additional								
1	285	1.83	(1.64, 2.04)	‡			1.27	(1.07, 1.52)
3	282	1.55	(1.41, 1.72)	‡			1.08	(0.91, 1.29)
5	284	1.31	(1.17, 1.46)	‡			0.91	(0.76, 1.09)
6A	283	1.33	(1.18, 1.49)	‡			0.93	(0.77, 1.11)
7F	285	2.59	(2.36, 2.85)	‡			1.81	(1.53, 2.14)
19A	285	3.26	(2.97, 3.59)	‡			2.27	(1.92, 2.69)

[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] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC to PCV7 reference. For the PCV7 serotypes, the reference value is the corresponding geometric mean concentration in the PCV7 group. For the additional serotypes, the reference value is serotype 23F from the PCV7 group.
[e] Two-sided 95% confidence intervals (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).
‡ Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 23F [1.44 (95% CI 1.25, 1.65)].
Source: 125324/0.2,m5.3.5.1, CSR69237-report body-infant.pdf, page 64 and 65 (Table 9-5 and 9-6).

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

Table 173 shows the response rates for the 6 additional serotypes among PCV7 recipients. These data were not shown in Table 172 because the PCV7 reference value (serotype 23F) was used to calculate the difference in proportions.

Table 173. Study 6096A1-006. 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	285	2.18	(1.98, 2.40)	279	2.99	(2.68, 3.33)
6B	284	0.98	(0.84, 1.14)	278	1.49	(1.27, 1.75)
9V	285	1.65	(1.51, 1.80)	279	1.96	(1.77, 2.17)
14	284	4.14	(3.68, 4.66)	279	4.61	(4.07, 5.23)
18C	285	1.94	(1.76, 2.14)	277	2.25	(2.04, 2.49)
19F	284	1.73	(1.56, 1.92)	277	2.86	(2.53, 3.24)
23F	284	1.26	(1.11, 1.43)	277	1.44	(1.25, 1.65)
Additional						
1	285	1.83	(1.64, 2.04)	277	0.03	(0.02, 0.03)
3	282	1.55	(1.41, 1.72)	272	0.05	(0.04, 0.06)
5	284	1.31	(1.17, 1.46)	244	0.20	(0.18, 0.23)
6A	283	1.33	(1.18, 1.49)	272	0.23	(0.20, 0.26)
7F	285	2.59	(2.36, 2.85)	276	0.04	(0.04, 0.05)
19A	285	3.26	(2.97, 3.59)	269	0.64	(0.58, 0.71)

[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] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
Source: 125324/0.2,m5.3.5.1, CSR69237-report body-infant.pdf, page 64 (Table 9-5).

Post-dose 3 OPA Results[4]

Among the 7 common serotypes, the lower limit of the 95% CI for the GMT ratio was < 0.5 for serotype 6B and 14. For the 6 additional serotypes, a higher proportion of PCV7 subjects than expected achieved OPA titers ≥ 1:8 against serotype 7F; this finding was also seen in study 004.

Table 174. Study 6096A1-006, Comparison of Subjects Achieving a Pneumococcal OPA Antibody Titer ≥ 1:8 After Dose 3 of the Infant Series (Evaluable Infant Immunogenicity Population)

	Vaccine Group As Randomized							
	13vPnC							
Serotype	N[a]	n[b]	%	(95% CI)[c]	N[a]	n[b]	%	(95% CI)[c]
PCV7								
4	92	92	100.0	(96.1, 100.0)	94	94	100.0	(96.2, 100.0)
6B	100	96	96.0	(90.1, 98.9)	94	93	98.9	(94.2, 100.0)
9V	89	89	100.0	(95.9, 100.0)	89	89	100.0	(95.9, 100.0)
14	95	95	100.0	(96.2, 100.0)	89	89	100.0	(95.9, 100.0)
18C	100	100	100.0	(96.4, 100.0)	94	93	98.9	(94.2, 100.0)
19F	100	96	96.0	(90.1, 98.9)	94	88	93.6	(86.6, 97.6)
23F	100	96	96.0	(90.1, 98.9)	93	89	95.7	(89.4, 98.8)
Additional								
1	100	93	93.0	(86.1, 97.1)	92	4	4.3	(1.2, 10.8)
3	100	99	99.0	(94.6, 100.0)	94	23	24.5	(16.2, 34.4)
5	100	99	99.0	(94.6, 100.0)	94	4	4.3	(1.2, 10.5)
6A	99	95	96.0	(90.0, 98.9)	93	67	72.0	(61.8, 80.9)
7F	99	99	100.0	(96.3, 100.0)	94	74	78.7	(69.1, 86.5)
19A	95	95	100.0	(96.2, 100.0)	94	16	17.0	(10.1, 26.2)

[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: 125324/0.2,m5.3.5.1, CSR69237-report body.pdf, page 67 (Table 9-7).

[4] Because no standard exists against which OPA results can be normalized, comparisons of OPA titers across serotypes are not appropriate.

Table 175. Study 6096A1-006, Comparison of Pneumococcal OPA GMTs After Dose 3 of the Infant Series (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]**
PCV7						
4	92	1573	(1283, 1929)	94	1861	(1540.00, 2248.41)
6B	100	744	(557, 995)	94	1161	(921.46, 1462.19)
9V	89	4938	(3615, 6745)	89	5380	(3935.51, 7353.34)
14	95	2140	(1570, 2916)	89	3345	(2473.27, 4524.50)
18C	100	1510	(1244, 1833)	94	1780	(1382.42, 2292.59)
19F	100	150	(117, 193)	94	166	(122.98, 223.23)
23F	100	1090	(795, 1494)	93	1071	(786.59, 1457.78)
Additional						
1	100	50	(39.39, 64.02)	92	4.2	(4.0, 4.3)
3	100	251	(205.52, 305.89)	94	6.1	(5.17, 7.23)
5	100	162	(126.31, 207.82)	94	4.6	(4.0, 5.4)
6A	99	1228	(883.49, 1708.11)	93	122.4	(74.1, 202.2)
7F	99	11545	(9364.02, 14233.34)	94	115.5	(75.2, 177.3)
19A	95	442.48	(361, 544)	94	6.7	(5.2, 8.7)

[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 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: 125324/0.2,m5.3.5.1, CSR69237-report body.pdf, page 69 (Table 9-8).

10.2.4.3.2 Dose 4 Pneumococcal Serotype Immunogenicity Outcomes

Post-dose 4 Seroresponse rates
Serotype 3 failed to meet the co-secondary objective within a -10% non-inferiority criterion; the lower limit of the 95% confidence interval for the difference in proportions was -10.2%. Results from the all-available infant immunogenicity population, however, show that the difference in proportions for serotype 3 was -5.8% (95% CI -10, -1.6).

Table 176. Study 6096A1-006, Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35µg/mL 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]
PCV7										
4	276	274	99.3	(97.4, 99.9)	263	261	99.2	(97.3, 99.9)	0.0	(-1.9, 2.1)
6B	273	271	99.3	(97.4, 99.9)	251	250	99.6	(97.8, 100.0)	-0.3	(-2.3, 1.5)
9V	277	277	100.0	(98.7, 100.0)	262	259	98.9	(96.7, 99.8)	1.1	(-0.2, 3.3)
14	276	273	98.9	(96.9, 99.8)	260	259	99.6	(97.9, 100.0)	-0.7	(-2.8, 1.2)
18C	276	275	99.6	(98.0, 100.0)	263	260	98.9	(96.7, 99.8)	0.8	(-1.0, 2.9)
19F	276	272	98.6	(96.3, 99.6)	263	255	97.0	(94.1, 98.7)	1.6	(-1.0, 4.6)
23F	277	272	98.2	(95.8, 99.4)	264	257	97.3	(94.6, 98.9)	0.8	(-1.8, 3.8)
Additional										
1	278	275	98.9	(96.9, 99.8)	‡				2.0	(-0.5, 4.9)
3	278	253	91.0	(87.0, 94.1)	‡				-6.0	(-10.2, -1.7)
5	276	276	100.0	(98.7, 100.0)	‡				3.0	(1.2, 5.9)
6A	274	269	98.2	(95.8, 99.4)	‡				1.2	(-1.6, 4.3)
7F	278	275	98.9	(96.9, 99.8)	‡				2.0	(-0.5, 4.9)
19A	271	271	100.0	(98.6, 100.0)	‡				3.0	(1.2, 5.9)

[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, expressed as a percentage. For the PCV7 serotypes, the reference value is the corresponding proportion in the PCV7 group. For the additional serotypes, the reference value is serotype 19F from the PCV7 group.
[e] Exact 2-sided confidence interval for the difference in proportions, 13vPnC - PCV7 reference, expressed as a percentage.
[‡] Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 19F [97.0% (95% CI 94.1, 98.7)].
Source: 125324/0.2,m5.3.5.1, CSR74361-report body.pdf, page 55 and 57 (Table 9-2 and 9-3).

Clinical Reviewer Note: GMCs are the preferred endpoint for the post-dose 4 analysis of immune responses. The proportion of children achieving the 0.35 µg/mL antibody concentration after the fourth dose at 12-15 months of age is less useful in evaluating of immune responses at this timepoint, as it is a low bar for these comparisons. The proportion of subjects achieving the 0.35 µg/mL antibody concentration is high in both groups, which limits the ability to determine differences, if any, between the products.

Pre-dose 4 Pneumococcal IgG GMCs

As expected, pre-dose 4 antibody levels are lower than post-dose 3 values within approximately 6-months of administration of the 3rd dose.

Table 177. Study 6096A1-006, Pneumococcal IgG Geometric Mean Concentrations (µg/mL) Before Toddler Dose (Evaluable Toddler 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	277	0.46	(0.42, 0.51)	264	0.58	(0.53, 0.64)	0.79	(0.68, 0.90)
6B	275	0.97	(0.87, 1.07)	261	1.06	(0.94, 1.20)	0.91	(0.78, 1.07)
9V	277	0.46	(0.42, 0.50)	265	0.52	(0.48, 0.57)	0.88	(0.78, 0.99)
14	273	2.2	(1.96, 2.48)	263	2.65	(2.34, 3.00)	0.83	(0.70, 0.99)
18C	277	0.33	(0.30, 0.36)	265	0.39	(0.36, 0.43)	0.85	(0.75, 0.96)
19F	276	0.68	(0.60, 0.76)	264	0.58	(0.52, 0.66)	1.16	(0.98, 1.37)
23F	275	0.33	(0.30, 0.37)	264	0.39	(0.34, 0.45)	0.86	(0.72, 1.02)
Additional								
1	277	0.52	(0.48, 0.57)	‡			1.34	(1.14, 1.57)
3	275	0.25	(0.23, 0.28)	‡			0.65	(0.55, 0.77)
5	275	0.74	(0.67, 0.81)	‡			1.89	(1.61, 2.23)
6A	276	0.76	(0.68, 0.85)	‡			1.95	(1.65, 2.32)
7F	277	0.99	(0.91, 1.08)	‡			2.54	(2.17, 2.97)
19A	277	1.28	(1.14, 1.45)	‡			3.29	(2.75, 3.94)

[a] 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] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC to PCV7 reference. For the PCV7 serotypes, the reference value is the corresponding geometric mean concentration in the PCV7 group. For the additional serotypes, the reference value is serotype 23F from the PCV7 group.
[e] Confidence intervals (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).
‡ Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 23F [0.39 (95% CI 0.34, 0.45)].
Source: 125324/0.2,m5.3.5.1, CSR74361-report body.pdf, page 64 (Table 9-6).

Post-dose 4 Pneumococcal IgG Geometric Mean Concentrations

With the exception of serotype 3, all serotypes met the 2-fold non-inferiority criterion for this co-primary endpoint. For serotype 3, the lower limit of the 2-sided 95% CI for the GMC ratio was less than 0.50.

Table 178. Study 6096A1-006, Comparison of Pneumococcal IgG GMCs (µg/mL) After Dose 4 (Evaluable Toddler 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	276	4.16	(3.75, 4.62)	263	5.07	(4.53, 5.67)	0.82	(0.70, 0.96)
6B	273	9.14	(8.14, 10.26)	251	9.85	(8.66, 11.22)	0.93	(0.78, 1.10)
9V	277	2.75	(2.52, 2.99)	262	3.36	(3.02, 3.73)	0.82	(0.72, 0.94)
14	276	8.34	(7.50, 9.28)	260	11.01	(9.87, 12.29)	0.76	(0.65, 0.88)
18C	276	2.79	(2.53, 3.07)	263	3.44	(3.08, 3.84)	0.81	(0.70, 0.94)
19F	276	5.99	(5.36, 6.68)	263	4.72	(4.12, 5.41)	1.27	(1.07, 1.51)
23F	277	3.36	(2.98, 3.78)	264	4.33	(3.75, 5.00)	0.78	(0.64, 0.93)
Additional								
1	278	4.25	(3.80, 4.75)	‡			1.27	(1.09, 1.48)
3	278	1.02	(0.92, 1.13)	‡			0.30	(0.26, 0.35)
5	276	3.56	(3.25, 3.89)	‡			1.06	(0.92, 1.22)
6A	274	5.88	(5.24, 6.59)	‡			1.75	(1.50, 2.04)
7F	278	4.79	(4.29, 5.34)	‡			1.43	(1.23, 1.66)
19A	271	9.58	(8.68, 10.58)	‡			2.85	(2.47, 3.30)

[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] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[d] Ratio of GMCs; 13vPnC to PCV7 reference. For the PCV7 serotypes, the reference value is the corresponding geometric mean concentration in the PCV7 group.For the additional serotypes, the reference value is serotype 9V from the PCV7 group.
[e] Confidence intervals (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).
‡ Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which in this analysis was serotype 9V [3.36 (95% CI 3.02, 3.73)].
Source: 125324/0.2,m5.3.5.1, CSR74361-report body.pdf, page 66 (Table 9-8).

Dose 4 OPA Results

For the 6 additional serotypes, a high proportion of subjects in the 13vPnC group achieved OPA titers ≥ 1:8 for all serotypes. Similar to post-dose 3, a higher proportion of PCV7 subjects than expected achieved OPA titers ≥ 1:8 against serotype 7F. Data show an improved response to 19A among PCV7 subjects than seen post-dose 3 and in study 004. A higher response rate than expected was seen in response to serotypes 3.

Table 179. Study 6096A1-006, 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]
PCV7								
4	92	92	100.0	(96.1, 100.0)	91	91	100.0	(96.0, 100.0)
6B	97	97	100.0	(96.3, 100.0)	95	94	98.9	(94.3, 100.0)
9V	97	97	100.0	(96.3, 100.0)	94	94	100.0	(96.2, 100.0)
14	97	97	100.0	(96.3, 100.0)	94	94	100.0	(96.2, 100.0)
18C	94	94	100.0	(96.2, 100.0)	92	92	100.0	(96.1, 100.0)
19F	98	97	99.0	(94.4, 100.0)	96	91	94.8	(88.3, 98.3)
23F	94	92	97.9	(92.5, 99.7)	91	87	95.6	(89.1, 98.8)
Additional								
1	97	96	99.0	(94.4, 100.0)	95	15	15.8	(9.1, 24.7)
3	98	96	98.0	(92.8, 99.8)	95	34	35.8	(26.2, 46.3)
5	96	95	99.0	(94.3, 100.0)	90	2	2.2	(0.3, 7.8)
6A	97	96	99.0	(94.4, 100.0)	93	86	92.5	(85.1, 96.9)
7F	88	88	100.0	(95.9, 100.0)	88	75	85.2	(76.1, 91.9)
19A	98	98	100.0	(96.3, 100.0)	91	62	68.1	(57.5, 77.5)

[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: 125324/0.2,m5.3.5.1, CSR74361-report body.pdf, page 73 (Table 9-12).

Table 180. Study 6096A1-006, 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]
4	92	2491	(1947, 3188)	91	2885	(2197, 3789)
6B	97	2687	(2167, 3331)	95	2907	(2242, 3769)
9V	97	13704	(11426, 16436)	94	16026	(12981, 19785)
14	97	3012	(2375, 3821)	94	4925	(3836, 6324)
18C	94	1326	(1024, 1716)	92	1762	(1339, 2317)
19F	98	345	(279, 425)	96	265	(189, 372)
23F	94	2854	(2092, 3894)	91	3738	(2537, 5507)
Additional						
1	97	198	(157, 250)	95	5.02	(4.35, 5.79)
3	98	188	(152, 231)	95	7.83	(6.14, 9.97)
5	96	327	(256, 419)	90	4.13	(3.93, 4.33)
6A	97	2502	(1916, 3266)	93	500.68	(340.52, 736.17)
7F	88	10213	(8015, 13016)	88	182.45	(119.02, 279.68)
19A	98	1349	(1089, 1672)	91	59.31	(37.47, 93.87)

[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 confidence interval based on the Student t distribution for the mean logarithm of the titers.
[d] Ratio of GMTs; 13vPnC to PCV7 reference.
[e] Confidence intervals (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: 125324/0.2,m5.3.5.1, CSR69238-report body.pdf, page 76 (Table 9-14).

10.2.4.4 Safety Outcomes

Antipyretic Use

Use of antipyretics/analgesics theoretically may affect the occurrence of some local or systemic adverse events. There were no statistically significant differences between the two study groups in the proportions of subjects who used antipyretics within 7 days following each vaccination.

Table 181. Study 6096A1-006, Number of subjects who received antipyretics to treat symptoms or to prevent symptoms within 4 days following each dose of 13vPnC or PCV7.

	Use of Antipyretics to Treat Symptoms		Use of Antipyretics to Prevent Symptoms	
Dose number	13vPnC n (%)	PCV7 n (%)	13vPnC n (%)	PCV7 n (%)
1	N[b]=263 53 (20.2)	N[b]=277 57 (21.4)	N[b]=261 23 (8.8)	N[b]=262 25 (9.5)
2	N=244 69 (28.3)	N=235 64 (27.2)	N=237 24 (10.1)	N=234 36 (15.4)
3	N=226 47 (20.8)	N=225 43 (19.1)	N=220 22 (10.0)	N=220 33 (15.0)
4	N=184 59 (32.1)	N=182 60 (33.0)	N=178 32 (18.0)	N=167 31 (18.6)

[b] Number of subjects reporting yes for at least 1 day or no for all days
Source: 125324/0.2,m5.3.5.1, CSR69237-report-body-infant.pdf (Table 10-5 to 10-7) and CSR74361-report body-toddler.pdf, page 89 (Table 10-3).

Immediate Reactions
Although immediate reactions were collected and reported along with other unsolicited adverse events, these events could not be idenitifed from the data submitted to the BLA. The specific time-to-onset of symptoms was not recorded, therefore reactions that occurred within 30 minutes of vaccination could not be identified.

10.2.4.4.1 Solicited Local Reactions

Table 182 presents the incidence of solicited local adverse events at the 13vPnC and PCV7 injection sites that occurred within 4 days following each of doses 1 through 4. Erythema was the most frequently reported local adverse event. The incidence of each local reaction, including mild, moderate, and severe reactions, peaked after dose 4. There was a tendency for a higher incidence of local reactions after dose 4 among PCV7 subjects compared to 13vPnC subjects. A statistically higher proportion of subjects in the 13vPnC group (28.2%) compared to the PCV7 group (20.5%) experienced any induration after dose 1.

Table 182. Percentage of subjects with solicited local adverse events, by severity, at the 13vPnC or PCV7 injection site within 4 days after each vaccination in Study 6096A1-006.

	Safety Populations by Dose[a]							
	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Local Reaction	**13vPnC** N[b]=259-267 %	**PCV7** N[b]=255-271 %	**13vPnC** N[b]=232-250 %	**PCV7** N[b]=222-252 %	**13vPnC** N[b]=214-238 %	**PCV7** N[b]=208-231 %	**13vPnC** N[b]=166-206 %	**PCV7** N[b]=152-185 %
Erythema[c]								
Any	28.2	36.4*	34.4	46.8*	34.9	39.8	47.4	56.0
0.5 - 2.0 cm	27.2	36.2*	33.6	45.6*	34.2	38.9	44.5	52.8
2.5 - 7.0 cm	1.9	1.6	1.7	3.6	4.6	2.4	11.6	15.2
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7
Induration[c]								
Any	28.2*	20.5	26.6	35.1*	26.1	28.6	36.8	43.8
0.5 - 2.0 cm	24.5	19.0	24.3	33.5*	24.8	27.8	33.3	40.7
2.5 - 7.0 cm	7.3	5.9	7.7	6.6	6.9	5.2	12.1	12.7
> 7.0 cm	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Tenderness								
Any	33.0	32.6	29.2	31.5	27.1	21.3	53.4	51.9
Interferes with limb movement	7.7	7.0	4.7	7.5	4.2	2.9	10.8	12.7

* Statistically significant difference between the two study groups ($p < 0.05$).
[a] Safety analysis populations: Dose 1: n_{13vPnc}=300, n_{PCV7}=303; Dose 2: n_{13vPnC}=296, n_{PCV7}=297; Dose 3: n_{13vPnc}=294, n_{PCV7}=293; Dose 4: n_{13vPnc}=290, n_{PCV7}=287.
[b] Number of subjects reporting yes for at least 1 day or no for all days.
[c] 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: 125324/0.2,m5.3.5.1, CSR69237-report body, pages 81-83 (Tables 10-2 to 10-4); CSR74361-report body, page 87 (Table 10-2).

10.2.4.4.2 Solicited Systemic Reactions

Table 183 presents the incidence of solicited systemic adverse events during the 4 days after each vaccination. During the infant series, increased sleep was the most frequently reported systemic adverse event; mild fever was the most frequently reported event after dose 4. With the exception of increased sleep, rates of each solicited systemic adverse event peaked after dose 4. The incidence of fever post-

dose 3 ≥ 38°C but ≤ 39°C was statistically significantly higher in the 13vPnC group (46.3%) than the PCV7 group (36.6%). There was a tendency towards higher rates of fever among 13vPnC subjects compared to PCV7 subjects. For other solicited systemic AEs, there were no notable differences between the groups.

Table 183. Percentage of subjects with solicited systemic adverse events within 4 days after each vaccination in Study 6096A1-006.

	Safety Populations by Dose[a]							
	Dose 1		Dose 2		Dose 3		Dose 4	
Graded Systemic Events	**13vPnC** N[b]=259-284 %	**PCV7** N[b]=256-272 %	**13vPnC** N[b]=233-258 %	**PCV7** N[b]=223-256 %	**13vPnC** N[b]=216-242 %	**PCV7** N[b]=209-241 %	**13vPnC** N[b]=166-213 %	**PCV7** N[b]=152-200 %
Fever[c]								
38.0°C ≤ x ≤ 39.0°C	43.5	38.7	46.8	48.4	46.3*	36.6*	58.7	62.0
39°C < x ≤ 40.0°C	4.2	1.6	8.8	4.4	3.7	1.4	12.6	8.9
> 40°C	0.0	0.0	0.0	0.0	0.9	0.0	0.6	0.0
Decreased appetite	33.1	30.3	33.7	34.3	33.1	30.2	43.6	46.4
Irritability	42.5	45.1	47.2	55.2	45.4	48.9	55.4	61.0
Increased sleep	61.6	58.8	53.9*	66.8*	49.6	49.4	56.4	54.8
Decreased sleep	25.2	26.1	23.8	23.1	20.9	24.4	31.8	28.8

* Statistically significant difference between the two study groups (p< 0.05).
[a] Safety analysis populations: Dose 1: n_{13vPnc}=300, n_{PCV7}=303; Dose 2: n_{13vPnC}=296, n_{PCV7}=297; Dose 3: n_{13vPnc}=294, n_{PCV7}=293; Dose 4: n_{13vPnc}=290, n_{PCV7}=287.
[b] Number of subjects reporting yes for at least 1 day or no for all days
[c] Fever gradings: mild (38.0°C ≤ x ≤ 39.0°C), moderate (39°C < x ≤ 40.0°C), and severe (> 40°C).
Source: 125324/0.2,m5.3.5.1, CSR69237-report body.pdf, pages 85-86 (Tables 10-5 to 10-7); CSR74361-report body.pdf, page 89 (Table 10-3).

10.2.4.4.3 Unsolicited Adverse Events

Unsolicited adverse events were reported in 73.6% of 13vPnC subjects and 75.3% of PCV7 subjects during the infant series, 52.9% of 13vPnC subjects and 51.1% of PCV7 subjects after the toddler dose, and 7-8% of subjects in each study group during the 6-month follow up time period. The most frequently reported adverse events in the 13vPnC group, reported in > 5 % of subjects, were as follows:

- During the infant series: upper respiratory tract infections (25.1%), bronchitis (16.4%), pyrexia (9.7%), rhinitis (8.0%), gastroenteritis (7.4%), conjunctivitis (7.4%), dermatitis diaper (7.4%), diarrhea (7.0%), and nasopharyngitis (6.4%).
- After the toddler dose: upper respiratory tract infection (13.8%), bronchitis (6.9%), gastroenteritis (5.9%), dermatitis diaper (5.9%), and rhinitis (5.5%).

There was only one statistically significant finding, suggesting a higher frequency of events reported during the infant series among 13vPnC subjects under the Respiratory, thoracic and mediastinal disorders System Organ Class.

Table 184. Rates of other events of interest are as follows:

	Post-dose 3		Post-dose 4	
MedDRA PT	13vPnC %	PCV7 %	13vPnC %	PCV7 %
Neutropenia	-	-	-	-
Convulsion	-	-	-	-
Febrile convulsion	-	-	0.0	0.4
Wheezing	0.3	0.0	-	-
Asthma	-	-	-	-
Bronchial hyperreactivity	0.3	0.0	-	-
Pneumonia	0.3	0.3	0.3	0.0
Otitis media	2.3	4.3	4.2	3.5

Source: 125324/0.2,m5.3.5.1, CSR69237-report-body-infant.pdf, pages 89-96 (Table 10-9)
CSR74361-report-body-toddler.pdf, pages 92-96 (Table 10-4).

Febrile convulsions occurred in 2 (0.7%) PCV7 group subjects during the 6-month f/u period. Bronchial hyperreactivity occurred in 1 (0.3%) subject in each study group during the 6-month f/u period. Asthma was reported in 1 subject (0.3%) in each study group during the 6-month f/u period.

10.2.4.4.4 Serious Adverse Events

No deaths occurred during the study or during the 6-month follow-up period. Serious adverse events occurred in 12 (4%) 13vPnC subjects and 10 (3.3%) PCV7 subjects during the infant series. Sixteen subjects in each group experienced SAEs > 30 days after dose 3 but before dose 4. After the toddler dose, 3 (1%) 13vPnC subjects and 4 (1.4%) PCV7 subjects experienced SAEs. The majority of these SAEs were reported under the Infections and Infestations System Organ Class. One SAE was assessed as related to study vaccine. This event involved a PCV7 subject 006-007-000244 with an underlying infection, who experienced a febrile convulsion on day 1 after the toddler dose.

Four subjects in the PCV7 group were discontinued from the study because of an adverse event. Subject 006-007-000244 (described above) had an underlying infection and experienced a febrile convulsion on day 1 after the fourth study vaccination. Subject 006-055-002164 experienced a febrile convulsion on day 48 after the third dose; this event was suspected to be related to a concurrent upper respiratory tract infection. Subject 006-026-001008 experienced gastroenteritis on day 77 after dose 1 and was discontinued because a series of infections (not suspected to be related to study vaccination) following the first dose caused continued delay in administration of further test articles. Subject 006-046-001809 experienced crying 1 day after dose 1 and was discontinued from the study by the parents.

Table 185 presents a line list of all SAEs occurring in 13vPnC subjects during study 006. There were no statistically significant differences in the incidence of SAEs between the vaccine groups.

Table 185. Study 6096A1-006, Subjects Who Experienced SAEs Within 30 Days After Any of Doses 1-3 of 13vPnC vaccine

Site No.	Subject No.	Dose	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Action	Outcome
Infant Series								
2	000055	1	Viral tonsillitis	23	6	Moderate	H	RES
		1	Decreased appetite	23	6	Moderate	H	RES
8	000282	3	Epididymitis	16	15	Moderate	H,C,UT	RES
	000283	1	Apnoeic attack	1	6	Moderate	H	RES
18	000693	1	Bronchitis	19	17	Severe	H,C,UT	RES
		3	Gastroenteritis rotavirus	6	4	Severe	H,C,UT	RES
		1	Failure to thrive	25	11	Mild	H,UT	RES
	000710	2	Pneumonia RSV	9	14	Severe	H,C,UT	RES
22	000848	1	Bronchitis	8	7	Moderate	H,C	RES
29	001139	3	Febrile infection	29	5	Moderate	H,C,ER	RES
	001141	2	Gastroenteritis rotavirus	10	8	Moderate	H,C,ER	RES
42	001658	3	Gastroenteritis	30	4	Moderate	H,C,ER	RES
44	001727	1	Bronchiolitis	21	3	Moderate	H,C,U	RES
47	001843	2	Urinary tract infection	5	5	Mild	H,C	RES
	001855	2	Pyelonephritis acute	8	12	Moderate	H,C	RES
After Infant Series								
1	000016	3	Concussion	219	3	Moderate	H, ER	RES
8	000285	3	Pneumonia	79	6	Severe	H, C, ER, U	RES
	000298	3	Viral infection	122	7	Severe	H, C, ER	RES
		3	Acidosis	122	7	Severe	H, C, ER	RES
18	000695	3	Gastroenteritis rotavirus	34	18	Severe	H, C, U	RES
	000697	3	Skeletal injury	54	2	Moderate	H	RES
	000698	3	Otitis media	209	8	Moderate	C, U	RES
		3	Febrile convulsion	209	2	Severe	H, C	RES
	000711	3	Chemical poisoning	131	2	Severe	H, C, ER	RES

23	000891	3	Muscle twitching	130	9	Mild	ER	RES
29	001139	3	Contusion	79	3	Mild	H, ER	RES
		3	Head injury	79	3	Mild	H, ER	RES
32	001243	3	Cystitis	155	5	Severe	H, C, ER	RES
36	001415	3	Skeletal injury	174	2	Mild	H	RES
39	001522	3	Failure to thrive	86	8	Severe	H, C, UT	RES
43	001684	3	Bronchitis	143	7	Severe	H, C	RES
		3		149	20	Moderate	C, UT	RES
		3	Bronchopneumonia	143	7	Severe	H, C, UT	RES
		3	Respiratory failure	143	7	Severe	H, C, UT	RES
48	001889	3	Gastroenteritis rotavirus	228	5	Moderate	H	RES
53	002091	3	Accidental exposure	180	4	Moderate	H	RES
61	002408	3	Gastroenteritis	71	4	Moderate	H, C	RES
Toddler Dose								
001	000003	4	Commotio cerebri	14	2	Severe	H	RES
018	002452	4	Rotavirus gastroenteritis	2	6	Severe	H, C, ER, U	RES
049	001927	4	Dehydration Gastroenteritis	5 3	6 8	Severe Severe	H H	RES RES
6-month follow-up								
001	000005	4	Gastroenteritis	152	2	Severe	H, C	RES
	000016	4	Commotio cerebri	80	3	Moderate	H	RES
002	000044	4	Brain contusion	75	3	Severe	H	RES
		4	Laceration of skull	75	3	Severe	H	RES
010	000369	4	Enteritis infectious (viral) Metabolic acidosis	47 51	7 3	Severe Severe	H, C H, C	RES RES
015	000565	4	Craniocerebral trauma	163	2	Moderate	-	-
018	002441	4	Otitis media Pharyngotonsillitis	56 54	4 6	Moderate Moderate	H, C, UT H, C, UT	RES RES
020	000765	4	Dehydration Rotavirus enteritis	78 75	3 8	Severe Severe	H, UT H, UT	RES RES
023	000884	4	Periorbital cellulitis	135	33	Mild	H, C	RES
032	001243	4	Dehydration Infectious gastroenteritis	110 110	6 6	Severe Severe	H, C, UT H, UT	RES RES
047	001855	4	Vesicoureteral reflux left	80	15	Severe	H, C	RES
054	002125	4	Gastroenteritis	97	3	Mild	H, C	RES

RSV: Respiratory Syncitial Virus
Source: 125324/0.2,m5.3.5.1, CSR69237-report-body-infant.pdf, page 200 (Table 15.86);
CSR74361-report-body-toddler.pdf, pages 100, 200, and 203 (Tables: 15.68 and 15.71);
CSR74361-follow-up-addendum.pdf, page 25 (Table 6.2).

10.2.4.4.5 Clinical Case Narratives

Clinical case narratives are provided for subjects who had SAEs that were determined by the study investigator to possibly be related to the study vaccine or AEs resulting in study withdrawal.

Subject 6096A1-006-046-001809:
A 3-month old female infant experienced an attack of crying on the day of vaccination with PCV7. The event resolved the same day. The subject was discontinued from the study by the parents.

Subject 6096A1-006-026-001008:
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. Other infections included an upper airways infection on day 8, which deteriorated and resulted in hospitalization due to suspected pneumonia on day 26. An acute bronchitis was diagnosed which resolved by day 28, at which time the subject was

discharged. The subject also developed a urinary tract infection (urine culture positive for Proteus mirabilis) which resolved by day 32.

Subject 6096A1-006-007-000244:
An 11-month old male infant with an underlying viral infection experienced a febrile convulsion 1 day after PCV7 dose 4 and was admitted for observation. Laboroatory and neurologic examination were unremarkable. The fever subsided by hospital day 2 and the infant was discharged on hospital day 3.

Subject 6096A1-006-055-002164:
A 7.5 month old boy, 48 days after PCV7 dose 3, developed a febrile convulsion lasting approximately 30 minutes. Temperature was 39.4^{o}C. The subject had an upper respiratory tract infection for some days prior to this adverse event. The subject was immediately seen by his pediatrician and subsequently admitted to the hospital. On admission, body temperature had decreased to 37.7^{o}C. Physical examination findings revealed bilateral bulging ear drums with red rims, inflamed throat with hypertrophied tonsils, enlarged maxillary lymph nodes, nasal breathing with purulent rhinitis, rhonchi, and no signs of meningismus. Laboratory tests revealed a C-reactive protein level of 11.8 mg/L, leukocytes 15,800/mcL, and positive blood culture for *Pseudomonas aeruginosa* and Micrococcus species with questionable clinical relevance. Cerebrospinal fluid culture done on day 48 showed no signs of meningitis. On day 52, the upper respiratory tract infection resolved. The subject was discharged in good health. Diazepam was recommended for emergency use. In the 6-months follow-up period, the subject experienced 2 more febrile convulsions on day 190 and on day 206 after third vaccination.

10.2.4.5 Summary and Conclusions

This was the pivotal European study to support licensure in Europe. Approximately 300 subjects were enrolled into each study group. For the purposes of U.S. licensure, serious adverse event safety data are relevant. Immunogenicity data are not viewed as supportive, because study vaccines were administered on a non-U.S. vaccination schedule and because this study included non-U.S. concomitant vaccinations. There were no imbalances in the rates of serious adverse events between the two vaccine groups. No deaths occurred during the study period. No new safety concerns were identified from the serious adverse event data from this study.

10.3 Clinical Study Protocol # 6096A1-3008

Clinical trials.gov registry identifier: NCT00475033

CSR # 73720: Infant series analyses.

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

10.3.1 Objective/Rationale

The study was designed to meet the objectives described below.

10.3.1.1 Primary objectives

1. To demonstrate that the immune response to meningococcal C antigen in NeisVac-C, when coadministered with 13vPnC, is noninferior to the immune response induced when NeisVac-C is given with PCV7, when measured 1 month after the 2-dose NeisVac-C infant series.
2. To demonstrate that the immune responses in to antigens contained in DTaP-IPV/Hib [Pentacel] when co-administered with 13vPnC are noninferior to immune responses to the same antigens when Pediarix is given with PCV7, when measured 1 month after the 3rd dose. Antibody responses to PRP-T, pertussis antigens (PT, FHA, PRN and FIM) components of Pentacel were evaluated.

10.3.1.2 Safety objective

To evaluate the acceptability of the safety profile of 13vPnC as measured by the incidence of local injection site reactions, systemic events, and adverse events (AEs).

10.3.1.3 Secondary objectives

1. To assess the immune response induced by NeisVac-C given with 13vPnC relative to the immune response induced by NeisVac-C given with PCV7, when measured 1 month after the toddler dose.
2. To assess the immune response to PRP-T in Pentacel when coadministered with 13vPnC vaccine relative to the immune response induced when Pentacel is given with PCV7 at an alternative cutoff level, when measured 1 month after the infant series.

10.3.1.4 13vPnC Immunogenicity Objectives

1. To assess the immune response to 13vPnC one month after the 3-dose infant series, as measured by serotype-specific serum IgG levels.
2. To assess the immune response to 13vPnC one month after the toddler dose, as measured by serotype-specific serum IgG levels.

10.3.2 Design Overview

Table 186. Study 6096A1-3008: Parallel-group, randomized, active-controlled, double-blind, multi-center study

Population n=482 (evaluable)	Vaccine	Dosing Schedule	Concomitant Vaccines
n= 241	13vPnC	2, 4, 6, and 12 mo	DTaP-IPV/Hib (Pentacel) at 2, 4, and 6 mo NeisVac-C at 2, 6, and 12 mo MMR and Varicella at 12 months
n= 241	PCV7 (Prevnar)		

Source: 125324/0.2,m5.3.5.1, CSR-73720-protocol-amend.pdf

10.3.3 Protocol

10.3.3.1 Population

10.3.3.1.1 Study Period
The study period was June 2007 to May 2008 (last infant series blood draw).

10.3.3.1.2 Study sites and recruitment
Study 6096A1-3008 was conducted at 12 sites in Canada.

10.3.3.1.3 Eligibility Criteria
Study 3008 contained similar inclusion and exclusion criteria compared to study 004. Criteria for temporarily delaying vaccine administration and for withdrawal of a subject were also similar to those described in study 004.

10.3.3.2 Concomitant medications
Antipyretic medications were permitted to prevent or treat symptoms related to study vaccination, and this information was collected on days 1 to 7 after vaccination. Topical and inhaled corticosteroids were permitted. Local anesthetic cream could be applied before blood draws.

10.3.3.3 Products mandated by the protocol
NeisVac-C and Pentacel were selected as the mandatory concomitant vaccines for this study. Children received the following study vaccines as per protocol:

13vPnC: Each 0.5ml dose contains 2.2ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4ug saccharide for 6B individually conjugated to cross-reacting material 197 (CRM_{197}). The final formulation contains 5mM succinate buffer with 0.125 mg aluminum as $AlPO_4$. The vaccine was filled in containers that were identical to those containing PCV7. Route: intramuscular (IM), anterolateral left thigh. Lot number: 7-5093-008A.

PCV7 [Prevnar; WLVP]: Each 0.5 ml dose includes 2.0ug of saccharide from pneumococcal serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4ug saccharide for 6B individually conjugated to cross-reacting material 197 (CRM_{197}). The final formulation contains 0.125 mg aluminum as $AlPO_4$. Route: IM, anterolateral left thigh. Lot number: 7-5092-009B.

DTaP-HBV-IPV [Pentacel; Sanofi Pasteur SA]: Each 0.5 mL dose contains diphtheria toxoid (30 international units (IU)), tetanus toxoid (40 IU), pertussis antigens (PT 20 µg, FHA 20 µg, PRN 3 µg, fimbriae types 2 and 3 (FIM) 5µg, inactivated poliovirus type 1 (40 D-antigen Units (DU)), type 2 (8 DU), and type 3 (32 DU), PRP-T 10 µg (24µg tetanus toxoid). Other ingredients per 0.5mL dose include 1.5mg aluminum phosphate (0.33mg Al), polysorbate 80 (~10 ppm) ≤ 5µg residual formaldehyde, < 50ng residual glutaraldehyde, ≤ 50ng residual bovine serum albumin, 3.3mg 2-phenoxyethanol, and < 4pg of neomycin and < 4pg polymyxin B sulfate. Route: IM, lower anterolateral right thigh. Lot number: C2823AA.

NeisVac-C [GSK Inc]: This vaccine is not approved in the U.S. Each 0.5ml dose contains 10ug N. meningitidis group C polysaccharide, 10-20µg tetanus toxoid, 0.5 g Aluminum as aluminum hydroxide, and sodium chloride. Route: IM into upper anterolateral right thigh. Lot number: 904511.

MMR [M-M-R II; Merck & Co, Inc]: This is a combined, attenuated, live-virus, lyophilized vaccine vaccine. Each 0.5 mL dose contains not less than 1000 $CCID_{50}$ (50% cell culture infectious doses) of measles virus, 5000 $CCID_{50}$ of mumps virus, and 1000 $CCID_{50}$ of rubella virus. Each reconstituted dose is calculated to contain sorbitol (14.5mg), sodium phosphate, sucrose (1.9mg), sodium chloride, hydrolyzed gelatin (14.5mg), recombinant human albumin (≤ 0.3 mg), fetal bovine serum (< 1ppm), other buffer and media ingredients and ~ 25µg of neomycin. The commercially available MMR vaccine was to be administered as a concomitant vaccine per local practice. Route: subcutaneously (SQ) into left or right deltoid or lower anterolateral right thigh. Lot number: 1844U.

Varicella [Varivax III; Merck & Co, Inc]: Each 0.5mL dose contains the following: a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus when the lyophilized preparation is reconstitued and stored at room temperature for 30 minutes, approximately 25mg of sucrose, 12.5 mg hydrolyzed gelatin, 3.2mg sodium chloride, 0.5mg monosodium L-glutamate, 0.45mg of sodium phosphate dibasic, 0.08mg of potassium phosphate monobasic, 0.08mg of potassium chloride, residual components of MRC-5 cells including DNA and protein, and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum. Route: SQ into left or right deltoid or lower anterolateral right thigh. Lot number: 0464U.

Permitted vaccines included the following (within certain permitted time windows)*:* rotavirus vaccine; influenza vaccine, a booster dose of Pentacel or MMR, and HBV vaccine. Any commercially available vaccines recommended by health authorities or requested by the subject's parent/legal guardian could be given during the study according to the following guidelines: was not given concomitantly with any test article; was given > 14 days (nonlive vaccine) or > 28 days (live vaccine, excluding rotavirus vaccine) before any test article; was given at least 7 days after any test article; and was not given between dose 3 and the post-dose 3 blood draw or between dose 4 and the post-dose 4 blood draw.

10.3.3.4 Endpoints

10.3.3.4.1 Primary Immunogenicity Endpoints

1. Proportion with anti-meningococcal C SBA ≥ 1:8 after 2 doses.
2. Proportion with anti-PT, anti-PRN, and anti-FHA antibody levels ≥ 5 EU/mL after 3 doses
3. Proportion with anti-FIM 2 and anti-FIM 3 antibody levels ≥ 2.2 EU/mL after 3 doses
4. Proportion with anti-PRP-T antibody levels ≥ 0.15 µg/mL after 3 doses.

10.3.3.4.2 Secondary Immunogenicity Endpoints

1. Proportion with anti-meningococcal C SBA ≥ 1:8 after 3 doses.
2. Proportion with post-dose 3 anti-PRP-T antibody levels ≥ 1.0µg/mL after 3 doses.

10.3.3.4.3 Pneumococcal Immunogenicity Endpoint

Proportion with post-dose 3 and post-dose 4 serotype-specific IgG antibody concentration ≥ 0.35 µg/mL.

10.3.3.4.4 Safety Endpoint

The primary endpoints for safety comparisons include incidence rates of solicited local injection site reactions, solicited systemic events (including fever and use of antipyretic medications), and other unsolicited AEs occurring within 4 days after each vaccination. Fever was defined as an axillary temperature ≥ 38.0^{o}C.

10.3.3.5 Surveillance

10.3.3.5.1 Safety Surveillance / Monitoring

Safety surveillance described in the protocol for study 3005 is identical to study 004 safety surveillance.

Table 187. Study 6096A1-3008 Flowchart

Visit No.	1	2	3	4	5	6	7
Visit ID	2-Month Visit	4-Month Visit	6-Month Visit	7-Month Visit	12-Month Visit	13 Month Visit	18 Month Visit
Study Interval	Vaccine dose 1	Vaccine dose 2	Vaccine dose 3	Post-infant series	Vaccine dose 4	Post-toddler dose	6-Month Follow-up
Visit Window	42-98 days of age	42-70 days after visit 1	42-70 days after visit 2	28-42 days after visit 3	365-395 days of age	28-42 days after visit 5	165-210 days after last study vaccine
Informed consent	X						
Review inclusion/ exclusion/delay criteria	X						
Medical Hx/PE	X						
Axillary temperature	X	X	X		X		
Randomization	X						
Study vaccination & 30 minute observation	X	X	X		X		
NeisVac-C vaccination	X		X		X		
Pentacel vaccination	X	X	X				
MMR vaccination					X		
Varicella vaccination					X		
Hepatitis A vaccination					X		
Confirm continued eligibility		X	X	X	X	X	
AE collection	⟷ x ⟶				⟷ x ⟶		
SAE collection	⟷ x ⟶						
Obtain blood sample				X		X	
E-diary, thermometer, calipers provided	X	X	X		X		
Review e-diary		X	X	X		X	
Collect e-diary				X		X	
Assess acute reactions	Day 1 to 4*	Day 1 to 4	Day 1 to 4		Day 1 to 4		
Record use of antipyretic medication	Day 1 to 4	Day 1 to 4	Day 1 to 4		Day 1 to 4		
Telephone call							X

*Day of vaccination is considered day 1.
Newly diagnosed chronic medical conditions since visit 4 were collected at visit 5.
Source: 125324/0.2,m5.3.5.1, CSR-73720-protocol-amend, pages 20-21 (Table 8-1)

10.3.3.6 Statistical considerations

Blinding:
This is a double blind study. The appearance of the 13vPnC and PCV7 vaccines were identical. Before analysis was performed, a blinded statistical review of the database occurred to ensure that all data were as expected, that the planned analyses could be performed, and that no underlying statistical assumptions were violated.

Randomization:
Eligible subjects were randomized in a 1:1 ratio to using Wyeth's CORE II system. Only subjects who withdrew before randomization could be replaced with additional subjects.

10.3.3.6.1 Sample Size/Statistical Power
The sample size chosen was selected to provide at least 91% overall power to declare non-inferiority of 13vPnC relative to PCV7 and non-inferiority of selected concomitant vaccine antigens.

10.3.3.6.2 Study Cohorts Analyzed
The safety population included all subjects who received at least 1 dose of the study vaccine, and subjects were analyzed according to the actual vaccine received. Separate safety populations were defined for each vaccination in addition to an additional infant series analysis population, which included any subjects included in the dose 1, dose 2, or dose 3 safety populations.

10.3.3.6.3 Statistical Analyses

Interim analyses:
The primary analysis was performed after all infant series assay results were available. All Type I error was spent for this analysis.

10.3.3.7 Changes in the Study Protocol (Protocol Amendments) and in the Planned Analyses

The two amendments to the original protocol (dated 02-Mar-07) are summarized below.

- Amendment 1 (29-Mar-07): Permitted influenza vaccination beginning 7 days after completion of the infant vaccine series, specified the HBV injection site as in the lower anterolateral left thigh when given concomitantly with pneumococcal conjugate vaccine, allowed visit 7 to be in person, clarified that a complete physical examination form performed no more than 2 days before enrollment could be accepted for study purposes if an additional brief examination and axillary temperature assessment were performed on the day of vaccination, and reworded powering of the study regarding non-inferiority of 13vPnC versus PCV7.
- Amendment 2 (15-Jan-08): Added rotavirus as a permitted nonstudy vaccination during anytime throughout the study.

10.3.4 Results

10.3.4.1 Populations Enrolled/Analyzed

10.3.4.1.1 Subject Disposition and Follow-up

Table 188. Study 6096A1-3008 Summary of Subject Disposition

	13vPnC N=300		PCV7 N=303		Total N=603	
	n	%	n	%	n	%
Subjects consented[a]	300	100.0	303	100.0	603	100.0
Subjects randomized	300	100.0	303	100.0	603	100.0
Subjects vaccinated						
Dose 1	300	100.0	303	100.0	603	100.0
Dose 2	297	99.0	296	97.7	593	98.3
Dose 3	293	97.7	294	97.0	587	97.3
Completed infant series	293	97.7	291	96.0	584	96.8
Withdrawn during infant series	7	2.3	12	4.0	19	3.2
Reasons for withdrawal:						
Failed to return	3	1.0	4	1.3	7	1.2
Parent / legal guardian request	1	0.3	5	1.7	6	1.0
Protocol violation	1	0.3	2	0.7	3	0.5
Lost to follow-up	2	0.7	0	0.0	2	0.3
Adverse Event*	0	0.0	1	0.3	1	0.2

* Subject 3008-009-001133 in the PCV7 group was withdrawn for mild urticaria which began 2 days after the third vaccination.
Source: 125324/0.2,m5.3.5.1, CSR-73720-report body, page 40 (Table 8-2).

10.3.4.1.2 Subject Demographics

The two study groups were similar with regards to demographic characteristics. The majority of subjects in each study group were White and non-Hispanic/non-Latino.

Table 189. Study 6096A1-3008, Demographic Characteristics for All Subjects by Randomized Group

	13vPnC N=300		PCV7 N=303		Total N=603	
	n	%	n	%	n	%
Gender						
Male	157	52.3	151	49.8	308	50.7
Female	143	47.7	152	50.2	295	48.5
Race						
White	246	82.0	251	82.8	497	81.7
Other	35	11.7	34	11.2	69	11.3
Asian	10	3.3	10	3.3	20	3.3
Black	9	3.0	8	2.6	17	2.8
Ethnicity						
Non-Hispanic and Non-Latino	286	95.3	297	98.0	583	95.9
Hispanic or Latino	14	4.7	6	2.0	20	3.3
Age at enrollment (months)						
Mean (SD)	2.1 (0.3)		2.1 (0.3)		2.1 (0.3)	
Min, Max	1.4, 3.2		1.4, 3.3		1.4, 3.3	
Weight at enrollment (lbs)						
Mean (SD)	5.4 (0.8)		5.4 (0.8)		5.4 (0.8)	
Min, Max	3.1, 9.8		3.1, 7.7		3.1, 9.8	

Source: 125324/0.2,m5.3.5.1, CSR-73720-report body.pdf, page 49 (Table 8-9).

10.3.4.2 Safety Outcomes

10.3.4.2.1 Unsolicited Adverse Events

Overall, a similar proportion of subjects in each study group reported unsolicited adverse events following any of doses 1-3. During the infant series (i.e. within 30 days following any of doses 1-3), unsolicited adverse events were reported by 76.3% (229/300) and 75.9% (230/303) of subjects in the 13vPnC and PCV7 groups respectively. The most frequently reported adverse events during the infant series were nasopharyngitis (13vPnC: 22.7%, PCV7: 19.8%), upper respiratory tract infections (13vPnC: 20.0%, PCV7: 17.5%), pyrexia (13vPnC: 11.0%, PCV7: 14.2%), nasal congestion (13vPnC: 10.3, PCV7: 6.9), diarrhea (13vPnC: 10.0%, PCV7: 9.6%), and cough (13vPnC: 9.7%, PCV7: 7.3%).

Unsolicited adverse events occurring in at least 1% of 13vPnC subjects and in more 13vPnC subjects compared to PCV7 subjects following any of the first three infant series doses included the following: nasopharyngitis (22.7, 19.8%), upper respiratory tract infection (20.0%, 17.5%), nasal congestion (10.3%, 6.9%), diarrhea (10.0%, 9.6%), cough (9.7%, 7.3%), rhinorrhea (7.7%, 6.6%), vomiting (7.3%, 6.3%), irritability (6.0%, 4.0%), bronchiolitis (5.3%, 4.6%), teething (5.3%, 4.6%), injection site erythema (5.0%, 4.6%), gastroenteritis (4.3%, 4.0%), constipation (4.3%, 1.0%, p=0.011), dermatitis diaper (4.0%, 2.3%), eye discharge (2.3%, 1.3%), oral candidiasis (2.3%, 0.7%), croup infectious (1.7%, 1.3%), gastroenteritis viral (1.7%, 0.7%), urticaria (1.3%, 1.0%), flatulence (1.3%, 0.7%), injection site bruising (1.3%, 0.3%), injection site swelling (1.3%, 0.3%), dry skin (1.0%, 0.7%), candidiasis (1.0%, 0.3%), and wheezing (1.0%, 0.0%).

A statistically significantly higher proportion of subjects in the 13vPnC reported constipation compared to the PCV7 group.

10.3.4.2.2 Serious Adverse Events

No deaths or severe or life-threatening events were reported during the infant series. Table 190 presents the number and percentage of subjects reporting serious adverse events during the infant series by MedDRA systemi organ class (SOC) and preferred terms (PT). Table 191 presents a line listing of all subjects who experienced a SAE following dose 1 to 3. Overall, a similar proportion of subjects in each treatment group reported the occurrence of any serious adverse event.

Table 190. Incidence of SAEs occurring after doses 1 to 3, by MedDRA system organ class and preferred term, study 6096A1-3008.

	Infant Series: Doses 1-3		
System Organ Class Preferred Term	**13vPnC N[a]=300 n (%)**	**PCV7 N[a]=303 n (%)**	**p-value[b]**
Any event	5 (1.7)	5 (1.7)	>0.99
Eye disorders	0 (0.0)	1 (0.3)	>0.99
Cataract	0 (0.0)	1 (0.3)	>0.99
Gastrointestinal Disorders	1 (0.3)	0 (0.0)	0.498
Vomiting	1 (0.3)	0 (0.0)	0.498
General Disorders and Administration Site Conditions	1 (0.3)	0 (0.0)	0.498
Pryexia	1 (0.3)	0 (0.0)	0.498
Infections and Infestations	5 (1.7)	3 (1.0)	0.503
Bronchiolitis	4 (1.3)	3 (1.0)	0.724
Gastroenteritis	0 (0.0)	1 (0.3)	>0.99
Respiratory syncytial virus infection	1 (0.3)	0 (0.0)	0.498
Viral infection	1 (0.3)	0 (0.0)	0.498
Injury, Poisoning and Procedural Complications	0 (0.0)	1 (0.3)	>0.99
Post procedural haemorrhage	0 (0.0)	1 (0.3)	>0.99

[a] Number of subjects reporting at least one event.
[b] Fisher exact test, 2-sided, used to calculate difference between vaccine groups in percentage of subjects reporting an event. p-values are not corrected for multiple comparisons.
Source: 125324/0.2,m5.3.5.1, CSR-73720-report-body, pages 91-92 (Table 10-10).

Table 191. Study 6096A1-3008, Subjects Who Experienced SAEs Within 30 Days After Any of Doses 1-3

Site-Subject Number	Vaccine Group	Dose Number	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Severity	Action[a]	Outcome
003-000429	13vPnC	2	Bronchiolitis	61	3	Moderate	H	Resolved
003-000438	13vPnC	2	Bronchiolitis	46	6	Severe	H, C, ER, UT	Resolved
003-000446	13vPnC	1	Bronchiolitis	34	7	Severe	H, C	Resolved
009-001142	13vPnC	2	Viral infection	10	6	Severe	H, C, ER	Resolved
010-001318	13vPnC	2	Vomiting	33	7	Moderate	E, U	Resolved
		2	Pyrexia	38	3	Moderate	H, C	Resolved
		1	Bronchiolitis	63	2	Moderate	H, C	Resolved
		1	RSV infection	10	3	Severe	H, C	Resolved
003-000421	PCV7	2	Bronchiolitis	51	8	Severe	H, C, ER	Resolved
003-000439	PCV7	2	Bronchiolitis	46	6	Severe	H, UT	Resolved
		3	Gastroenteritis	19	7	Severe	H, ER	Resolved
005-000737	PCV7	2	Bronchiolitis	53	13	Severe	H, C, UT	Resolved
006-000841	PCV7	1	Post-procedural haemorrhage	19	2	Moderate	H, C, ER	Resolved
006-000886	PCV7	2	Cataract	29	23	Moderate	H	Resolved
		2	Cataract	52	32	Moderate	H, C	Resolved

RSV: Respiratory Syncytial Virus
[a] Action abbreviations: C – concomitant medication; D – discontinued test article permanently; E – ER visit/no tests or procedures; ER – ER visit/tests or procedures; H – hospitalized; U – Unscheduled clinic visit/no tests or procedures; UT – Unscheduled clinic visit/tests or procedures.
Source: 25324/0.1,m5.3.5.1, Adverse Event Listings, pages 1-159.

10.3.4.2.3 Safety-Related Discontinuations

One subject, subject 009-001133, was withdrawn from the study during the infant series because of an adverse event.

Table 192. Study 6096A1-3008, Subject Withdrawn Because of an Adverse Event

Subject number	Vaccine Group	Preferred Term	Vax #	Time to Onset (days)	Duration (days)	Severity	Action[a]	Outcome	SAE
009-001133	PCV7	Urticaria	2	2	1	Mild	W, C, U	Resolved	No

[a] Action abbreviations: C – concomitant medication; U – Unscheduled clinic visit/no tests or procedures; W – Withdrawn from study.
Source: 125324/0.1,m5.3.5.1, CSR69238-report body.pdf, page s170-173 (Tables 10-20 – 10-25.).

10.3.4.2.4 Clinical case narratives

A clinical case narrative is provided for the subject who experienced an adverse event resulting in withdrawal from the study.

Subject 6096A1-3008-009-1133

Two days after the 3rd dose of PCV7, this 5 month old white, male infant experienced mild urticaria. The event resolved on the same day and the event was not considered a serious adverse event. The subject was withdrawn because of the adverse event.

10.3.4.3 Summary and Conclusions

Study 3008 was a phase 3 study designed to evaluate the compatibility of Prevnar 13 with routine childhood vaccinations in Canada as a primary study objective. This study also evaluated the safety profile of Prevnar 13 compared to Prevnar. For the purposes of U.S. licensure, the review of study 3008 focused on serious adverse event safety data. No deaths or severe or life-threatening events were reported during the infant series. There were no imbalances in the rates of serious adverse events between the two vaccine groups. Five subjects (1.7%) reported any SAE in each vaccine group. Events classified as Infections and Infestations were most common, and bronchitis was reported most frequently. One subject withdrew from the study due to an adverse event. This 5 month old subject subject experienced mild urticaria 2 days after receiving the 2nd does of Prevnar; the event resolved the same day

11.0 Additional Supportive Studies

11.1 Study 6096A1-002

Protocol Title: A Randomized, Controlled Trial of the Safety, Tolerability, and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine in Healthy Adults

Study Design: This study was a phase 1 open-label, randomized, single center, safety and immunogenicity trial. Thirty healthy U.S. adults, aged 18-50 years old, received one dose of 13vPnC – P80 (n=15) or a licensed 23-valent pneumococcal polysaccharide (PPV23) vaccine (n=15).

The primary objective was to evaluate the safety of 13vPnC, as assessed by local AEs (Days 0-14), temperature (Day 0-7), and unsolicited/ serious adverse events occurring during a 28 day post-vaccination period. Use of acetaminophen or ibuprofen prior to vaccination and during a 14 day post-vaccination was recorded on a case report form. A secondary objective was to assess serotype-specific IgG and OPA antibody responses for the 13 vaccine serotypes contained in 13vPnC. Serotype 6A is not a PPV23 vaccine antigen. Pneumococcal IgG antibody was measured by 22F-ELISA. Blood samples were collected pre- and 28 days post-vaccination.

Study period: 02-Jun-2004 to 06-Jul-2004

Results: All participants completed the study. Twice as many women (66.7%) were enrolled in the 13vPnC group compared to the PPV23 group. All 13vPnC participants were Caucasian. Of PPV23 participants, 80.0% were Caucasian, 13.3% were African American, and 6.7% were Native American. There were no substantive differences in age.

Safety: In both study groups, tenderness occurred most often. Significant tenderness (tenderness interfering with limb movement) was 2.5 times more frequent in 13vPnC recipients than in PPV3 recipients (n=10 of 15 (67%) 13vPnC; n=4 of 15 (27%) PPV23). No participant reported fever ≥38°C or a serious adverse event. Information about acetaminophen or ibuprofen use was not provided.

Immunogenicity:
Baseline serotype-specific IgG antibody

- All participants had pneumococcal serotype-specific IgG antibody prior to vaccination.
- The 95% confidence intervals for pre-vaccination IgG GMCs overlapped for 12 serotypes. Baseline serotype 18C IgG GMC was 0.99 ug/mL (95% CI 0.53, 1.85) and 0.35 ug/mL (95% 0.15, 0.78) among 13vPnC participants and PPV23 participants, respectively.

13vPnC vs. PPV23 postvaccination IgG and OPA antibody responses

- After 13vPnC vaccination, serotypes 18C, 6A, 6B, and 23F IgG GMCs were 3-7 times higher than the corresponding PPV23 post-vaccination GMCs; the 95%CIs for the 4 serotypes did not overlap. OPA GMT responses supported IgG results for each serotype.

PPV23 participants: serotype 6A

- PPV23 postvaccination GMC compared to baseline
  - Serotype 6A post-vaccination GMC increased compared to baseline, which might be due to some serotype 6B cross-reactivity.
- PPV23 postvaccination GMC vs. 13vPnC postvaccination GMC
  - After 13vPnC vaccination, 6A IgG GMC was 4 times higher than PPV23 post-vaccination GMC. Serotype 6A included as a vaccine antigen is more immunogenic than an elicited 6A antibody response due to cross-reactivity with 6B.

Summary: One 13vPnC dose in adults elicited increased IgG responses to 13 serotypes, especially to 18C, 6A, 6B, and 23F. Serotype 6A antibody response in 13vPnC participants compared to PPV23 participants suggests that 6A included as a vaccine antigen is more immunogenic than a 6A antibody response due to 6B cross-reactivity. The choice of selected dose and dosing regimen for Phase 2 and 3 studies is supported by safety and immunogenicity results in this study.

12.0 Other Supportive Safety Studies

In 9 studies enrolling 4381 healthy infants, 2322 received at least one dose of 13vPnC vaccine. Eight studies included control group recipients given at least one PCV7 (n=2059) vaccination. Occurrences of serious adverse events (SAEs) and newly diagnosed chronic illnesses provided additional comparative safety data to support 13vPnC U.S. licensure. 13vPnC-P80 vaccine was the formulation evaluated in all controlled trials. 13vPnC safety was evaluated according to routine infant vaccination schedules in Europe, Canada and India. Concomitant immunizations were given according to country recommendations. Since country-specific recommended schedules and certain co-administered vaccines differed from U.S. medical practices, solicited and unsolicited AE evaluations were not included in the overall 13vPnC U.S. safety database. All studies were conducted between Oct 2006 and May 2008.

Table 193. Supportive Safety Studies

			Vaccinated Participants (as randomized)		
#	Study #	Country	**13vPnC** (n)	**PCV7** (n)	**Concomitant Vaccine Schedule (age in months)**
1	6096A1-007[b]	UK	139	139	Pediacel (2, 3, 4) NeisVacC (2, 4) Menitorix (12)
2	6096A1-3000	Poland	268	0	Pentaxim (2, 3, 4) Engerix-B (2) Priorix (12)
3	6096A1-3007[a]	Spain	218	226	Infanrix hexa (2, 4, 6) NeisVac-C (2, 4, 15) MMR (12) Infanrix-IPV+Hib (15)
4	6096A1-011[a]	India	178	175	Easy5 (6, 10, 14 weeks) Bipolio (6, 10, 14 weeks)
5	6096A1-500[c]	Italy	302	302	Infanrix hexa (3, 5, 11)
6	6096A1-501[c]	Spain	314	302	Infanrix hexa (2, 4, 6) Neis Vac-C (2, 4, 15) MMR (12) Infanrix-IPV+Hib (15)
7	6096A1-008[b]	France	302	309	Pentavac (2, 3, 4, 12)
8	6096A1-3008[a]	Canada	300	303	Neis Vac-C (2, 6, 12) Pentacel (2, 4, 6) MMR (12)
9	6096A1-006[c]	Germany	301	303	Infanrix hexa (2, 3, 4 11-12)

The biologics license application (BLA) included:
[a] Safety data 1 month after the last infant vaccination.
[b] Safety data 1 month after the toddler vaccination.
[c] Safety data 6 months after the toddler vaccination
Engerix-B: Hepatitis B. *Infanrix*: DTaP; *Infanrix hexa*: DTaP-HBV-IPV;
Pediacel/Pentacel/Pentaxim/Pentavac: DTaP-IPV/Hib; *Easy5*: DTwP-IPV-Hib; *Bipolio*: OPV
Priorix: MMR; *NeisVacC*: Serogroup C meningococcal – tetanus toxoid conjugate vaccine (MenC-TT)
Menitorix: Tetravalent (A, C, W, Y) meningococcal polysaccharide vaccine

Safety evaluation *(9 studies)*
Study participants were observed for immediate adverse reactions within 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 ≥ 38.0°C) occurring within 4 days after each vaccination were recorded daily in an electronic diary. Unsolicited adverse events occurring within 30 days after each vaccination were collected at the next scheduled clinic visit. Newly diagnosed chronic

medical conditions and serious adverse events (SAEs) reported during the study period and were obtained by a scripted telephone interview.

All comparative trials except -011 included a 6 month post-toddler safety evaluation. In study -011, pre-specified 13vPnC safety monitoring was up to 1 month after the toddler dose.

Serious Adverse Events
SAEs, newly diagnosed chronic illnesses and safety-related study discontinuations are summarized by individual study. SAEs case narratives were provided for events lead to safety-related study discontinuation.

Study 6096A1-007 (United Kingdom)
Infants received 13vPnC or PCV7 at 2, 4 and 12 months old. The all available infant safety population evaluated for SAEs included 278 participants (13vPnC n=139, PCV7 n=139). The randomized study population was Caucasian (88.5%), and also included African American (3.8%), Asian populations (2.4%) and individuals of other racial backgrounds (5.2%). The all available toddler safety population evaluated for SAEs included 253 participants (13vPnC n=130, PCV7 n=123).

During the study period through 1 month post-toddler vaccination, 16 SAEs occurred in 15 individuals (13vPnC n=7; PCV7 n=7, events =8). All SAEs resulted in hospitalization. Respiratory events included bronchiolitis (13vPnC, 3 events), wheezing (13vPnC, 1 event) and pneumonia (PCV7, 2 events). The remaining participants reported other infections (mastoiditis PCV7, 1 event; cellulitis PCV7, 1 event), GI related conditions (gastroenteritis, gastrointestinal reflux), a breath holding episode (PCV7, 1 event) hemiplegia, and bodily injury.

Four participants (13vPnC n=1, PCV7 n=3) withdrew from the study due to an adverse event. None of the events were categorized as a SAE.

- *13vPnC*: inconsolable crying ~ 24 hours after DTaP-IPV/Hib vaccination. The duration of crying lasted 2-3 hours/ per day for 3 days. No concomitant vaccines were given.
- *PCV7*: mild facial flushing, wheezing and concomitant vaccine injection site reactions after dose 1. Recurrent symptoms and high pitched crying occurred after dose 2. Both PCV7 doses were co-administered with DTaP-IPV/Hib and MenC-TT. Symptoms resolved without medical intervention; *PCV7*: macular, erythematous, blanching truncal rash, which spontaneously resolved 1 hour after the first vaccination. The rash was not associated with respiratory symptoms; *PCV7*: congenital hemiplegia.

Study 6096A1-3000 (Poland)
Infants received 13vPnC at 2, 3, 4 and 12 months old. This study was an immunogenicity bridging of manufacturing and pilot scale 13vPnC vaccine lots. Comparison of manufacturing and pilot 13vPnC safety profile was assessed by the incidence rates of local reactions, systemic events, and non-serious adverse events (AEs) and SAEs. A PCV7 control group was not needed for 13vPnC lot consistency comparisons.

Study 6096A1-3007 (Spain)
Infants received 13vPnC or PCV7 at 2, 4, 6 and 15 months old. The all available infant safety population evaluated for SAEs included 444 participants (13vPnC n=218, PCV7 n=226). The randomized study population was 98.2% Caucasian, 0.4% African American and 1.3% individuals of other racial backgrounds. Hispanic and Latino ethnic groups comprised 4.9% of the population.
During the study period up through 1 month after the last infant vaccination, 16 SAEs occurred in 14 individuals (13vPnC n=6, events =8; PCV7 n=8). All SAEs resulted in hospitalization. Respiratory events included bronchiolitis (13vPnC, 1 event; PCV7, 2 events) wheezing (13vPnC, 1 event) and pneumonia (13vPnC, 1 event). One 13vPnC and one PCV7 participant, respectively, developed pyrexia. The remaining participants reported GI related conditions (gastrointestinal reflux, gastroenteritis), gastrourinary infection (UTI, pyelonephritis), and other infections (orchitis, viral). No participants withdrew from the study due to an adverse event.

Study 6096A1-011 (India)
Infants received 13vPnC or PCV7. The planned vaccination schedule was 6, 10, 14 weeks and 12 months old. Approximately 2.5 months after study start, enrollment was stopped during an SAE review. Based on the available data, sudden unexpected death of infancy (SUDI) was the likely cause of death. During the 2 month safety review process, many subjects withdrew to avoid lapsed routine childhood vaccinations. All participants, regardless of study discontinuation, were encouraged to continue follow-up safety evaluations. An additional 354 participants (cohort 2) were enrolled after the study re-started. Cohort 2 is representative of children vaccinated according to the routine childhood immunization schedule (6, 10, 14 weeks and 12 months old). The study was paused again ~1 month after completed cohort 2 enrollment. A 3.5-month old PCV7 died from presumed viral myocarditis, dilated cardiomyopathy and subsequent cardiac arrest. Safety data for cohort 2 (infant, toddler) and cohort 1 (toddler dose) are anticipated to be available at a later date. Cohort 1 infant safety and immunogenicity data were included in the BLA. Of 352 vaccinated infants, 113 (63.8%) 13vPnC and 110 (62.5%) PCV7 cohort 1 participants completed the study. Voluntary study discontinuation was mainly due to temporary study pause (13vPnC 31%; PCV7 32.4%). The all available infant safety population evaluated for SAEs included 352 participants (13vPnC n=177, PCV7 n=175). The mean age for 13vPnC doses 1, 2 and 3 was 7.2 weeks (standard deviation 1.1), 13.5 weeks (SD 2.4) and 19.6 weeks (SD 2.3), respectively. The randomized study population was 99.4% Asian and 0.6% individuals of other racial backgrounds. More girls were enrolled in both 13vPnC and PCV7 groups (range 54.4%-58.2%).

During the study period through 1 month after the last infant vaccination, 10 SAEs occurred in 8 individuals (13vPnC n= 5, events= 8; PCV7 n=3, events= 4). All SAEs resulted in hospitalization. Respiratory illness events included bronchiolitis (13vPnC, 1 event; PCV7, 1 event), pneumonia (13vPnC, 2 events), and respiratory infection not otherwise specified (PCV7, 1 event). Other events included colic and viral infections.

A 2-month old girl, who developed a febrile seizure and presumed meningitis, withdrew from the study. Fever and runny nose started 43 days after 13vPnC dose 1. She was evaluated in the emergency room, diagnosed with bronchiolitis, and prescribed oral cephalexin. The next day, she was hospitalized after occurrence of tonic-clonic movements and T40.3C. CSF indices were suggestive of bacterial meningitis. Her symptoms resolved following antibiotic treatment, phenytoin and acute care management. CSF and blood cultures, obtained after the start of antibiotic treatment, showed no growth. She recovered without sequelae.

Study 6096A1-500 (Italy)
Infants received 13vPnC or PCV7 at 3, 5 and 11 months old. The all available infant safety population evaluated for SAEs included 604 participants (13vPnC n=302, PCV7 n=302). The randomized study population was 93.8% Caucasian, 0.3% African American, 0.5% Asian and 5.4% individuals of other racial backgrounds. Hispanic and Latino ethnic groups comprised 8.6% of the population. The all available toddler safety population evaluated for SAEs included 569 participants (13vPnC n=287, PCV7 n=282).

During the 16 month study period, 59 individuals reported 87 SAEs (13vPnC n=26, events= 39; PCV7 n=33, events= 48). All SAEs resulted in hospitalization. Respiratory related events included bronchiolitis/bronchitis (13vPnC, 4 events; PCV7, 5 events), wheezing (PCV7, 1 event), asthma (PCV7, 1 event), pneumonia (PCV7, 3 events) and bronchospasm (13vPnC, 1 event). Neurological conditions included hypokinesia, nystagmus and decreased loss of consciousness.

One PCV7 participant developed meningitis-like symptoms, and two participants reported pyrexia. Febrile seizures occurred in five 13vPnC participants and one PCV7 participant. An infant in each study group reported an ear infection. A toddler in the 13vPnC group developed orbital cellulitis. Participants in the PCV7 group developed microcytic anemia, congenital disease and atrioventricular heart block, respectively. Other hospitalizations were for common childhood illnesses such as GI related illness/conditions, pharyngitis and viral infections.

Four participants withdrew from the study due to a SAE. One event occurred in 13vPnC participant (Kawasaki disease). Hypokinesia, infantile spasms, congenital disease, respectively occurred in three separate PCV7 participants.

Study 6096A1-501 (Spain)
Infants received 13vPnC or PCV7 at 2, 4, 6 and 15 months old. The all available infant safety population included 619 participants (13vPnC n=314, PCV7 n=300). The randomized study population was 99.0% Caucasian and 0.3% African American, and 0.3% individuals of other racial backgrounds. Hispanic and Latino ethnic groups comprised 5.0% of the population. The all available toddler safety population evaluated for SAEs included 582 participants (13vPnC n=292, PCV7 n=289).

During the 16 month study period, 63 individuals reported 85 SAEs (13vPnC n=31, events= 39; PCV7 n=32, events= 46). One death occurred due to SIDS. The remaining SAEs resulted in hospitalization. Respiratory events included bronchiolitis/bronchitis (13vPnC, 9 events; PCV7, 10 events), pneumonia (13vPnC, 2 events; PCV7, 3 events) and apnea (13vPnC, 1 event). An infant, 2 days after PCV7 dose 3, was hospitalized for fever and a bulging fontanelle. The infant recovered without sequelae. Two children in the 13vPnC group developed viral meningitis and a non-febrile seizure, respectively. Diabetes mellitus occurred in one 13vPnC participant.

Five participants (13vPnC n=1, PCV7 n=4) reported a febrile seizure as a SAE. Four seizure events resulted in study discontinuation. Three of the four events occurred >3 months after the 3rd vaccination.
A 2- month old girl developed a febrile seizure 2 days after the 3rd PCV7 dose. Loss of consciousness and clonic movements lasted ~5 minutes. Hospital laboratory evaluation was non-contributory. She recovered without sequelae.

Other hospitalizations were for common childhood illnesses such as GI related illness/conditions, pharyngitis, UTI, joint inflammation (synovitis, arthritis), injury and viral infections.

Study 6096A1-008 (France)
Infants received 13vPnC or PCV7 at 2, 3, 4 and 12 months old. Participants received one of three regimens: study group #1: four 13vPnC doses (13v/13v); (b) study group #2: four PCV7 doses (7v/7v); (c) study group #3: three 13vPnC doses at 2, 3 and 4 months old, and a toddler (12m) PCV7 dose (7v/13v).
The all available infant safety population evaluated for SAEs included 611 participants (13vPnC n=302, PCV7 n=309). The randomized population was 93.7% Caucasian, 4.7% African American, 0.3% Asian and 1.3% individuals of other racial backgrounds. Hispanic and Latino ethnic groups comprised 0.4% of the population. The all available toddler safety population evaluated for SAEs included 562 participants (13v/13v n=273, 7v/7v n=152, 7v/13v n=137).

During the study period up to 1 month after the toddler vaccination, 27 individuals reported 34 SAEs (13vPnC n=17, events =21; PCV7 n=10, events =13). Respiratory related events included bronchiolitis/bronchitis (13vPnC, 6 events; PCV7, 1 event), asthma (13vPnC, 1 event), pneumonia (PCV7, 1 event), foreign body aspiration (PCV7, 1 event) and lung disorder not otherwise specified (13vPnC, 1 event). One 13vPnC and one PCV7 participant, respectively, developed pyrexia. Other reported events included GI/GU related conditions (gastrointestinal reflux, gastroenteritis, UTI, pyelonephritis), ear infection, pharyngitis, hypotonia (13vPnC, 1 event), and bodily injury. All SAEs resulted in hospitalization.

Subject 008-002-000057, an 11-month-old female infant, was noted to appear "pale" by her mother on 18 Jan 2008. The subject was examined by her physician on the same day and findings on physical examination were unremarkable. The subject was hospitalized on 19 Jan 2008 and laboratory test data revealed severe anemia with hemoglobin -5.4 g%, hematocrit 17.2 %, and low platelet count. White blood cell (WBC) count was 12,600 cu.mm3 with normal differential. Serum iron was in the lower range of normal , with normal serum bilirubin levels. A tentative diagnosis of postviral hemolytic, regenerative, normochromic, normocytic anemia was made. The subject received blood transfusion of 150 mL on 19 Jan 2008. She was discharged on 20 JAN 2008.
The medical history was unremarkable. The last dose of study vaccine (V3) was given on 29 May 2007.
The subject was withdrawn from the study because of the adverse event (AE) and subsequent blood transfusion. The AE was unrelated to test article or protocol. The follow-up visit on 02 May 2008 revealed that

the baby was in good condition. The laboratory test values showed a hemoglobin of 13.1 gm%, hematocrit 39.4 and normal WBC and platelet counts. The follow-up of 6-month safety update via telephone contact was advised. Both the investigator and the sponsor considered the serious adverse event (SAE) unrelated to the study vaccine or protocol.

Four participants (13vPnC n=2, PCV7 n=2) withdrew due to an AE. Three of the 4 events were SAEs.

- *13vPnC (SAE):* hemolytic anemia. The event occurred 236 days after the 3rd study dose. A diagnosis of postviral hemolytic, regenerative, normochromic, normocytic anemia was made, and the event was considered by the study investigator to be unrelated to vaccination. The subject was withdrawn because of the adverse event and subsequent blood transfusion.
- *13vPnC:* Recurrent urticaria that was mild after the 2nd dose and moderate following the 3rd dose.
- *PCV7 (SAE):* a 2-month old boy developed fever and ill appearance, which occurred 15 days after the 1st vaccination. Subsequent hospital evaluation was non-diagnostic. He responded to empiric antibiotic treatment. Initial and repeat CSF cultures showed no growth, and the C-reactive protein normalized. Discharge diagnosis was presumed meningitis.
- *PCV7 (SAE):* anaphylaxis that occurred 7 days after the 3rd PCV7 dose. After fruit ingestion, severe generalized urticaria occurred, which responded to antihistamine and betamethasone treatment. The infant had a history of penicillin and food (nut, fruit) allergy.

Study 6096A1-3008 (Canada)
Infants received 13vPnC or PCV7 at 2, 4, 6 and 12 months old. During the study period up to 1 month after the infant vaccination, 15 SAEs occurred in 10 individuals. All SAEs resulted in hospitalization. Additional details are located in sections 10.3.4.2.4 [study -3008.
One PCV7 participant withdrew from the study due to a non-serious adverse event. Urticaria characterized as mild, developed 2 days after the 3rd vaccination and spontaneously resolved the same day.

Study 6096A1-006 (Germany)
Infants received 13vPnC or PCV7 at 2, 3, 4 and 11-12 months old. During the 16 month study time period, 86 individuals reported 119 SAEs. All SAEs resulted in hospitalization.
Four febrile convulsions (SAE n=2, non-serious AE n=2) occurred in 4 participants (13vPnC n=1; PCV7 n=3). Two febrile convulsions were events occurring >130 days after vaccination.

- PCV7 (SAE): A 6-month old boy developed a febrile seizure, which occurred 48 days after dose 3. Unresponsiveness and generalized limb twitching were followed by a post-ictal period. His temperature was 39.4C. Hospital physical exam findings included rhinitis, otitis media, pharyngitis, and no meningitis-like symptoms. EEG showed overlapping beta waves. Illness symptoms resolved, and no further seizures occurred during the 4-day observational hospital stay. Febrile seizures, however, recurred 6 months later.
- PCV7 (SAE): An 11-month old boy developed a febrile seizure concurrent with T38.1C and URI illness symptoms. Symptoms occurred one day after co-administered PCV7 and DTaP-HBV-IPV vaccinations. Hospital diagnoses included otitis media and pharyngitis. The fever resolved following antipyretic treatment, and no further seizures occurred. Neurological and laboratory evaluations showed no abnormalities.

Three PCV7 participants withdrew due to an adverse event (SAE n=1, non-serious AE n=2). A febrile seizure in a 6-month old boy is described in the preceding paragraph. The second participant, who had a head deformity and history of colic, experienced a crying episode. The third PCV7 developed gastroenteritis.
SAE and non-serious adverse event details are located in sections 10.2.4.4.6 [study -006].

13.0 Overview of Immunogenicity (Effectiveness) Across Trials

13.1 Study Design and Methods

Of the 14 studies which evaluated the immunogenicity of Prevnar 13 in healthy children, two studies are most relevant to this review: the phase 3 U.S. non-inferiority study (study 004) and the phase 3 U.S. lot consistency study (study 3005). In both studies, Prevnar 13 and Prevnar were administered according to the schedule approved in the U.S., and all concomitant vaccinations were U.S. licensed vaccines. Study 004 was the pivotal immunogenicity trial for inferring effectivness in infants and toddlers and for supporting U.S. licensure. Compatability of Prevnar 13 with routine U.S. licensed childhood concomitant vaccinations was assessed in both studies 004 and 3005.

Although there was one other phase 3 non-inferiority study conducted in Germany (study 006), Prevnar 13 and Prevnar were used according to a schedule that is not approved in the U.S. (2, 3, 4, 11-12 month); in addition, the study included use of a non-US licensed concomitant vaccine (Infanrix hexa). All other studies submitted to the BLA assessed a schedule that is not approved in the U.S. or included non-US licensed concomitant vaccines in the study protocol.

In the two phase 3 U.S. studies (004 and 3005), all subjects received four doses of Prevnar 13 or Prevnar at 2, 4, 6, and 12 or 12-15 months of age in the left anterolateral thigh; all subjects also received Pediarix and ActHib in the right anterolateral thigh at 2, 4, and 6 months of age. Subjects enrolled in study 004 received PedvaxHib and VAQTA in the anterolateral right thigh and ProQuad in the deltoid at 12-15 months of age. Due to shortages of ProQuad, subjects enrolled in study 3005 received MMRII and Varivax in the deltoid and Havrix in the right anterolateral thigh at 12 months of age. A 4th dose of a Hib vaccine was not included in the protocol because a fourth dose of ActHIB is only licensed for administration at 15-18 months; in addition, PedvaxHib, which can be administered at 12 months of age, was not available because of a vaccine shortage.

In both studies 004 and 3005, blood samples were collected one month after the 3rd study vaccination, just prior to the fourth study vaccination, and one month after the 4th study vaccination. A blood draw within 27 to 56 days after the third or fourth study vaccination was required for inclusion in the post-dose 3 and post-dose 4 immunogenicity analysis populations respectively. Additional criteria for inclusion in the immunogenicity population included receipt of the first study vaccination at 41-99 days of age, receipt of the fourth study vaccination at 364-456 days of age (the upper age limit was defined as 396 days of age in study 3005), and no other protocol violations. Immunogenicity analyses were based on subjects' randomized treatment assignment.

For the Prevnar 13 immunogenicity data presented in this review, the composition of Prevnar 13 used in study 3005 was the same as intended for licensure in the U.S., as described in Section 1.2.3. The formulation of Prevnar 13 used in study 004 did not contain polysorbate 80.

13.2 Pneumococcal Immunogenicity Endpoints

In the U.S. phase 3 non-inferiority study (study 004), the proportion of subjects achieving an anti-pneumococcal IgG antibody concentration ≥ 0.35µg/mL 1 month after the third study dose and the geometric mean IgG antibody concentrations one month after the fourth study dose for each of the 13 pneumococcal vaccine serotypes were evaluated as co-primary endpoints. The criteria for non-inferiority for each of the 13 vaccine serotypes were defined as (1) a lower limit of the 2-sided 95% CI for difference in the proportion of subjects achieving the pre-specified anibody concentration (13vPnC – PCV7) > -10% and (2) a lower limit of the 2-sided 95% CI for the GMC ratio (13vPnC/PCV7) > 0.5.

As discussed in Section 4.3, in the absence of an established correlate of protection, a single-antibody reference value of 0.35 µg/mL after the third dose was included as a co-primary endpoint for all pneumococcal serotypes. This value is based on pooled efficacy estimates from three clinical efficacy trials that evaluated Prevnar or an investigational 9-valent CRM_{197} conjugate vaccine (Wyeth) against IPD; it does not necessarily predict protection in an individual subject. For new serotypes not included in Prevnar, non-inferiority comparisons of the 13vPnC vaccine were made to the lowest response rate observed among the

Prevnar serotypes in Prevnar recipients. Because all serotypes in Prevnar are considered effective in preventing IPD, the lowest serotype response would still be considered a comparison to an effective serotype. Additional pneumococcal immunogenicity endpoints, including functional antibody responses, were also evaluated.

13.3 Concomitant Vaccine Antigen Immunogenicity Endpoints

In studies -004 and -3005, 13vPnC was co-administered with routine childhood immunizations recommended in the U.S. At the time of trial conduct, children received DTaP, HBV, IPV, Hib, rotavirus, MMR, varicella and Hepatitis A vaccines. All study-004 participants received a combination MMRV vaccine at 12-15 months old. Study -3005 participants receiving measles, mumps, rubella and varicella vaccines as a combined or separately administered MMR and Varicella was acceptable. Rotavirus vaccination was permitted during the study period. However, the subgroup of subjects who received rotavirus vaccinations were not evaluated separately for safety.

Study 004 evaluated post-dose 3 antibody responses to diphtheria toxoid and pertussis antigens (FHA, PT, and PRN) contained in DTaP-HBV-IPV (Pediarix) when co-administered with 13vPnC relative to the corresponding antibody responses when Pediarix was co-adminsitered with Prevnar. Primary endpoints included the proportion of subjects who achieved an anti-diphtheria toxoid antibody concentration ≥ 0.1 IU/mL and the proportion of subjects who achieved anti-pertussis antibody concentrations achieved by 95% of Prevnar recipients (anti-FHA antibody concentration ≥ 40.5 EU/mL; anti-PT antibody concentration ≥ 16.5 EU/mL; and anti-PRN antibody concentration ≥ 26 EU/mL). [See Clinical Reviewer Note in study 004 section 7.1.3.4.1] The criteria for non-inferiority for each assessed antigen was defined as the lower limit of the 2-sided 95% CI for the difference in two proportions (13vPnC – PCV7) > -10%.

Study 004 also evaluated immune responses to MMRV, measured one month after vaccination, when co-administered with 13vPnC relative to the corresponding antibody responses when MMRV was co-administered with Prevnar. This study was not powered to demonstrate lack of interference of immune responses when Prevnar 13 is concomitantly administered with routine childhood vaccines to prevent measles, mumps, rubella, or varicella. These concomitant vaccine antigens were assessed as secondary study objectives; the non-inferiority criterion was -5% for measles, mumps, and rubella and -10% for varicella.The secondary study endpoints included the proportion of subjects who achieved anti-measles and anti-mumps antibody concentrations ≥ 1.10 I.V., anti-rubella antibody concentrations ≥ 15 IU/mL, and anti-varicella antibody concentrations ≥ 1.09 I.V. The criteria for non-inferiority were defined as the lower limit of the 2-sided 95% CI for the difference in two proportions (13vPnC – PCV7) > -5% for measles, mumps, and rubella and > -10% for varicella.

Study 3005 evaluated post-dose 3 antibody responses to tetanus toxoid, hepatitis B, and poliovirus (types 1, 2, and 3) antigens contained inDTaP-HBV-IPV (Pediarix) when co-administered with 13vPnC relative to the corresponding antibody responses when Pediarix was co-administered with Prevnar. Primary endpoints included the proportion of subjects who achieved an anti-tetanus-toxoid antibody concentration ≥ 0.1 IU/mL, the proportion of subjects who achieved an anti-hepatitis B antibody concentration ≥ 10.0 mIU/mL, and the proportion of subjects achieving an anti-poliovirus antibody titer ≥ 1:8 for types 1-3. The criteria for non-inferiority were defined as the lower limit of the 95% CI for the difference in two proportions (13vPnC-PCV7) > -10%.

13.4 Pneumococcal Immunogenicity Findings

The evaluable post-dose 3 immunogenicity population in the U.S. non-inferiority study (study 004) included 252 Prevnar 13 recipients and 252 Prevnar recipients. The evaluable post-dose 4 immunogenicity population in study 004 included 239 Prevnar 13 recipients and 223 Prevnar recipients. Males constituted approximately 51% and 58% of subjects enrolled in the Prevnar 13 and Prevnar group respectively. Most subjects enrolled were of White/Caucasion origin. The mean age at enrollment was 2.1 months in each study group.

For three serotypes in the 13vPnC vaccine, the non-inferiority 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 non-inferiority margin of -10% and was -10.9%, -12.4%, and -36.2% for serotypes 6B, 9V, and 3 respectively. For serotype 3, the non-inferiority 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 non-inferiority margin of 0.5. Otherwise, the non-inferiority criteria for the primary endpoints were met.

Among those serotypes that failed to meet the primary endpoints, serotype 6B failed 1 out of 5 secondary endpoints, serotype 9V failed 2 out of 5 secondary endpoints, and serotype 3 failed all 5 secondary endpoints. Each of the 13 serotypes contained in Prevnar 13, including serotype 3, elicited functional opsonophagocytic antibody titers and these titers were higher one month after the fourth dose compared to one month after the third dose. When evaluating the proportion of subjects achieving an IgG antibody concentration ≥ 0.35 µg/mL just prior to the fourth study dose, with the exception of serotype 19F, responses among Prevnar 13 recipients appeared to wane more by the time of the 4th study dose compared to Prevnar recipients. Less than 60% of Prevnar 13 recipients achieved an antibody concentration ≥ 0.35 µg/mL to serotypes 4, 9V, 18C, 23F, and 3 just before the 4th dose, indicating the need for a fourth dose to improve immune responses to these five serotypes in particular. A similar trend, with the exception of serotype 14, was seen with pre-dose 4 GMC data.

Of note, a high proportion of PCV7 recipients achieving anti-6A OPA titers ≥ 1:8 and anti-6A IgG concentrations of ≥ 0.35 µg/mL is consistent with functional antibody production due to cross-reactivity with serotype 6B. A lower proportion of PCV7 recipients achieving anti-19A OPA titers ≥ 1:8 compared to the proportion of PCV7 recipients achieving anti-19A IgG concentrations titers ≥ 0.35 µg/mL is consistent with cross-reactivity between 19F and 19A resulting in production of non-functional antibodies. A higher than expected proportion of PCV7 subjects achieved OPA titers ≥ 1:8 against serotype 7F; this was observed in both U.S. and European infants. The reason for this high rate is unclear, as PCV7 does not contain serotype 7F and cross-reactivity with other vaccine-serotypes was not expected.

Table 194: Immunogenicity Summary: 7 Common Serotypes

	Primary endpoint Non-inferiority Comparisons		Secondary endpoint Non-inferiority Comparisons (Study not powered for these evaluations)				
Common Serotypes	% ≥ 0.35 Post-dose 3	GMC Post-dose 4	% ≥ 0.35 Post-dose 4	GMC Post-dose 3	% ≥ 1.0 Post-dose 3	% ≥ 1.0 Post-dose 4	GMC Pre-dose 4*
4	✓	✓	✓	✓	Failed	Failed	✓
6B	Failed	✓	✓	✓	Failed	✓	✓
9V	Failed	✓	✓	✓	Failed	Failed	✓
14	✓	✓	✓	✓	✓	✓	✓
18C	✓	✓	✓	✓	Failed	Failed	✓
19F	✓	✓	✓	✓	Failed	✓	✓
23F	✓	✓	✓	✓	Failed	Failed	✓

Non-inferiority criteria: lower limit of the 2-sided, 95% CI for the difference in two proportions > -0.1 and lower limit of the 2-sided, 95% CI for the GMC ratio > 0.5 (2-fold criterion).
* Calculated by CBER

Table 195: Immunogenicity Summary: 6 Additional Serotypes[a]

	Primary endpoint Non-inferiority Comparisons		Secondary endpoint Non-inferiority Comparisons (Study not powered for these evaluations)				
Additional Serotypes	% ≥ 0.35 Post-dose 3	GMC Post-dose 4	% ≥ 0.35 Post-dose 4	GMC Post-dose 3	% ≥ 1.0 Post-dose 3	% ≥ 1.0 Post-dose 4	GMC Pre-dose 4[b]
1	✓	✓	✓	✓	✓	✓	✓
3	Failed	Failed	Failed	Failed	Failed	Failed	Failed
5	✓	✓	✓	✓	Failed	✓	✓
6A	✓	✓	✓	✓	✓	✓	✓
7F	✓	✓	✓	✓	✓	✓	✓
19A	✓	✓	✓	✓	✓	✓	✓

Non-inferiority criteria: lower limit of the 2-sided, 95% CI for the difference in two proportions > -0.1 and lower limit of the 2-sided, 95% CI for the GMC ratio > 0.5 (2-fold criterion).
[a] Table compiled by CBER.
[b] GMC ratio calculated by CBER

Analysis of gender effects on immunogenicity were not evaluated by the applicant. There was a male predominance in study 004, and the impact of any potential gender differences in immunogenicity on the non-inferiority assessments is not known. Future studies assessing gender effects on immunogenicity are warranted.

13.5 Concomitant Vaccine Antigen Immunogenicity Findings

In study 004, non-inferiority criteria for co-primary endpoints evaluating post-dose 3 immune responses to the diphtheria toxoid and pertussis antigens contained in Pediarix and post-dose 3 immune responses to ActHib were met. Although non-inferiority criteria for secondary endpoints evaluating post-toddler dose immune responses to PRP (Hib), measles, mumps, rubella, and vaircella antigens were met, the seroresponse rates were noted to be low to mumps (73-77%) and varicella (22-27%). In addition, the seropositivity cut-off for rubella (≥ 15 IU/mL) analyses in study 004 was higher than the cut-off indicated for the rubella assay used in study 004 b(4) IU/mL). Anti-rubella antibody levels ≥ 10 IU/mL are considered positive with the –b(4)---------- Rubella G assay).

In the setting of low antibody responses to mumps and varicella, non-interference could not be reliably demonstrated from study 004 alone. The low seroresponse rates to mumps and varicella were likely due to the low sensitivity of the commercial Trinity Biotech Captia IgG Mumps and Varciella ELISA assays used in study 004. Extra sera from subjects in study 3005 were available and assayed using Merck's more sensitive Mumps ELISA and VZV gpELISA assays. Children were considered positive for mumps if the antibody concentration was ≥ 10.0 ELISA units/mL using Merck's Mumps ELISA. Seropositivity for varicella was defined as an antibody concentration ≥ 5 gpELISA units/mL as measured by the varicella gpELISA. A response rate based on ≥ 5 gpELISA units/mL has been shown to be highly correlated with long-term protection.[27] The antibody responses using the Merck assays were higher for mumps (96-98%) and varicella (98-99%) in both study groups compared to responses using the commercial assays. However, the non-inferiority criterion was not met for mumps; the lower limit of the 95% conficence interval for the difference in the two proportions was -6.5%.

CBER also requested re-analysis of the Rubella immunogenicity data in study 004 subjects using a seropositivity cut-off of –b(4)------, which is the accepted cut-off for the assay used in study 004. The -5% non-inferiority criterion was not met for rubella using the –b(4)-------- cutoff; the lower limit of the 95% CI for the difference in the two proportions was -5.9%.

13.6 Immunogenicity Data to Support Manufacturing Consistency

Study 3005 was designed to evaluate, as a primary objective, equivalency of the immune responses induced by 3 lots of Prevnar 13 when measured one month after the third study dose. The criterion for equivalency was a maximum difference between the log of the geometric mean IgG concentrations from subjects receiving any two lots being < 0.693 and > -0.693; this corresponds to a GMC ratio between any two lots being > 0.5 and < 2.0. The equivalency criterion was met for all vaccine serotypes.

13.7 Immunogenicity Conclusions

Based on pre-specified objectives in study 004, Prevnar 13 was non-inferior to Prevnar in inducing antibodies against 10 out of 13 serotypes contained in Prevnar 13. Among the 7 common serotypes, serotypes 6B and 9V did not meet the non-inferiority criteria based on the proportion of subjects achieving an antibody concentration ≥ 0.35 µg/mL one month after the third vaccination. Among the 6 additional serotypes, serotype 3 did not meet the post-dose 3 and post-dose 4 non-inferiority criteria in comparisons to the lowest PCV7-vaccine serotype antibody concentration induced by Prevnar. Serotype 6B and 9V geometric mean IgG antibody concentrations achieved by Prevnar 13 recipients one month after the fourth dose were non-inferior to the corresponding GMCs achieved by Prevnar recipients.

Interpretation of the data for those serotypes that failed to meet at least one primary study endpoint in study 004 requires some caution, as the primary study endpoints (both based on IgG antibodies measured by ELISA) are not correlates of protection. In particular, it is not clear if the use a single IgG antibody reference value of 0.35 µg/mL has the same clinical significance across all pneumococcal serotypes. Although the antibody responses to serotypes 6B and 9V did not meet the non-inferiority criteria for the post-dose 3 primary endpoint (the proportion of subjects achieving a pneumococcal antibody concentration of ≥ 0.35 µg/mL one month after dose 3), there is additional supportive data to suggest that these two serotypes may be effective. Both serotypes 6B and 9V met the non-inferiority criteria for the post-dose 3 GMC secondary endpoint. Serotype 9V also elicited higher functional antibody levels one month after the 3rd dose among Prevnar 13 recipients compared to Prevnar recipients.

Similar supportive data are more limited witth regards to serotype 3, which failed to meet each of the primary and secondary study endpoints, Some functional anti-serotype 3 antibody response was elicitied after dose 3, and this response was higher after the fourth dose compared to the third dose. However, there is no helpful comparator when assessing serotype 3 exploratory OPA data, because Prevnar lacks serotype 3.

The available data therefore support the inclusion of serotypes 6B and 9V in the Prevnar 13 indication for the IPD indication. The failure of serotype 3 to meet the pre-specified non-inferiority criteria lessens our confidence that a protective response will be elicited among a high proportion of vaccines for this serotype. Therefore, the available data do not support the effectiveness of serotype 3 in preventing type 3 invasive pneumococcal disease and do not support inclusion of serotype 3 in the Prevnar 13 IPD indication. Because serotype 3 may be beneficial in eliciting some functional antibody response in children, I would, however, not recommend removing this serotype from the vaccine formulation.

Safety and immunogenicity data from the two studies support co-administration of U.S. licensed DTaP-HBV-IPV, Hib, and MMR and varicella vaccines. The non-inferiority criteria for concomitant vaccine antigens are defined in clinical review sections 7.1.3.6.3.1 and 7.2.3.6.3.1. The pre-specified non-inferiority criteria were met for antigens contained in DTaP-HBV-IPV and Hib vaccines.

Non-inferiority criteria for measles (study 004 data) and varicella (study 004 data supplemented with data from study 3005 subjects) antibody responses were met. For mumps and rubella components, a 5% percent difference between vaccine groups could not be ruled out with 95% confidence. The mumps seroconversion rate, initially measured in I.V. units, was lower than expected in both study groups. Mumps seroconversion ≥ 1.10 I.V. occurred in 76.5% of 13vPnC and 72.9% of PCV7 recipients in study 004; the expected rate based on a similar assay was > 90%. Merck's mumps ELISA assay testing of any remaining sera from study 3005 were consistent with expected ELISA assay results. The lower limit of the 95% confidence interval for the difference in mumps seroconversion rate (13vPnC- PCV7; ELISA assay results) was -6.5%, which exceed the -5% non-inferiority criteria. However, study 3005 was not powered to evaluate mumps responses among

13vPnC recipients for non-inferiority comparisons to the responses among PCV7 recipients. Rubella immunogenicity analyses included comparisons of seroresponse rates using a cutoff of –b(4)----------, which is the cut-off value for a positive result with the assay used in study 004. The lower limit of the 95% confidence interval for the difference in the rubella seroresponse at the –b(4)--------- cut-off value (13vPnC-PCV7) was -5.9%, which exceeded the -5% non-inferiority criteria by a small margin.

14 Overview of Safety Across Trials

14.1 Overall Safety Database

Thirteen clinical trials evaluated the safety of Prevnar 13 in 4,729 infants and toddlers who received at least one dose of Prevnar 13 and 2,760 infants and toddlers who received at least one dose of Prevnar active control. There were no substantive differences in demographic characteristics between the vaccine groups. Approximately half of subjects were male. By race, 84.0% of subjects were White, 6.0% were Black or African-American, 5.8% were Asian and 3.8% were of 'Other' race. A total of 2512 children received the 4th dose of Prevnar 13 and 1492 children received the 4th dose of Prevnar. By race, 92% of subjects were White, 4.4% Black or African American, and 2.5% were of 'Other' race.

Three primary safety studies conducted in the U.S. evaluated the safety of Prevnar 13 when administered concomitantly with routine U.S. pediatric vaccinations at 2, 4, 6, and 12-15 months of age. A total of 1,908 subjects received at least 1 dose of Prevnar 13. The vaccination schedule and concomitant vaccinations used in the remaining infant trials were consistent with country-specific recommendations and local clinical practice.

In addition to the thirteen infant studies, the BLA included one catch-up study conducted in Poland in which 354 children (7 months through 5 years of age) received at least one dose of Prevnar 13. All subjects in this study were White, non-Hispanic, non-Latino.

14.2 Safety Assessment Methods

In the three primary safety studies conducted in the U.S., solicited local and systemic adverse events were recorded daily. In studies 004 and 3005, parents/guardians recorded events in an electronic diary for 7 consecutive days following each vaccination (i.e., day of vaccination and the next 6 days). In study 003, parents/guardians recorded events in a paper diary for 8 to 15 days, depending on the symptoms monitored and the stage of the study.

In the catch-up study conducted in Poland, solicited local and systemic adverse events were monitored for 4 consecutive days following each vaccination (i.e. day of vaccination and next 3 days). Unsolicited adverse events were monitored in each group from signing of the informed consent form until 30 days after the last study vaccination. Serious adverse events were monitored throughout the study period. There was no control group included in the study design, therefore safety data from this study were descriptive and there were no statistical comparisons.

In study 009, which assessed Prevnar 13 with and without polysorbate 80, solicited local and systemic adverse reactions were assessed for 4 days after each vaccination. Urticaria was not included as a solicited systemic adverse event. All other safety monitoring details were identical to the safety monitoring performed in the 3 primary U.S. studies.

For the remaining nine supportive studies, only data on serious adverse events and unsolicited adverse events of interest were reviewed. Among these nine studies, one study was a lot consistency study conducted in Poland and included no Prevnar control group.

14.3 Significant/Potentially Significant Events

14.3.1 Deaths

In the 15 clinical studies submitted to BLA and among the 7489 vaccinated infants with data included in the integrated safety database, 4 subjects died. Each death was suspected to be due to sudden infant death syndrome (SIDS). Three deaths occurred in Prevnar 13 recipients and one death occurred in a Prevnar recipient. Autopsy reports were available for 3 subjects. In 2 of the deaths, the medical examiner considered SIDS to be the likely cause of death; in 1 death, the cause of death was considered unknown.

Possible alternative contributing factors were identified in the deaths of two Prevnar 13 recipients. The two remaining deaths occurred 76 days after the third Prevnar 13 dose and 13 days after the first Prevnar dose. The applicant calculated the expected number of deaths caused by SIDS in the Prevnar 13 clinical trials based on age-specific SIDS incidence rates that were available from the state of California for the birth cohort of calendar year 2000 (prior to introduction of Prevnar). The calculated standardized mortality ratio (SMR) of observed SIDS deaths over expected SIDS deaths was less than 1 and not statistically significant

Narratives for each death are described below.

Subject 6096A1-3005-002-000107
Thirteen days after receipt of the first dose of PCV7, this healthy 83 day old white, male infant was found supine, unresponsive, blue, and not breathing in the crib at day care. Resuscitative measured failed. The cause of death was reported as SIDS. Autopsy results were reported after data were locked for this CSR, concluding that the finding were consistent with SIDS.

Subject 6096A1-3005-004-00320
Fourteen days after receipt of the first dose of 13vPnC manufacturing scale lot, this 71 day old white, male infant was found unresponsive, blue, and not breathing by his Father in his crib. Resuscitative measures failed. An autopsy revealed that the subject died of undetermined causes. The autopsy report also revealed that the Father had drunk several beers and laid down in bed with the infant (on his stomach) with multiple sheets and blankets after feeding him half a bottle of formula at 1am. The investigator concluded this infant died from sudden unexplained infant death.

Subject 6096A1-3005-079-007651
Three days after receipt of the second dose of 13vPnC pilot scale lot 2, this 127 day old white, female infant died. The infant was reportedly found unresponsive and cyanotic by the Father, who had been sleeping in bed with the infant. The cause of death was reported as asphyxiation or SIDS. Autopsy results describe no organic pathology, negative toxicology, and negative metabolic screenings. Parental cosleeping was identified as a possible contributor to the event. The opinion of the medical examiner agreed with the possibility of SIDS or accidental airway obstruction.

Subject 501-009-000452
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).

14.3.2 Serious Adverse Events (SAEs)

Serious adverse events occurred in 4% of subjects from dose 1 through the post-dose 3 blood draw, in 3-5% from the post-dose 3 blood draw to the 4th study dose, in 1% within 30 days following the 4th dose, and in 3% during the 6-month safety follow-up period. The most frequently reported types of SAEs by MedDRA System Organ Class (SOC) term were infections and infestations. Within this SOC, the most frequently reported MedDRA preferred terms (PTs) were bronchioloitis, gastroenteritis, pneumonia, bronchitis, and respiratory syncytial virus bronchiolitis.

Table 196. Incidence of Serious Adverse Events 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=4023 n (%)**	**PCV7 N=4023 n (%)**	**13vPnC N=3718 n (%)**	**PCV7 N=1690 n (%)**	**13vPnC N=3313 n (%)**	**PCV7 N=1600 n (%)**
Combined AE Terms								
Wheezing	57 (1.2)	31 (1.1)	20 (0.5)	8 (0.4)	6 (0.2)	3 (0.2)	15 (0.5)	8 (0.5)
Pneumonia	31 (0.7)	7 (0.3)	19 (0.5)	6 (0.3)	0 (0.0)	2 (0.1)	11 (0.3)	5 (0.3)
Gastroenteritis	19 (0.4)	8 (0.3)	38 (0.9)	10 (0.5)	7 (0.2)	3 (0.2)	16 (0.5)	8 (0.5)
Convulsions	4 (0.1)	1 (0.0)	8 (0.2)	3 (0.1)	3 (0.1)	2 (0.1)	7 (0.2)	5 (0.3)
Meningitis	3 (0.1)	2 (0.1)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic Reactions	4 (0.1)	1 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Croup	3 (0.1)	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Breath holding	2 (0.0)	2 (0.1)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abscess	1 (0.0)	0 (0.0)	1 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	1 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Otitis media	3 (0.1)	2 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)†	3 (0.2)†

† p=0.045 (Fisher exact test, 2-sided, is used due to non-convergence of the generalized mixed model).

* 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 post-infant series data from ten 6096A1 studies [003, 004, 006, 007, 008, and 3005], and pooled six-month follow-up data from 6 studies: 003, 004, 006, 009, 500, 501, and 3005.

Wheezing combined terms: asthma, bronchiolitis, bronchitis, wheezing, bronchial hyperreactivity, bronchospasm, status asthmaticus, allergic respiratory disease, and stridor

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

Gastroenteritis combined terms: gastroenteritis, vomiting, diarrhea (nausea, abdominal pain, esophagitis, gastritis, infantile spitting up, regurgitation.

Convulsion combined terms: infantile spasms, convulsion, epilepsy, febrile convulsion, partial seizures, postictal paralysis.

Meningitis combined terms: meningitis, meningitis aseptic, meningitis bacterial, meningitis enteroviral, meningitis meningococcal, meningitis pneumococcal, meningitis viral, meningococcal sepsis.

Allergic reactions combined terms: hives/urticaria, anaphylactic reaction, swelling face, bronchospasm, laryngospasm, and stridor.

Croup combined terms: croup infectious, laryngotracheobronchitis (LLT or verbatim).

Breath holding combined terms: breath holding, apnoea, apnoeic episode, sleep apnoea syndrome, apnoeic attack.

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

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.

Source: 125324/0.74, m1.11 Information Amendment, pages 5-6 (Table 1-1).

14.3.3 Adverse Events Resulting in Withdrawals From Study Vaccination

A total of 39 subjects experienced an adverse event which resulted in withdrawal from study vaccination; the subjects included 22 (0.47%) Prevnar 13 recipients and 17 (0.62%) Prevnar recipients. All of these events occurred either during the infant series or during the period between the infant series and the toddler dose. The events most frequently resulting in withdrawal from vaccination were within the Nervous System Disorders SOC (8 13vPnC recipients and 9 PCV7 recipients) and Infections and Infestations SOC (5 13vPnC recipients and 3 PCV7 recipients). There were no withdrawals due to an AE in catch-up study 3002.

Eight subjects were withdrawn from vaccination because of febrile convulsions, including 1 subject in each vaccine group during the infant series and 3 subjects in each vaccine group between the infant series and toddler dose. The two febrile seizures that occurred during the infant series included subject 3005-091-008821 and 501-019-001430. Subject 3005-091-008821 experienced febrile seizures that started 52 days after the 2nd 13vPnC dose and occurred in association with urosepsis and fever which developed 15 days after surgical repair of hypospadias. Subject 501-019-001430 experienced a febrile seizure 1 day after vaccination with the 3rd dose PCV7; an association with study vaccination could not be ruled out. The 6 remaining subjects all experienced febrile seizures ≥ 48 days after the 3rd study dose. Five of these 6 subjects experienced febrile seizures in association with an infection and each of these events was reported to resolve; one subject (subject 501-033-002371) who received 13vPnC was diagnosed with cryptogenic focal epilepsy which was noted to be persistent at the conclusion of the study.

Two subjects who received 13vPnC withdrew because of convulsions; the convulsions occurred in association with acute pyogenic meningitis in 1 subject and in association with fever in the second subject.

Table 197. Listing of AEs Resulting in Withdrawal From Study Vaccination (All 13 Infant Studies)

Study-Site-Subject #	MedDRA PT Term	Verbatim Term	Vaccine Received	Last Dose	Days Since Last Dose	Duration (days)	Severity
003-009-000343	Febrile convulsion	Febrile seizure	13vPnC	3	193	1	MO
004-014-001428	Febrile convulsion	Complex febrile seizure	13vPnC	3	189	1	SE
004-021-001978	Near drowning	Near drowning	13vPnC	2	73	1	LT
004-029-002554	Thrombocytopenia	Recurrent thrombocytopenia	13vPnC	2	22	100	SE
004-029-002566	Convulsion	Recurring intermittent seizures	13vPnC	1	32	C	SE
004-029-002566	Convulsion	Seizure	13vPnC	1	8	1	SE
007-013-001133	Crying	Inconsolable crying, 3 hours	13vPnC	Pediacel	2	1	MO
008-002-000057	Haemolytic anaemia	Anaemia hemolytic	13vPnC	3	236	C	MO
008-036-002546	Urticaria	Recurrent urticaria on the upper and lower extremities	13vPnC		3	8	MO
009-005-000420	Bronchitis	Bronchitis	13vPnC	3	2	6	MO
009-005-000435	Breath holding	Breath- holding spells	13vPnC	3	167	1	MO
009-007-000625	Hypertonia	Increased muscle tone	13vPnC	2	1	202	MO
009-011-01036	Hydrocephalus	Acquired non-communicating post-inflammatory hydrocephalus	13vPnC	2	62	10	SE
009-011-001036	Meningitis meningococcal	Meningococcal meningitis serotype c	13vPnC	2	8	37	SE
009-011-001036	Meningococcal sepsis	Meningococcal septicemia.	13vPnC	2	8	37	SE
009-013-001215	Gastrooesophageal reflux disease	Gastroesophageal reflux.	13vPnC	1	32	21	MO

009-013-001215	Pneumonia	Pneumonia.	13vPnC	1	32	21	MO
009-014-001416	Leukocytosis	Leukocytosis	13vPnC	3	247	C	MO
011-010-000922	Convulsion	Seizure	13vPnC	1	43	1	SE
011-010-000922	Meningitis bacterial	Acute pyogenic meningitis	13vPnC	1	43	C	SE
500-004-002362	Kawasaki's disease	Kawasaki disease	13vPnC	2	162	C	MO
501-033-002371	Febrile convulsion	Febrile seizures	13vPnC	3	261	14	MO
3005-030-002857	Allergy to vaccine	Vaccine allergic reaction	13vPnC	2	1	8	MI
3005-083-008062	Injection site reaction	Injection site reaction on right thigh at injection site of acthib	13vPnC	2	1	2	MO
3005-083-008063	Urticaria	Urticaria	13vPnC	2	4	6	MI
3005-091-008821	Febrile convulsion	Febrile seizures	13vPnC	2	52	5	SE
3005-091-008840	Pyrexia	Elevated temperature	13vPnC	2	1	1	SE
003-001-000004	Meningitis pneumococcal	Pneumococcal meningitis	PCV7	3	57	18	LT
004-003-000160	Nephroblastoma	Bilateral wilms tumor	PCV7	3	117	C	LT
004-006-000377	Muscular weakness	Right arm weakness	PCV7	1	54	C	MI
004-029-002559	Varicella	Varicella (chicken pox)	PCV7	3	159	15	MO
006-026-001008	Gastroenteritis	Gastroenteritis	PCV7	1	77	8	MO
006-046-001809	Crying	Attack of crying on first day after vaccination	PCV7	1	1	1	MO
006-055-002164	Febrile convulsion	Febrile convulsion	PCV7	3	48	5	SE
007-004 000132	Hemiplegia	Congenital left hemiplegia	PCV7	2	107	C	MO
007-013 001114	Crying	Inconsolable crying	PCV7	2	1	1	MO
007-013 001114	High-pitched crying	High-pitched crying	PCV7	2	1	1	MO
007-013 001114	Injection site erythema	Erythema at right thigh injection site	PCV7	2	1	1	MO
007-013 001114	Injection site swelling	Swelling at right thigh injection site	PCV7	2	1	1	MO
007-013 001114	Rash erythematous	Confluent erythematous rash, posterior neck	PCV7	2	1	1	MI
007-013 001114	Wheezing	Wheeze, noisy breathing" "	PCV7	2	1	1	MO
007-013-001115	Rash	Rash - blanching, macular, on trunk. onset within 5 mins. resolved within 2h	PCV7	1	1	1	MI
007-013-001115	Somnolence	Drowsiness circa 5 mins. after vaccination. rousable. duration 45-50 mins.	PCV7	1	1	1	MI
500-003-000602	Pelizaeus-merzbacher disease	Pelizaeus merzbacher like disorder	PCV7	2	175	C	SE
500-004-000784	Hypokinesia	Delay in the development of motor stage	PCV7	1	73	6	MI
500-011-001824	Infantile spasms	Infantile spasms	PCV7	2	38	C	SE
501-017-001012	Febrile convulsion	Febrile seizure	PCV7	3	113	1	MI
501-019-001430	Febrile convulsion	Febrile seizures	PCV7	3	2	2	SE
501-033-002432	Febrile convulsion	Febrile seizure	PCV7	3	153	1	MI
3008-009-001133	Urticaria	Urticaria	PCV7	3	2	1	MI

Abbreviation: C = continuing, Mild (MI), moderate (MO), severe (SE), or life-threatening (LT).
Source: 125324/0.4, m5.3.5.3.28, Integrated Summary of Safety, pages 290-293 (Table 8-30).

14.4 Other Safety Findings

14.4.1 Solicited Local Reactions and Systemic Adverse Events in the Three Primary U.S. Safety Studies

The tables below provide pooled data for solicited local and systemic adverse events from the three primary U.S. safety studies.

There were no statistically significant differences in the rates of solicited local adverse events among subjects in the three primary U.S. safety studies. The most frequently reported solicited local adverse event among U.S. subjects was tenderness (59-65%), followed by redness (24-41%) and swelling (20-32%). Most solicited local events were mild. There were no severe cases of rendess or tenderness (> 7cm).

Table 198: Percentage of U.S. Infant and Toddler Subjects Reporting Solicited Local Reactions at the Prevnar 13 or Prevnar Injection Sites Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age[a]

	Dose 1[a]		Dose 2[a]		Dose 3[a]		Dose 4[a]	
Graded Local Reaction	**Prevnar 13** (N[b]=1375-1612)	**Prevnar** (N[b]=516-606)	**Prevnar 13** (N[b]=1069-1331)	**Prevnar** (N[b]=405-510)	**Prevnar 13** (N[b]=998-1206)	**Prevnar** (N[b]=348-446)	**Prevnar 13** (N[b]=874-1060)	**Prevnar** (N[b]=283-379)
Redness[c]								
Any	24.3	26.0	33.3	29.7	37.1	36.6	42.3	45.5
Mild	23.1	25.2	31.9	28.7	35.3	35.3	39.5	42.7
Moderate	2.2	1.5	2.7	2.2	4.6	5.1	9.6	13.4*
Severe	0	0	0	0	0	0	0	0
Swelling[c]								
Any	20.1	20.7	25.2	22.5	26.8	28.4	31.6	36.0*
Mild	17.2	18.7	23.8	20.5	25.2	27.5	29.4	33.8
Moderate	4.9	3.9	3.7	4.9	3.8	5.8	8.3	11.2*
Severe	0	0	0.1	0	0	0	0	0
Tenderness								
Any	62.5	64.5	64.7	62.9	59.2	60.8	57.8	62.5
Interferes with limb movement	10.4	9.6	9.0	10.5	8.4	9.0	6.9	5.7

* Statistically significant difference $p < 0.05$

[a] Data are from three primary U.S. safety studies: the U.S. phase 2 infant study, pivotal U.S. non-inferiority study, and the U.S. consistency study . All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

[b] Number of subjects reporting Yes for at least 1 day or No for all days.

[c] 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. Intensity of induration and erythema were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

A statistically significantly higher proportion of Prevnar recipients reported increased sleep after dose 4 than Prevnar 13 recipients. There were no other statistically significantly differences in the rates of other solicited systemic adverse events. Fever, which was was reported in 24-38% of subjects, peaked after dose 4 in the Prevnar 13 group and after dose 2 in the Prevnar group. The majority of fever reports were mild.

Table 199: Percentage of U.S. Infant and Toddler Subjects Reporting Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age[a,b]

	Dose 1[a]		Dose 2[a]		Dose 3[a]		Dose 4[a]	
Graded Systemic Events	**Prevnar 13** (N^b=1360 - 1707)	**Prevnar** (N^b=497-640)	**Prevnar 13** (N^b=1084-1469)	**Prevnar** (N^b=409-555)	**Prevnar 13** (N^b=997-1361)	**Prevnar** (N^b=354-521)	**Prevnar 13** (N^b=178-284)	**Prevnar** (N^b=170-276)
Fever[c]								
Any	24.3	22.1	36.5	32.8	30.3	31.6	31.9	30.6
Mild	23.6	21.7	34.9	31.6	29.1	30.2	30.3	30.0
Moderate	1.1	0.6	3.4	2.8	4.2	3.3	4.4	4.6
Severe	0.1	0.2	0.1	0.3	0.1	0.7	1.0	0
Decreased appetite	48.3	43.6	47.8	43.6	47.6	47.6	51.0	49.4
Irritability	85.6	83.6	84.8	80.4	79.8	80.8	80.4	77.8
Increased sleep	71.5	71.5	66.6	63.4	57.7	55.2	48.7	55.1
Decreased sleep	42.5	40.6	45.6	43.7	46.5	47.7	45.3	40.3

[a] Number of subjects reporting yes for at least 1 day or no for all days
[b] Data are from three primary U.S. safety studies: from the U.S. phase 2 infant study, pivotal U.S. non-inferiority study, and the U.S. consistency study. All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.
[c] Fever gradings: mild (≥38°C but ≤39°C), moderate (>39°C but ≤40°C), and severe (> 40°C). No other systemic event other than fever was graded. Parents reported the use of antipyretic medication to treat or prevent symptoms in 62 to 75% of subjects after any of the 4 doses. There were no differences between the Prevnar 13 and Prevnar groups.

The most frequently reported solicited local adverse events in study 3002 were redness, followed by swelling, and tenderness. Reports of redness and swelling peaked after dose 1 in children 7 to < 12 months of age and in children 12 to < 24 months of age. Rates of events were higher among children 7 to < 12 months of age and higher in children 12 to < 24 months of age and in children 24 to < 72 months of age. Although children in study 3002 reported higher rates of erythema and induration in study 3002, the sample size in study 3002 was small. In addition, the rates of erythema and induration were lower than those in study 004.

The most frequently reported solicited systemic adverse events in study 3002 were irritability, followed by decreased lseep and decreased sleep. Fever was reported in 3-8% of children 7 to < 12 months of age, 4-5% of children 12 to < 24 months of age and 1% of subjects 24 to < 72 months of age. There were no reports of sever fever (> 40°C).

In study 3011, children 15 months to < 5 years of age with three or more prior doses of Prevnar were evaluated after receiving one or two doses of Prevnar 13. The most frequently reported solicited local adverse events were tenderness followed by redness and swelling. Rates were similar to those seen in infants.

Table 200: Percentage of Subjects Previously Vaccinated with Prevnar 15 Months Through 5 Years of Age Reporting Solicited Local Reactions Within 7 Days After Each Prevnar 13 Vaccination

15 months to < 24 months			24 to < 72 months
Graded Local Reaction	**Dose 1** N[a]=90-108 %	**Dose 2** N[a]=68-87 %	**Dose 1** N[a]=138-155 %
Redness[b]			
Any	39.8	35.5	34.9
Mild	31.3	33.8	31.5
Moderate	12.8	7.1	9.9
Severe	0.0	0.0	0.0
Swelling[b]			
Any	25.8	23.3	22.2
Mild	21.3	22.2	20.3
Moderate	9.6	2.9	5.7
Severe	0.0	0.0	0.0
Tenderness			
Any	50.9	57.5	61.9
Interferes with limb movement	7.6	8.8	10.6

[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. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

The most frequently reported solicited systemic adverse events were irritability, followed by decreased appetite and increased sleep. Rates of fever were lower than those observed in infants.

Table 201: Percentage of Subjects Previously Vaccinated with Prevnar 15 Months Through 5 Years of Age Reporting Solicited Systemic Adverse Reactions Within 7 Days After Each Prevnar 13 Vaccination

Toddlers 15 to < 24 months			Children 24 to < 72 months
Systemic Reaction	**Dose 1** N[a]=90-108 %	**Dose 2** N[a]=68-86 %	**Dose 1** N[a]=138-151 %
Fever[b]			
Mild	16.3	14.3	5.1
Moderate	4.4	4.4	0.7
Severe	0.0	0.0	0.7
Decreased appetite	42.4	40.3	24.8
Irritability	60.2	65.1	39.7
Increased sleep	32.7	29.3	15.9
Decreased sleep	22.7	28.6	14.0

[a] Number of subjects reporting yes for at least 1 day or no for all days.
[b] Fever gradings: mild (≥38°C but ≤39°C), moderate (>39°C but ≤40°C), and severe (> 40°C). No other systemic event other than fever was graded.

14.4.2 Unsolicited Adverse Events in All 13 Infant Studies

In the integrated safety analysis for all unsolicited adverse events (Table 202), Prevnar 13 recipients experienced a statistically significantly higher rate of otitis media (including reports of otitis media, otitis media acute, otitis media chronic, and otitis media viral) during the infant series compared to Prevnar recipients (13.0% vs 10.2%, p=0.03), However, these rates include reports from studies in which Prevnar 13 was administered concomitantly with non-U.S. vaccines and on a non-U.S. schedule and thus require cautious interpretation.

Table 202. Incidence of Adverse Events by Combined MedDRA Preferred Terms and Other Events of Interest, Integrated Analysis*

	Infant Series[a]		Between Infant Series and Toddler Dose[a]		Toddler Dose[a]		6-month Follow-Up[a]	
System Organ Class/ Preferred Term	**13vPnC N=4723 n (%)**	**PCV7 N=2754 n (%)**	**13vPnC N=4023 n (%)**	**PCV7 N=4023 n (%)**	**13vPnC N=3718 n (%)**	**PCV7 N=1690 n (%)**	**13vPnC N=3313 n (%)**	**PCV7 N=1600 n (%)**
Combined SAE Terms								
Wheezing	634 (13.4)	344 (12.5)	90 (2.2)	40 (2.0)	93 (2.5)	70 (4.1)	51 (1.5)	17 (1.1)
Pneumonia	83 (1.8)	22 (0.8)	27 (0.7)	6 (0.3)	12 (0.3)	4 (0.2)	17 (0.5)	7 (0.4)
Gastroenteritis	647 (13.7)	401 (14.6)	63 (1.6)	25 (1.2)	217 (5.8)	112 (6.6)	31 (0.9)	14 (0.9)
Convulsions	5 (0.1)	1 (0.0)	10 (0.2)	4 (0.2)	3 (0.1)	2 (0.1)	7 (0.2)	6 (0.4)
Meningitis	3 (0.1)	2 (0.1)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic Reactions	33 (0.7)	23 (0.8)	2 (0.0)[b]	3 (0.1)[b]	12 (0.3)	4 (0.2)	2 (0.1)	1 (0.1)
Croup	73 (1.5)	24 (0.9)	0 (0.0)	2 (0.1)	22 (0.6)	10 (0.6)	2 (0.1)[c]	5 (0.3)[c]
Breath holding	2 (0.0)	5 (0.2)	2 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Crying	21 (0.4)	22 (0.8)	1 (0.0)	0 (0.0)	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)
Abscess	4 (0.1)	0 (0.0)	1 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	23 (0.5)	4 (0.1)	9 (0.2)	2 (0.1)	11 (0.3)	6 (0.4)	2 (0.1)	1 (0.1)
Otitis media	613 (13.0)[d]	281 (10.2)[d]	29 (0.7)	11 (0.5)	139 (3.7)	80 (4.7)	19 (0.6)	20 (1.3)

[a] Infant series = from dose 1 through post-infant series blood draw. Between infant series and toddler dose = from the post-infant series blood draw through the toddler dose. Toddler dose = from the toddler dose through the post-toddler dose blood draw. Six-month follow-up = from post-toddler dose blood draw to 6-month follow-up contact.
[b] p=0.005 (Fisher exact test, 2-sided, is used due to non-convergence of the generalized mixed model).
[c] p=0.007 (Fisher exact test, 2-sided, is used due to non-convergence of the generalized mixed model).
[d] p = 0.03 (Fisher exact test, 2-sided, is used due to non-convergence of the generalized mixed model).
* 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 post-infant series data from ten 6096A1 studies [003, 004, 006, 007, 008, and 3005], and pooled six-month follow-up data from 6 studies: 003, 004, 006, 009, 500, 501, and 3005.
Wheezing combined terms: asthma, bronchiolitis, bronchitis, wheezing, bronchial hyperreactivity, bronchospasm, status asthmaticus, allergic respiratory disease, and stridor.
Pneumonia combined terms: pneumonia, bronchopneumonia, pneumonia primary atypical, pneumonia viral, pneumonia respiratory syncitial viral, lobar pneumonia, pneumonia bacterial, and pneumonia aspiration.
Gastroenteritis combined terms: gastroenteritis, vomiting, diarrhea (nausea, abdominal pain, esophagitis, gastritis, infantile spitting up, regurgitation.
Convulsion combined terms: infantile spasms, convulsion, epilepsy, febrile convulsion, partial seizures, postictal paralysis.
Meningitis combined terms: meningitis, meningitis aseptic, meningitis bacterial, meningitis enteroviral, meningitis meningococcal, meningitis pneumococcal, meningitis viral, meningococcal sepsis.
Allergic reactions combined terms: hives/urticaria, anaphylactic reaction, swelling face, bronchospasm, laryngospasm, and stridor.
Croup combined terms: croup infectious, laryngotracheobronchitis (LLT or verbatim).
Breath holding combined terms: breath holding, apnoea, apnoeic episode, sleep apnoea syndrome, apnoeic attack.
Abscess combined terms: abscess, abscess neck, abscess oral, perianal abscess, perirectal abscess, rectal abscess.
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.
Source: 125324/0.74, m1.1, Information Amendment, pages 7-8 Table 1-2

14.4.3 Post-Marketing Experience

No post-marketing data with Prevnar 13 are available.

14.5 Safety Conclusions

The safety data from the fifteen pediatric studies and one adult phase 1 study raise no particular concerns about the safety of Prevnar 13 when administered as a four dose series to infants at 2, 4, 6, and 12-15 months or when administered to previously unvaccinated children 7 months through 5 years of age based on the catch-up schedule studied in study 3002. These studies, combined with the pre-licensure and post-licensure experience with Prevnar, support the safety of Prevnar 13 for use in infants starting at 6 weeks of age and for use in previously unvaccinated children from 7 months through 5 years of age as a catch-up schedule.

15.0 Additional Clinical Issues

15.1 Directions for Use

In clinical studies of Prevnar 13, the liquid vaccine was supplied in single-dose vials and administered intramuscularly into the left anterolateral thigh of infants and toddlers and in the deltoid muscle of the upper arm in toddlers and young children.

Prevnar 13 intended for use in the U.S. commercially will be supplied as a 0.5mL dose within a disposable pre-filled 1mL glass synringe with a latex-free rubber tip cap, sealed with a latex-free rubber stopper. The use of pre-filled syringes is expected to reduce the risk of medication error. The proposed directions for use are as follows:

1. Shake the suspension vigoursly immediately prior to use to obtain a homogeneous, white suspension in the vaccine container
2. Do not use the product if particulate matter or discoloration is observed
3. Inject the 0.5mL dose intramuscularly
4. The preferred sites are the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in toddlers and young children.

The proposed storage and handling instructions specify the following:

1. Store refrigerated at +2^{o}C to +8^{o}C (36^{o}F to 46^{o}F)
2. Do not freeze; discard if the vaccine has been frozen.
3. Prevnar 13 has been shown to be stable at temperatures of –b(4)----------. These data are not recommendeds for shipping or storage, but may gjuide decisions for use in case of temporary temperature excursions.

Pleaes refer to the CBER product review of the Prevnar 13 BLA for CBER's assessment of stability data and the acceptability of the proposed directions for storage and handling of Prevnar 13.

15.2 Dose Regiman

Wyth has proposed that for infants, Prevnar 13 is to be administered as a four-dose series at 2, 4, 6, and 12-15 months of age. The first dose is to be given as early as 6 weeks of age. The recommended dosing interval between doses 1, 2, and 3 is 4 to 8 weeks. The fourth dose is to be administered at approximately 12-15 months of age, at at least 2 months after the third dose.

Catch-up Schedule:

For children who are beyond the age of the routine infant schedule and have not received Prevnar or Prevnar 13. The applicant has proposed the following catch up schedule:

- For children 7 to 11 months of age, Prevnar 13 is to be administered as a 3 doses series. The first 2 doses are to be administered at least 4 weeks apart. The third dose is to be administered after the one-year birthday and separated from the second dose by at least 2 months.
- For children 12-23 months of age, Prevnar 13 is to be administered as a 2 dose series at least 2 months apart.
- For children ≥ 24 months through 5 years of age, Prevnar 13 is to be administered as 1 dose.

Transition Schedule:
For children who have received one or more doses of Prevnar, the applicant proposes that the 4-dose series may be completed with Prevnar 13. For children 12 months through 5 years of age who have received 4 doses of Prevnar, the applicant proposes that one dose of Prevnar 13 is to be administered.

The available data do not provide evidence of clinical protection against the 13 vaccine serotypes for the catch-up schedule or for clinical protection against the 6 additional serotypes for the transition schedule. In addition, the safety data supporting a fifth dose of a pneumococcal conjugate vaccine are very limited.

15.3 PREA requirements

Table 203 below summarizes how the requirements of the Pediatric Research Equity Act (PREA) will be addressed.

Table 203: Summary of Approach to PREA requirements for Prevnar 13

Pediatric Age Group	How PREA Requirements Are Addressed	
	IPD Indication	Otitis Media (OM) Indication
0 to < 6 weeks	Waiver request	Waiver request
6 weeks to 5 years (prior to 6th birthday)	Population studied	Population studied
6 years to 17 years	Deferral request	Waiver request

15.3.1 Infants 0 to < 6 Weeks of Age: Request for Waiver of Studies of IPD and OM Indications

The pediatric study requirement in infants from birth to < 6 weeks of age is waived for the invasive pneumococcal disease and otitis media indications. This partial waiver is based on Section 505B(a)(4)(B)(iii) of PREA: the drug or biological product – (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (II) is not likely to be used in a substantial number of pediatric patients in that age group.

With the exception of Hepatitis B vaccine, for which a birth dose is routinely recommended to prevent perinatal transmission of hepatitis B virus, infant immunizations in the U.S. can be administered as early as 6 weeks of age.

A U.S. maternal immunization study was conducted to evaluate pneumococcal serotype-specific IgG antibody response in maternally immunized infants, who received a 7-valent pneumococcal conjugate vaccine (PCV7) according to the routinely recommended childhood. Pregnant women received either a 9-valent pneumococcal conjugate vaccine or saline. Of the 7 serotypes common to both vaccines, a summary of preliminary results indicated that at 6 months of age, mean IgG antibody concentrations to 5 serotypes were lower in maternally immunized infants, compared to control group infants. One month after the 3rd PCV7 vaccination (i.e., 7 months of age), mean IgG antibody concentrations to 6 six serotypes were lower in infants of maternally immunized mothers.[28] Because of the similarities between the 13vPnC and PCV7 vaccines, these results are pertinent to the 13vPnC vaccine.

Due to limitations of the neonatal immune response discussed above, vaccinating U.S. infants from birth up through 5 weeks of age against *Streptococcus pneumoniae* will not provide a meaningful therapeutic benefit over vaccination according to the currently recommended schedule which begins at a minimum age of 6 weeks.

In addition, based on experience with a similar pneumococcal conjugate vaccine (PCV7; Prevnar), greater benefit to neonates may result from indirect protective effects via herd immunity. Decreases in nasopharyngeal carriage in vaccinated infants, when the vaccine is widely used, are thought to interrupt pneumococcal transmission to unvaccinated children. Experience with Prevnar in the U.S. has shown that IPD rates among infants too young to receive PCV7 (0-60 days) decreased from 7.3 (95% CI 5.6, 9.5) per 100,000 live births in the pre-PCV7 years (1998-2000) to 4.2 (95% CI 3.0, 5.9, p=0.1) per 100,000 in the post-PCV7 years (2001-2004); this represents a 42% decrease.[29] A similar indirect effect resulting from a routinely immunized 4.1 million U.S. birth cohort is expected with the 13vPnC vaccine. In view of the

potential risks of neonatal vaccination and the lack of added benefit to earlier vaccination against *Streptococcus pneumoniae*, the 13vPnC vaccine is not likely to be used by a substantial number of U.S. infants from birth to 6 weeks of age.

15.3.2 Children 6 years to 17 years of age: Request for Deferral of Studies for IPD Indication

The pediatric study requirement in children 6 to 16 years of age is deferred for the IPD indication, because Prevnar 13 is ready for approval for use in children 6 weeks through 5 years of age and the pediatric study in children 6 to 16 years of age has not been completed. Waiting for results of a study of Prevnar 13 in children 6 to 16 years of age would delay licensure of Prevnar 13, and therefore delay delivery of vaccine supply that is expected to provide coverage of pneumococcal serotypes not currently included in the only U.S. licensed pneumococcal conjugate vaccine (Prevnar).

The applicant has submitted a clinical trial protocol, study 6096A1-3011, to fulfill the PREA requirement for pediatric studies for the age group 6 years to 16 years of age. This is a phase 2, open-label, non-controlled, multicenter study designed to evaluate the safety and immunogenicity of Prevnar 13 when administered to healthy children > 15 months to < 18 years of age. The trial is exploratory and assesses the safety profile of > 4 doses of a pneumococcal conjugate vaccine. The applicant has completed enrollment of all subjects in this trial, and plans to analyze the data and submit a final study report after having an opportunity to discuss the analysis plan with CBER following approval of Prevnar 13.

15.3.3 Children 6 to 17 years of age: Request for Waiver of Studies for OM Indication

The pediatric study requirement in children 6 to 17 years of age is waived for the otitis media indication. This partial waiver is based on Section 505B(a)(4)(B)(iii) of PREA: the drug or biological product – (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (II) is not likely to be used in a substantial number of pediatric patients in that age group.

Acute otitis media occurs primarily in children less than 5 years of age. The peak age for acute otitis media in the United States is between 6 and 18 months of age.[30] The incidence of acute otitis media in children aged 6 to 16 years is low, and pneumococcal conjugate vaccination is not routinely recommended in this age group. In addition, immunization with a pneumococcal conjugate vaccine does not represent a meaningful therapeutic benefit over existing antibiotic therapy in this age group.

16.0 Overall Conclusions

The available safety and immunogenicity data from clinical studies, combined with the pre-licensure efficacy studies with Prevnar and post-marketing safety experience with Prevnar, support Prevnar 13 effectiveness in preventing IPD caused by pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, and 23F when administered to infants as a 4 dose series at 2, 4, 6, and 12-15 months of age. Failure of serotype 3 to meet all pre-specified non-inferiority criteria lessens our confidence that a protective response will be elicited among a high proportion of vaccinees for this serotype. Its inclusion in Prevnar 13, however, may offer some benefit in eliciting some functional anti-serotype 3 antibody response.

Safety and immunogenicity data from the two phase 3 U.S. studies support co-administration of U.S. licensed DTaP-HBV-IPV, Hib, MMR, and varicella vaccines. The pre-specified non-inferiority criteria were met for antigens contained in DTaP-HBV-Hib and Hib vaccines. The criteria for concomitant vaccine antigens are defined in clinical review sections 7.1.3.6.3.1 and 7.2.3.6.3.1. Mumps responses met the pre-specified non-inferiority criteria. However, the responses to mumps were lower than expected in study 004 due to the low sensitivity of the commercial Mumps assay used in study 004. Evaluation of sera from study 3005 with a more sensitive Mumps assay resulted in adequately high responses which were similar between the two study groups. In addition, rubella antibody response rates based on a cut-off of ≥ 15 IU/mL met the pre-specified non-inferiority criterion. Re-evaluation of rubella antibody responses using the assay-specific cut-off of –b(4)-- missed the non-inferiority criterion of -5% by a small margin; the lower limit of the 95% CI was -5.9%. Responses to diphtheria toxoid, tetanus toxoid, pertussis, polio types 1, 2, and 3, hepatitis B, PRP-T, PRP-OMP, measles, and varicella antigens in Prevnar 13 recipients were comparable to those in Prevnar recipients. Based on limited data, responses to mumps and rubella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients.

The safety and immunogenicity of Prevnar 13 as a catch-up regimen in children 7 months through 5 years of age who received no prior Prevnar immunizations was evaluated in an open label, descriptive study conducted in Poland. The data from descriptive analyses suggest lower IgG GMCs for most of the serotypes than were observed following a 4 dose infant and toddler immunization series with Prevnar 13. In children 24 months through 5 years, descriptive analyses suggest lower IgG GMCs for some serotypes than were observed following three Prevnar 13 infant series doses (given at 2, 4, and 6 months). It is not known whether the observation of lower GMCs is predictive of diminished effectiveness in preventing invasive disease in these older children. Functional OPA responses, which are typically necessary for assessing immune responses among children beyond 7 months of age, were not assayed in this study.

The immunogenicity of 1 dose of Prevnar 13 when administered at 12 months of age to children with 3 prior Prevnar doses (administered at 2, 3, and 4 months of age) was evaluated in study 008 (France). The data from this study suggest that one does of Prevnar 13 at 12 months of age results in lower IgG GMCs for most of the 6 additional serotypes than are observed following a 4-dose infant and toddler immunization series with Prevnar 13. OPA GMTs were also lower for three of the 6 additional serotypes in children who received one dose of Prevnar 13 at 12 months of age than were observed following a 4-dose infant and toddler immunization serieis with Prevnar 13. The immunogenicity of 2 or 3 doses of Prevnar 13 when administered to children with 2 or 1 prior doses of Prevnar respectively (to complete the 4-dose infant and toddler immunization series) was not evaluated in pre-licensure clinical trials.

The immunogenicity and safety of 1 or 2 doses of Prevnar 13 when administered to children < 5 years of age with at least 3 prior doses of Prevnar was evaluated in study 3011. The data from descriptive analyses suggest lower IgG GMCs in study 3011 subjects for some of the additional 6 serotypes than were observed following a 4-dose infant and toddler immunization series with Prevnar 13. It is not known whether the observation of lower GMCs is predictive of diminished effectiveness in preventing invasive disease in these older children. Functional OPA responses were not provided from study 3011.

The immunogenicity data from the U.S. pivotal immunogenicity study suggest that there is some interference in antibody responses as a result of the additional serotypes in Prevnar 13. This resulted in lower antibody responses elicited by Prevnar 13 compared to Prevnar against several of the 7 common serotypes. The

phenomenon of immunogenicity creep should therefore be considered in future assessments of new pneumococcal conjugate vaccines which may be compared to Prevnar 13.

As discussed previously, the effectiveness of Prevnar 13 against otitis media was not assessed in pre-licensure clinical trials submitted to the BLA. This issue was presented and discussed at the November 18, 2009 VRBPAC meeting. Although the committee did not vote on this subject, the majority of the Committee agreed that an otits media indication for Prevnar 13 is adequately supported by Prevnar efficacy data (for the 7 common serotypes) and comparative immunogenicity data from Prevnar 13 clinical trials. However, the majority of Committee members expressed concern regarding the lack of efficacy data for the 6 additional serotypes.

This reviewer concludes that the effectiveness of Prevnar 13 in preventing otitis media has not been demonstrated in the Prevnar 13 BLA. The 0.35 µg/mL reference value used for non-inferiority comparisons between Prevnar 13 and Prevnar applies only to IPD and not to otitis media or other non-invasive disease endpoints. It has been suggested that higher serum antibody concentrations are required to prevent otitis media and carriage compared to the concentrations required to prevent IPD. However, there is no consensus regarding the serologic criteria for assessing effectiveness of new pneumococcal conjugate vaccines against otitis media. The non-inferiority comparisons between Prevnar 13 and Prevnar using a higher antibody concentration of 1.0 µg/mL showed that 6 out of the 7 original Prevnar serotypes would have failed to meet the -10% non-inferiority criterion for the post-dose 3 endpoint. This data suggests that interference with Prevnar 13 is more pronounced at higher antibody concentrations, and that Prevnar 13 is inferior to Prevnar in eliciting higher antibody concentrations to the 7 common serotypes; these higher antibody concentrations are thought to be necessary to prevent otitis media. Therefore, there are insufficient data to support an otitis media indication for Prevnar 13 for the prevention of otitis media caused by serotypes contained in the vaccine. Data from post-marketing OM surveillance studies may be submitted when available in support of an otitis media efficacy supplement.

17.0 Recommendations

17.1 Approval Recommendation

I recommend approval of Prevnar 13 for the prevention of invasive pneumococcal disease caused by *S. pneumoniae* serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in children 6 weeks through 5 years of age. There are insufficient data to support the effectiveness of serotype 3 for the prevention of IPD caused by this serotype. However, the inclusion of serotype 3 in Prevnar 13 may offer some benefit as it will elicit some functional anti-serotype 3 antibody response in children.

17.2 Recommendations on Postmarketing Actions

A comprehensive discussion of CBER's recommendations on post-marketing actions is contained in the approval letter for Prevnar 13 published at the time the license was granted. The clinical reviewer concurs with the recommendations as stated in the approval letter.

IPD Effectiveness Studies:

The applicant's proposed post-marketing studies to evaluate post-licensure vaccine effectiveness of Prevnar 13 are not considered "confirmatory studies." Nonetheless, the Agency recognizes the importance of collecting and analyzing IPD surveillance data after U.S. licensure and introduction of Prevnar 13 as a means to evaluate the impact of Prevnar 13 on rates of IPD in the U.S pediatric population, particularly for the 6 new serotypes (1, 3, 5, 6A, 7F, and 19A). Of note, the proposed post-marketing IPD effectiveness studies include the items described below.

(1) An observational database study will be conducted to evaluate the impact of Prevnar 13 in preventing vaccine-serotype IPD in children ≤ 5 years of age following its introduction in the Northern California Kaiser Permanente (NCKP) system. The study duration is planned to be a five year surveillance period (2010 – 2014). Rates will be compared to baseline IPD incidence rates prior to Prevnar 13 licensure (during routine use of Prevnar). Cases of IPD will be identified through a laboratory-based surveillance system within NCKP.

(2) IPD surveillance data from a case-control study, conducted by the CDC, will be used to assess the effectiveness of one or more doses of Prevnar 13 against vaccine-serotype IPD. Data will be collected through CDC's Active Bacterial Core Surveillance (ABCs) system. With a larger sample size compared to the NCKP study, this study may be able to provide serotype-specific effecteness data for the most common serotypes that cause IPD in the U.S. (i.e. serotype 19A).

Otitis Media Effectiveness Studies:
The applicant also plans to conduct the following post-marketing studies to evaluate the effectiveness of Prevnar 13 against otitis media:

(1) An observational study to evaluate the effectiveness of Prevnar 13 in reducing acute otitis media and nasopharyngeal colonization in young children caused by vaccine serotypes. Children will be recruited prospectively beginning at 2 months of age and followed until 30 months of age. Children presenting with AOM will undergo typmpanocentesis and middle ear fluid will be obtained, cultured, and isolates will be serotyped. Rates of AOM caused by vaccine serotypes will be compared to rates to a pre-Prevnar 13 baseline period. The effectiveness of Prevnar 13 in reducing nasopharygeal carriage will also be assessed.

(2) An ecologic study to assess trends in the diagnosis of all-cause otitis media in the U.S. over time as an indirect marker of effectiveness against OM. Data will be based on outpatient visits to healcare facilities obtained from the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Care Survey (NHAMCS) from three time periods: pre-Prevnar (1994-1999), post-Prevnar (2000-2008), and post-Prevnar 13 (~2010-2012).

(3) A study to monitor the impact of Prevnar 13 routine use in reducing AOM caused by serotypes in the vaccine via the United States Pediatric Multicenter Pneumococcal Surveillance Group (USPMPSG), a laboratory-based surveillance network of eight pediatric hospitals across the United States. In this study *S. pneumoniae* isolates from identified AOM cases will be serotyped.

17.2.1 Clinical Trial Postmarketing Requirement
There were no safety signals identified in the Prevnar 13 clinical trials that would have necessitated a post-marketing requirement.

17.2.2 Pharmacovigilance Plan
Please refer to the CBER epidemiology review for the Prevnar 13 BLA for CBER's assessment and recommendations regarding the applicant's pharmacovigilance plan for Prevnar 13.

17.3 Recommendations Regarding PREA
I recommend a partial waiver for infants from birth to less than 6 weeks of age for the IPD and OM indications and a partial waiver for children 6 years to 16 years of age for the OM indication based on the assessment that Prevnar 13 in these age groups does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients in these age groups. I recommend that the requirement for pediatric studies in the age group 6 years to 16 years for the IPD indication be deferred. The applicant has completed enrollment for this deferred study, which will be a post-marketing requirement for the purposes of PREA. The projected date for the submission of this pediatric assessment is in 2010. The requirement for pediatric studies in the age group 6 weeks through 5 years of age for the IPD indication is fulfilled with approval of this BLA.

18.0 Labeling
CBER communicated with the applicant to achieve consistency with CBER's current guidance on the intent and format of package inserts. The final label was reviewed by the clinical team and by the Advertising and Promotional Labeling Branch (APLB) and found to be acceptable.

19.0 References

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