Prevnar 13

Pre-meeting Package

for

VRBPAC Meeting

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INTRODUCTION

This briefing document presents a summary of data from the clinical evaluation of Wyeth's candidate 13-valent pneumococcal conjugate vaccine (13vPnC) in support of the current biologic license application (BLA). In total, safety and immunogenicity data were obtained from more than 4700 infants, more than 4300 of whom completed the infant series. In addition, there are "catch-up" data from 354 older infants and children who had not previously received a pneumococcal vaccine.

This application is supported by the extensive clinical safety and efficacy experience gained with Wyeth's licensed 7-valent pneumococcal conjugate vaccine (7vPnC), Prevnar (labeled Prevenar in most countries outside of the U.S.),[a] which was licensed in 2000 in the United States. Prevnar is currently indicated for the prevention of invasive pneumococcal disease (IPD) and acute otitis media (AOM) caused by the 7 *Streptococcus pneumoniae* serotypes found in the vaccine. To date, over 195 million doses of Prevnar have been distributed worldwide. Prevnar is the standard upon which the safety and the immunogenicity of 13vPnC have been evaluated in the clinical development program.

1.0 INDICATION AND PRODUCT DEVELOPMENT RATIONALE

1.1 Indication

Wyeth has developed Prevnar 13, a 13 valent pneumococcal CRM_{197} conjugate vaccine (13vPnC), as a successor to the currently registered vaccine, Prevnar, for active immunization of infants and toddlers for the prevention of invasive disease (including sepsis, meningitis, bacteremia, bacteremic pneumonia, and empyema) caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. Wyeth also seeks a 13vPnC indication for active immunization of infants and toddlers against otitis media caused by serotypes included in the vaccine. However, as with the 7-valent Prevnar, protection against otitis media is expected to be lower than protection against invasive disease.

Prevnar 13 is to be administered as a 4-dose series at 2, 4, 6, and 12-15 months of age. Prevnar currently has a labeled indication in the U.S. for prevention of invasive disease and otitis media caused by *Streptococcus pneumonia* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

[a] PREVNAR and PREVENAR are registered trademarks of Wyeth.

1.2 Serotypes contained in Prevnar (7vPnC) and 13vPnC

Prevnar is a 7 valent pneumococcal CRM_{197} conjugate vaccine (7vPnC) that contains pneumococcal serotype specific conjugated polysaccharides 4, 6B, 9V, 14, 18C, 19F, and 23F. Since licensure, the effectiveness of Prevnar in preventing invasive and noninvasive diseases in infants has been consistently documented. Nonetheless, new pneumococcal conjugate vaccines with expanded serotype coverage are needed to address the varying epidemiology of pneumococcal infections in different regions of the world and the changing epidemiology of infection in the United States and other countries that have adopted general use of Prevnar. In addition to the serotypes contained in Prevnar, 13vPnC contains serotypes 1, 3, 5, 6A, 7F, and 19A. The 13 serotypes in 13vPnC are responsible for the majority of IPD cases in the United States and worldwide. Overall, the 6 new serotypes added to 13vPnC are responsible for approximately 50% to 65% of the current IPD cases occurring among children targeted for vaccination in the United States. Serotype 19A has now become the predominant pneumococcal serotype causing IPD in US children, accounting for approximately 40% of the residual IPD in 2005 in children <5 years of age. (See Appendix 13.2)

2.0 IMMUNOBIOLOGY OF *STREPTOCOCCUS PNEUMONIAE* AND THE ROLE OF CONJUGATE PNEUMOCOCCAL VACCINE IN PROTECTION AGAINST PNEUMOCOCCAL DISEASE IN INFANTS AND CHILDREN

2.1 The pneumococcal polysaccharide capsule

The importance of *Streptococcus pneumoniae* (pneumococcus) as a cause of bacteremic illness, pneumonia, and acute otitis media (AOM) has been well established. Since its discovery,[1, 2] the serotype specific polysaccharide capsule of the pneumococcus has been shown to be fundamental to pathogenesis and development of protective immunity in the exposed human host.

The pneumococcal polysaccharide capsule is an important virulence factor. It inhibits phagocytosis by interfering with immune recognition of cell wall constituents by complement or antibody and interferes with intracellular killing.[3] Pneumococci that lack a polysaccharide capsule are typically avirulent, due to an inability to resist innate immunity. Serum derived immunity to pneumococcus , coined *humoral immunity* was shown to protect rabbits and induce opsonization, from the Greek “to cater a meal” based on phagocytosis of pneumococci.[4, 5]

These observations led to the development of the Quellung or capsular swelling test,[6,7] which became the basis for the standardized serotyping of the more than 90 serotypes of pneumococci based on serotype specific antibody response to the pneumococcus polysaccharide capsule. The nomenclature now conforms to the familiar Danish system, Statens Serum Institut, Copenhagen, which uses Arabic numerals and letters to designate serotypes.

2.2 The important role of serotype specific antibody to capsule in protection against pneumococcal disease

By 1933 it became clear that serotype specific antibody was protective but a heat inactivated substance (complement) was required to opsonize pneumococci, followed by phagocytosis by inflammatory cells.[8, 9] We now know that antibody to pneumococcal type-specific capsular polysaccharides binds to the capsule of the bacterium, thereby opsonizing the pneumococcus. The Fc portions of the attached antibodies bind to Fc receptors on phagocytic cells, leading to the phagocytosis and degradation of the pneumococcal bacterium. The antipolysaccharide antibodies can also activate complement proteins, which in turn bind to phagocyte complement receptors, further enhancing pneumococcal opsonization and phagocytosis. Until the advent of antibiotics, passive immunization using horse or rabbit derived antipneumococcal sera derived demonstrated some evidence of clinical benefit, and the stage was set for vaccine development.[5]

2.3 Purified pneumococcal capsular polysaccharide vaccine development

After mixed experiences with whole-cell pneumococcal vaccines in the early 1900s, attention focused on development of vaccines containing combinations of capsular polysaccharides from pneumococcal serotypes known to be important causes of infection. Based on the work of Robert Austrian and others,[10] it became clear that antimicrobials were not likely to eliminate the impact of pneumococcal disease, and an appropriately constituted polysaccharide vaccine containing multiple serotypes might have value in providing protection against pneumococcal disease. Building on the efficacy demonstrated by Macleod in 1945 with a quadravalent purified polysaccharide vaccine,[11] a 13-valent PS vaccine was shown to reduce vaccine type pneumococcal pneumonia by 82%, 78.5% against vaccine-type bacteremia and pneumonia combined, and 53% against radiographically confirmed pneumonia in a population of South African gold miners with otherwise high rates of pneumococcal disease.[12, 13] As reviewed by Fedson and Musher[14] and Makela and Butler,[15] a number of additional studies have supported the value of PS vaccine in protecting older children and adults against IPD, but several large studies and meta- analyses have not documented effectiveness against lower respiratory tract

infections without bacteremia in elderly populations for which the vaccine is most commonly targeted. Protection also appears to wane over a period of 3-5 years.[16]

By the 1970s, attention turned to the potential use of PS vaccine in children. The unmet medical need for such interest is clear. Worldwide, pneumococcal infection causes more than 500,000 deaths each year in children less than 5 years of age; in countries including the United States;[17] the highest pediatric attack and death rates are seen in children less than two years of age. Several lines of evidence supported the view that, like the experience in adults, capsule serotype specific antibody was likely to be associated with protection in young children. Disappearance of maternally acquired antibody, which is present in infants until the age of 6 months, coincides with an increasing rate of IPD. Despite evidence of protection afforded by passive immunization using bacterial polysaccharide immune globulins (BPIG), against otitis media[18] and IPD,[19,20,21,22] the ability of polysaccharide vaccine to induce antibody to capsular polysaccharide and provide protection in infants and young children has proved disappointing. Purified polysaccharide antigens are poorly immunogenic in young children, particularly those less than 2 years of age.[23, 24, 25, 26] This poor immunogenicity has been accompanied by no evidence of protection against AOM in infants in controlled clinical trials.[27, 28, 29, 30] In addition, no convincing evidence of efficacy has been shown against IPD or respiratory disease morbidity following PS immunization of young infants and children in developing country settings with high pneumococcal disease attack rates.[31, 32]

The type of immune response generated by PS conspires against effective protection of infants. Purified PS antigens act as T-cell independent antigens. Polysaccharide antigens do not associate with major histocompatibility complex class II (MHC-II) molecules and do not recruit classical T-cell help, which appears to be particularly important in generating protective immune responses in naïve infants and young children.[33, 34] Consequently, PS antigens induce antibody responses primarily of IgM class with inadequate class switching, reduced somatic hypermutation, and poor immunologic memory.[23]

2.4 Development of protein conjugated pneumococcal polysaccharide vaccine

Fortunately, based on work first described in the 1930s,[35] covalent linkage of polysaccharide antigens to immunogenic proteins has been shown to overcome many of the limitations of polysaccharide alone. Such covalent linkage induces protective high titer IgG responses with

shifts to Ig isotypes of high affinity that are capable of functional activity. These linkages were first used to advantage with *Haemophilus influenzae* type b and *Neisseria meningitidis* vaccines to convert poorly immunogenic T-cell independent polysaccharide antigens in infants, to highly immunogenic vaccines capable of recruiting CD4+ T-cell help, with establishment of memory. Such vaccines have now led to the virtual eradication of *Haemophilus influenza*e type b and meningococcal C invasive disease in countries where the vaccines have been broadly applied. Therefore, to overcome the poor immunogenicity of PS vaccines in young children, the protein conjugation technology has been applied to the development of Prevnar and successor pneumococcal vaccines. In Prevnar and 13vPnC, each of the polysaccharides is covalently conjugated to the diphtheria cross-reactive material 197 (CRM_{197}) protein, which acts as an immunologic carrier. In contrast to the poor performance of PS alone, Prevnar has been associated with robust IgG binding antibody and opsonophagocytic antibody which in turn have been associated with reductions in pneumococcal IPD, AOM, and pneumonia in infants and children. Prevnar has also been associated with reduction in IPD in all age groups, presumed due to a herd immunity effect by reducing carriage in infants and children. [36, 37, 38, 39,119] 13vPnC provides promise of extending this protection to the additional six pneumococcal serotypes in the vaccine, which have been recognized as significant contributors to pneumococcal disease in the U.S. and worldwide.

3.0 COMPOSITION OF 13VPNC AND DETERMINATION OF DOSE

13vPnC is a sterile suspension of pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to the nontoxic variant of diphtheria toxin, CRM_{197} protein, as in Prevnar and adsorbed to aluminum phosphate.

A clinical trial to assess the vaccine dose response in 2-month-old infants was conducted in 1992 to 1993 with an experimental 5-valent vaccine that contained CRM_{197} conjugated capsular polysaccharides of serotypes 6B, 14, 18C, 19F and 23F. In this trial, dosages of 0.5 µg, 2.0 µg, and 5.0 µg per serotype were compared. The results of this trial (Wyeth study 92-5, not included in this application, but originally submitted as part of the BLA for Prevnar) demonstrated that a dosage of 2.0 µg per polysaccharide resulted in a higher immune response to all 5 serotypes compared with a dosage of 0.5 µg per polysaccharide. In addition, for the majority of the serotypes, increasing the dosage to 5.0 µg per polysaccharide did not result in a substantial increase in the immune response. Accordingly, a dosage of 2.2 µg per serotype polysaccharide,

except for serotype 6B (dosage 4.4 μg), was selected for the 7-valent vaccine used in the efficacy trial that was conducted at Northern California Kaiser Permanente (NCKP) from 1995 to 1998. High efficacy was demonstrated in this trial (94%) that formed the basis of U.S. licensure of Prevnar in year 2000. The vaccine's efficacy has been confirmed through postmarketing surveillance in the U.S. and other countries. Hence, the same dosage was maintained for the Prevnar serotypes in 13vPnC and the 2.2 μg dosage was selected for the additional serotypes that were added to the 13vPnC formulation.

13vPnC contains a modified serotype 19F conjugate. The polysaccharide conjugation process for this serotype was optimized to increase the molecular weight of the conjugate and improve the consistency of the polysaccharide conjugate size distribution . Succinate buffer is also included in the vaccine formulation for 13vPnC to improve process control and to provide further pH control following the addition of aluminum phosphate. Aluminum phosphate likely serves as depot for antigen and is presumed to enhance uptake by antigen presenting cells for presentation of the protein component to CD4+ T- helper cells.[40, 41] In addition, 0.02% polysorbate 80 (P80) is included in the final vaccine formulation to improve the robustness of the manufacturing process. During the conduct of phase 3 clinical trials, precipitates identified as conjugate were rarely identified in vaccine syringes. This proved to be due to interaction with the silicone coating of the syringe. Addition of 0.02% P80 was shown to resolve this issue. Since the decision to add P80 was made after the initiation of the phase 3 clinical studies, a comparative formulation clinical study (61096A1-009) was performed, which demonstrated immunologic non-inferiority and a comparable safety profile of the P80 containing formulation.

The 13vPnC clinical program was designed to demonstrate that this dosage is both safe and immunologically non-inferior to the effective Prevnar serotypes. Demonstration that the immune response of 13vPnC is comparable to the responses of Prevnar for both the serotypes in common and the new 6 serotypes, establishes a direct link to antibody responses that were correlated with efficacy trials of pneumococcal conjugate vaccines. The results of the 13vPnC trials discussed in this overview confirm that the selected dosage is indeed non-inferior and therefore likely to be effective when used in the general population.

TThe efficacy and effectiveness profile of Prevnar to which 13vPnC will be linked is discussed in Appendices 13.1 and 13.2.

4.0 APPROACH TO CLINICAL DEVELOPMENT OF 13VPNC

4.1 Clinical Development of 13vPnC

Given the availability of an effective pneumococcal vaccine, clinical trials to assess the efficacy of a vaccine with expanded serotype coverage, using an unvaccinated control group, cannot be performed. Furthermore, relative efficacy assessments using rare clinical endpoints such as IPD would require very large study populations, because controls would have to be vaccinated with the available vaccine. On the other hand, it is well established that protection against pneumococcal disease is mediated by the opsonophagocytic capacity of type-specific pneumococcal capsular antibodies. Consequently, the immune response induced by the new pneumococcal conjugate vaccine can be used to provide an assessment of the protective efficacy of the vaccine.

4.1.1 Rationale for use of immunologic response to CRM_{197} pneumococcal conjugate vaccines as a basis for licensure and description of antibody assays

Immunoglobulin G (IgG) binding antibodies directed to the capsular polysaccharide, and the associated opsonophagocytic activity (OPA) of these antibodies, are immunologic correlates of protection. To maintain the link with the demonstrated efficacy of Prevnar, it is critical that the immune responses induced by the new vaccine be compared in head-to-head comparative trials with the immune responses elicited by Prevnar. The World Health Organization (WHO) has issued a technical report series (TRS 927, annex 2) with recommendations for the evaluation of new pneumococcal conjugate vaccines that reflect these principles.[42] The WHO recommendations provided the basis for the clinical assessment of 13vPnC immune response as reviewed in this document.

4.1.2 Overview of criteria used for assessment of 13vPnC immune response

WHO TRS 927[42] provides guidance for evaluation and licensing of new pneumococcal conjugate vaccines using serologic criteria. According to TRS 927 annex 2, this evaluation should be based on (1) IgG antibody responses to pneumococcal polysaccharides measured using a standardized ELISA, (2) functionality of antibody as documented by OPA, and (3) induction of immunologic memory. Head-to-head comparison with 7vPnC to demonstrate immunogenicity that is non-inferior to that of 7vPnC is required and allows bridging to the established efficacy of 7vPnC against IPD.

4.1.2.1 Primary criterion for assessment of immune response to serotypes in 13vPnC vaccine

The WHO TRS 927 document describes a standardized enzyme-linked immunosorbent assay (ELISA) for measurement of anticapsular polysaccharide IgG concentrations, and suggests a single ELISA IgG antibody concentration of 0.35 µg/mL, measured 1 month after the infant series, as a reference antibody concentration for assessment of vaccine efficacy against IPD.[42] The WHO recommends the use of this reference concentration as a primary endpoint to evaluate non-inferiority of new pneumococcal conjugate vaccine formulations as compared with 7vPnC.

This antibody concentration was derived from a meta-analysis of 3 double-blind, randomized, placebo-controlled efficacy trials of 7vPnC and 9vPnC.[43, 44, 45] The pooled efficacy estimate was 93.0% (95% confidence interval [CI]: 81, 98.2) for 7vPnC serotypes across the 3 trials. Using pooled antibody concentrations measured 1 month after the third dose of vaccine, and applying a step function model, an anticapsular polysaccharide IgG ELISA concentration of 0.35 µg/mL was determined to correlate with protection against IPD. [46, 47]

This 0.35 µg/mL IgG antibody threshold is based on the assumption that protective concentrations are similar across serotypes and that protection is primarily driven by the immune response obtained after the infant vaccination series. This is likely to be an oversimplification and overly conservative in some circumstances, since 0.35ug/mL may in fact exceed protective levels for some serotypes and some populations. In addition, this value in and of itself does not provide direct information on the functional activity of the antibody response, perhaps best evidenced by failure of 19F to provide protection against 19A, despite high IgG responses to the latter. Therefore, OPA responses are important to consider in providing a thorough assessment of the likelihood of protection. The comparison of immune response after the infant series is a stringent assumption, because it does not take into account the higher antibody concentrations achieved following the toddler dose and the potential contribution of immunologic memory to protection. Therefore, additional criteria consistent with WHO TRS 927 annex 2 guidelines were predefined to provide a comprehensive assessment of immune response (see next section 4.1.2.2). The antibody threshold serves as a correlate for protection against IPD only and is only applicable on a population basis; it cannot be used to predict protection against IPD on an individual basis.

In addition, clinical studies have reported that 7vPnC is also protective against AOM. While serotype-specific IgG antibody concentrations associated with protection against AOM have not been established, comparisons of immune responses elicited by 13vPnC to those observed in 7vPnC-vaccinated children, in settings in which the effectiveness of 7vPnC against AOM and/or nasal acquisition of pneumococci have been demonstrated, support the perspective that 13vPnC will be equivalently effective against AOM (see Section 9.3).

4.1.2.2 Additional Pre-defined Objectives for Evaluation of 13vPnC Immune Response

The WHO TRS 927 document states that "Noninferiority to antibody response for each of the serotypes in the registered vaccine is desirable, but not an absolute requirement. Registration of products in which one or more serotypes do not meet non-inferiority criteria would have to be decided on an individual basis."[42] Therefore, the following additional analyses, as agreed upon by Wyeth and CBER, FDA, are included in an overall evaluation of the merits of a given serotype:

- Assessment of GMC ratios (2-fold criterion) included as a co-primary endpoint for the 61096A1-004 U.S. non-inferiority trial at the toddler dose and a secondary endpoint for the 61096A1-006 German non-inferiority trial after the infant series.
- Assessment of the relative margin of failure at the 0.35 µg/mL threshold (e.g., -11% non-inferiority is of less concern than -50%).
- Assessment of non-inferiority using the IgG ELISA threshold of 0.15 µg/mL. This value is relevant because it reflects the protective antibody threshold established with the current ELISA in the Northern California population using sera from the original Prevnar NCKP efficacy trial. (Please see 4.2.1 below)
- Assessment of the elicitation of specific OPA antibody. The WHO TRS 927 document states: "Opsonophagocytic antibody titres were available from two of the three studies and analysis of the data showed that antibody concentrations in the range of 0.20–0.35mg/ml correlated best with an opsonophagocytic antibody titre of 1 : 8, which in turn correlates best with protective efficacy."[42] GMTs and percent responders at an OPA titer of 1:8 are assessed for the seven serotypes in common with 7vPnC and for the 6 additional serotypes. Additional analysis is provided for serotype 7F at an experimentally defined response cutoff of 1:2048. (Please see 4.2.2.1 Definition of a clinically relevant OPA response)
- Assessment of the immune responses following the toddler dose.

- Review and comparison of the reverse cumulative distribution curves (RCDCs) embodying the overall antibody response distribution across the entire study population (all evaluated population).
- For the 6 additional serotypes, comparison of the proportion of responders at ≥0.35 μg/mL, GMCs, and OPA antibody titers to the actual responses elicited by 7vPnC against these serotypes.

The serologic assessments of vaccine immunogenicity were performed using sera collected 1 month after the infant series and, where available, after the toddler dose. In the pivotal phase 3 trials, the primary non-inferiority comparisons were made following the infant series. The serologic criteria used for comparison of 13vPnC to 7vPnC were derived from the WHO TRS 927 guidance (See section 4.2 below for description of methods).[42]

The primary serologic comparisons are based on assays of anticapsular polysaccharide binding IgG antibody that mediate protection against pneumococcal disease through bacterial opsonophagocytosis.

4.2 Determinants of primary criterion and supplementary analysis to establish non-inferiority of 13vPnC immune response to that of 7vPnC

4.2.1 Assay for capsular polysaccharide-binding antibodies

Capsular polysaccharide-binding IgG antibody concentrations are measured by a standardized ELISA that uses serotype-specific capsular polysaccharides as substrate. The assay is validated and is derived from the assay originally described by Quataert et al.[48] It is designed to measure binding IgG concentrations through the use of an established antibody standard following guidelines contained in the WHO TRS 927 document.[49] The assay specifically measures IgG antibodies, as this antibody isotype is known to mediate biologically relevant antibacterial opsonophagocytic activity.

The assay was originally designed to include a test serum preabsorption step with pneumococcal common capsular polysaccharide (C-PS) to remove nonspecific antibodies. In recent years, the WHO has recommended the addition of a second absorption step with capsular polysaccharide from serotype 22F, so as to further enhance the assay's specificity. (The 22F polysaccharide is not included in any of the pneumococcal conjugate vaccines that are currently available or are

undergoing development.) Given the need to compare the results from this modified assay to results using the original assay, Wyeth performed a study to assess the effect of the added 22F absorption step on the IgG concentration values originally established for sera in these older trials.[50] This study was carried out using sera from the original Prevnar efficacy trials, and both the original and modified assays were performed simultaneously in the same laboratory with the 22F second absorption step as the only change, so as to eliminate any uncontrolled variables.

The effect of the added 22F absorption was found to be modest on sera from immunized infants from all 3 populations that contributed to the pooled analysis that originally defined the antibody concentration level associated with protection. When recalculating this reference concentration using sera from the Prevnar NCKP trial immunogenicity subset, the analysis yielded a potential adjustment from 0.35 µg/mL to 0.32 µg/mL. However, given this small change, it was decided to maintain the level of 0.35 µg/mL as a primary endpoint comparator for the current trials of 13vPnC. Data from this 22F absorption study were also used to recalculate the IgG antibody concentration correlated with the 97% efficacy in the Prevnar NCKP efficacy trial.[50] This analysis yielded a value of 0.142 µg/mL compared with 0.20 µg/mL from the original assay. Hence, an antibody concentration of 0.15 µg/mL is considered an appropriate secondary comparator for populations with socioeconomic and epidemiologic features similar to those in the NCKP study.

4.2.1.1 Capsular binding antibodies for the 7 Common Serotypes

The proportion of subjects achieving an IgG ELISA concentration ≥0.35 µg/mL was calculated for each serotype and for each vaccine group. The difference in proportions (13vPnC-7vPnC) was then calculated, along with the corresponding 2-sided 95% CI. Non-inferiority for a given serotype was declared if the lower limit of the CI for the difference was numerically greater than -0.10 (i.e., -10% when converted to a percentage for display).

The IgG ELISA antibody geometric mean concentrations (GMCs) were determined for each serotype and for each vaccine group. Non-inferiority for a given serotype was declared if the lower limit of the 2-sided, 95% CI for the geometric mean ratio (GMR) (13vPnC relative to 7vPnC) was greater than 0.5 (i.e., no greater than 2-fold).

4.2.1.2 Capsular Binding Antibodies for the 6 Additional Serotypes

The proportion of subjects achieving an IgG ELISA antibody concentration ≥0.35 μg/mL was calculated for each serotype among 13vPnC recipients. These values were then compared with the lowest response among all of the common serotypes in the 7vPnC recipients. The difference in proportions was then estimated, along with the corresponding 2-sided 95% CI. Non-inferiority for a given serotype was declared if the lower limit of the CI for the difference was numerically greater than -0.10 (i.e., -10% when converted to a percentage for display).

The IgG ELISA antibody GMCs were determined for each serotype among the 13vPnC recipients. These values were then compared with the lowest response among all of the common serotypes in the 7vPnC recipients. Non-inferiority for a given serotype was declared if the lower limit of the 2-sided, 95% CI for the GMR (13vPnC relative to 7vPnC) was greater than 0.5 (i.e., no greater than 2-fold).

Supplementary analysis for the 6 additional serotypes included a comparison of the proportion of responders at ≥0.15 μg/mL, GMCs, and OPA antibody titers to the actual responses elicited by 7vPnC against these serotypes.

4.2.2 OPA assays

Functional activity data for each of the 13 serotypes, expressed as the proportion of study subjects with an opsonophagocytic titer ≥ 1:8 as well as the geometric mean of OPA titers (GMTs) 1 month after the infant series and after the toddler dose, are presented for a subset of study subjects.

Unlike the IgG ELISA, the OPA assays are not standardized to an external reference serum. The reported OPA titers can be compared for a given serotype but cannot be compared across serotypes. Therefore, the OPA response elicited by 13vPnC is assessed primarily by comparison with that elicited by 7vPnC, for each individual serotype. This comparison is particularly informative.

Although the OPA assays lack an external reference for standardization, the Wyeth assay was evaluated as part of an ongoing WHO-mediated effort to standardize the pneumococcal OPA assays. A WHO Workshop on Standardization of the Pneumococcal Opsonophagocytic Assay[51]

was convened in Geneva on 25-26 January, 2007 to review current progress in pneumococcal OPA development and to discuss the process of standardizing a reference OPA. Annex 2 of the WHO TRS No. 927, 2005 refers to the OPA method of Romero-Steiner *et al*, 1997[52,53] as the reference assay. Although the CDC assay was one of the earliest pneumococcal OPA methods described and used for pneumococcal serology, no reference or standard OPA has been formally designated by the WHO.

It was unclear to the participants of the WHO workshop whether the OPA described by Romero-Steiner *et al* [52, 53] (and used in a subsequent interlaboratory study[54]) was sufficiently standardized and validated to serve as a reference assay. There was also recognition that an advanced level of OPA development and validation had been already achieved by Glaxo SmithKline (GSK) and Wyeth as part of their pneumococcal conjugate vaccine development efforts. Therefore, a multiphase approach to assay standardization was proposed and agreed upon. Phase 1 of this standardization effort was a pilot interlaboratory study designed primarily to evaluate the level of agreement between the validated/qualified OPA of Wyeth, GSK and three additional laboratories, using a panel of shared specimens. Assuming some reasonable level of agreement between the GSK and Wyeth assays in the phase 1 comparison, phase 2 would be designed, if required, to evaluate critical assay parameters and components that would include: target strains and growth conditions, acceptance criteria for HL-60 effector cells, qualification of complement, and evaluation of a candidate reference serum. Phase 3 would then evaluate the matching of multiplex and non-killing opsonic assays.

Based on the outcome of these discussions at WHO in January 2007, Wyeth felt that the participation in phase 1 of the assay standardization was more important to demonstrate equivalence of OPA results to other laboratories including GSK, than as a direct comparison to only the CDC assays. It should be also noted that the Wyeth OPA assay format was based on the CDC assay protocol, and that the procedures are very similar. The results of this evaluation demonstrated that the Wyeth OPA assay yields results, as well as response patterns, that are comparable to the other evaluated assays. Given this comparability and the association between "positive" OPA responses and clinical efficacy for the common serotypes in 7vPnC (and partially for the cross-reactive type 6A), a similarly "positive" response in the Wyeth assay is considered to be clinically meaningful.

4.2.2.1 Definition of a clinically relevant OPA response

For the 7 common serotypes in 13vPnC and 7vPnC and for serotype 6A, the definition of a clinically relevant response was determined based on data and criteria presented in the report by Jodar et al. using the LLOQ of the OPA assay, and is consistent with WHO TRS 927 annex 2 recommendations.[46] That is, OPA titers ≥ 1:8 were determined to denote an effective clinical response for the 7vPnC serotypes, as this response correlated with 0.20ug/mL -0.35ug/mL IgG levels which in turn correlated with protective efficacy for the 7vPnC serotypes. The same definition is proposed for serotype 6A, given the nature of the functional OPA responses against this serotype elicited by 7vPnC and the known effectiveness of the 7-valent vaccine against type 6A-specific IPD.

For the remaining 5 additional serotypes in 13vPnC, OPA titers that are associated with serotype-specific efficacy have not been formally established. Hence, each serotype-specific OPA assay must be individually evaluated. OPA GMTs from the 7vPnC recipients, pooled across all studies with evaluable OPA data for these serotypes, are provided below (Table 4-1) to assess the distribution of plausible mean responses for the known non-efficacious vaccine (7vPnC).

Table 4-1: Postinfant Series OPA GMTs in 7vPnC Recipients – Additional Serotypes

		7vPnC		
Serotype	**Assay Type**	**N**	**GMT**	**95% CI**
1	OPA	215	4.3	(4.1, 4.6)
3	OPA	211	6.0	(5.3, 6.8)
5	OPA	194	4.5	(4.1, 4.9)
7F	OPA	207	90.1	(65.9, 123.0)
19A	OPA	200	6.6	(5.6, 7.9)

Note: Excluding serotype 6A.
Extracted from Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/Immunogenicity/Delivery 1.zip (modified)

Consistent with previous studies of 7vPnC efficacy, OPA titers ≥1:8 (the assay LLOQ) likely denote a functional antibody response for serotypes 1, 3, 5, and 19A that will be clinically meaningful, as the OPA GMTs for these types clearly fall below 8 (see the upper limit of the 95% confidence interval for the GMT in Table 4-1) in recipients of the non-effective (against these additional 4 serotypes) 7-valent vaccine.

However, for serotype 7F, the recipients of 7vPnC exhibit an OPA GMT that is significantly higher than the 1:8 titer assay LLOQ. This may be due to an extraordinary sensitivity of the type 7F assay compared to the assays used for the other serotypes. Potential explanations for this apparent increased sensitivity have been explored by Wyeth as described below.

Two serotype 7F strains (a Wyeth clinical isolate and the ATCC clinical isolate strain 10351) were available at the time the OPA assay was developed. A CDC strain was not available at that time. Both the Wyeth and ATCC serotype 7F strains have a medium size capsule but appear more sensitive to complement-mediated non-specific killing than other serotype strains. Since the ATCC strain exhibited less non-specific kill than the Wyeth strain, the ATCC strain was selected for use in the Wyeth serotype 7F OPA. We know that the non-specific killing is not caused by antibodies to other serotypes, as specificity analyses have shown excellent type-specificity for the serotype 7F OPA during assay validation.

In addition, antibody depleted sera (negative controls) show no activity against the serotype 7F strains, and these controls were used to determine the true assay LLOQ. Potential low level pre-existing IgG titers to serotype 7F are also not causing this effect, as the very sensitive 7F ELISA assay does not detect such activity. Maternal antibodies that could potentially explain the responses in the 7vPnC group after the postinfant series, cannot explain the posttoddler responses, as maternal antibodies will have waned by the toddler age. IgM antibodies generated after natural exposure to 7F are also not likely to be responsible for the OPA responses seen in the 7vPnC group. If IgM antibodies would be responsible, then one would expect an increased 7F OPA response rate posttoddler compared to postinfant vaccination, which is not observed. Wyeth believes that the serotype 7F strains used by Wyeth and other laboratories are more sensitive to non-specific killing, as exemplified by the reporting of high OPA titers for immune sera in the WHO interlaboratory study and the recently published results for a 10-valent pneumococcal conjugate vaccine (PD-CV).[55] Significant background responder rates were also seen in the control 7vPnC (7vCRM) arm in clinical trials assessing the PD-CV vaccine. The nature of this apparent background response in the serotype 7F OPA of Wyeth and other laboratories is not clear, but we know based on our 7vPnC experience that this response is not clinically significant. Therefore, an additional cut-off has been set based on the the 95th percentile of the observed individual responses in 7vPnC. The cut-off was determined to be a titer of 1:2048. This is a conservative measure of the upper limit of a known non-efficacious 7F OPA response. Comparison of the responses between the 13vPnC and the 7vPnC groups at this cut-off is shown below (Table 4-2).

Table 4-2: Summary of Subjects Achieving a Pneumococcal OPA Antibody Titer ≥95th Percentile in 7vPnC Group After the Infant Series – Evaluable Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7F	410	374	91.2	(88.1, 93.8)	207	19	9.2	(5.6, 14.0)	82.0	(76.6, 86.4)

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 ≥95th percentile in 7vPnC group for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC–7vPnC reference, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC–7vPnC reference, expressed as a percentage.
Program ID: Study 6096A1-ISE/CP IMM_PNC_OPA_RESP_POP.SAS. Runtime ID: 03APR2009 15:10
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/Europe Questions/MAR09/SWE Q37/SWE Q37.zip/imm_pnc_opa_resp_95per_evl_i_eu.htm(modified)

Based on the conservatively adjusted cut-off, it is clear that the inclusion of the serotype 7F immunogen in 13vPnC results in a significantly greater proportion of 13vPnC vaccinated subjects exceeding the anti-7F OPA response levels seen in 7vPnC vaccinated subjects. These analyses for OPA assays support a clinical cut-off (suggesting clinical efficacy based on our experience with Prevnar serotypes) of 1:8 as appropriate for the new serotypes 1, 3, 5, 6A, and 19A, and a more stringent clinical cut-off of 1:2048 for serotype 7F.

4.2.3 Induction of Immunologic Memory

The ability of a primary vaccination series with a protein-conjugated polysaccharide vaccine to elicit immunologic memory has been classically evaluated by the administration of a challenge dose of unconjugated purified polysaccharide vaccine (PS) given 6 to 12 months after the primary series. For example, vaccination with 2 or 3 infant doses of a Wyeth 9vPnC–meningococcal C vaccine primed effectively for an immunologic response after administration of PS, thereby supporting establishment of memory with as few as two doses of conjugate pneumococcal polysaccharide in infants.[56] Although the medical consequences are unknown, there are emerging data that indicate a potential risk of immunologic hyporesponsiveness after PS exposure. Given the existing data on successful priming after conjugate, limited value of additional PS data in guiding immunization strategy, the clear value of a toddler dose of 7vPnC as the current standard of care, and an interest in preserving durable immunologic responsiveness for infants, an evaluation of PS boosting was not conducted for 13vPnC. Instead, the ability of the 13vPnC antibody response to be boosted was evaluated for each serotype using geometric mean fold rise (GMFR) in antibody concentration following a toddler dose of 13vPnC.

5.0 OVERVIEW OF CLINICAL STUDIES

This application includes safety and immunogenicity data obtained from more than 4700 infants who received at least 1 dose of 13vPnC and from 354 older infants and young children. The safety and efficacy record of Prevnar is the basis for the clinical evaluation of 13vPnC for the immunization of infants, toddlers, and young children to prevent disease caused by serotypes of *S. pneumoniae* included in the vaccine. Therefore, in most clinical trials, 13vPnC was compared with 7vPnC. In general, the phase 3 trials in infants were designed to demonstrate that 13vPnC:

- Elicits immune responses that are non-inferior to those induced by 7vPnC for the 7 pneumococcal serotypes contained in 7vPnC (based on the set of criteria outlined in section 4.1.2)
- Elicits immune responses to the 6 additional pneumococcal serotypes 1, 3, 5, 6A, 7F, and 19A that are non-inferior to the lowest immune response induced by the 7 serotypes contained in 7vPnC (based on the set of criteria outlined in section 4.1.2)
- Elicits an increase in antibody levels, as a result of a toddler dose of 13vPnC, by comparing posttoddler dose levels with pretoddler dose levels

- Is compatible with routine childhood vaccines, including diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), hepatitis B, poliovirus, meningococcal type C, measles, mumps, rubella, varicella, hepatitis A, and rotavirus vaccines as contained in pediatric vaccines marketed in the United States, Canada, and the European Union
- Has an acceptable safety profile
- Can be manufactured using the intended commercial scale of production to yield vaccine preparations that consistently elicit the desired immune responses

The clinical program began with a phase 1 study in US adults, showing that 13vPnC is well tolerated and immunogenic when compared with 23-valent pneumococcal plain polysaccharide vaccine (23vPS). The safety data from this study supported proceeding with stage 1 of the phase 1/2 infant study (003) in a small number of healthy infants. Stage 1 of this phase 1/2 study showed that 13vPnC was well tolerated and immunogenic, allowing the study to proceed to stage 2, in which approximately 200 additional subjects were recruited. The data from this study supported a decision to proceed with phase 3 clinical trials. An overview of the clinical studies included in this BLA is presented in Table 5-1, along with a description of the purpose for each study. This review of clinical trials will focus on children who received 4 doses of vaccine in a 2-,4-,6-, 12- month ("3+1") regimen.

Table 5-1: Overview of 13vPnC Clinical Studies

Study	Country	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
Pivotal Pneumococcal Non-inferiority Trials					
6096A1-004	United States	Demonstrate that the PnC serotype-specific IgG responses (proportion of responders at ≥0.35 µg/mL) induced by 13vPnC are non-inferior to those induced by 7vPnC or 7vPnC reference[a] measured 1 month after the infant series. Demonstrate that the serotype-specific geometric mean IgG concentrations induced by 13vPnC are non-inferior to those induced by 7vPnC or 7vPnC reference[a] measured 1 month after the toddler dose. Assess the non-inferiority of antigen-specific response (Dip, PT, FHA, PRN, Hib) 1 month after dose 3 of PnC and concomitant vaccine in the 13vPnC group relative to the 7vPnC group.	13vPnC or 7vPnC (2, 4, 6, 12-15)	Pediarix (2, 4, 6) ActHIB (2, 4, 6) PedvaxHIB (12-15) ProQuad (12-15) VAQTA (12-15)	13vPnC: 332 7vPnC: 331
6096A1-006	Germany	Demonstrate that the PnC serotype-specific IgG responses induced by 13vPnC are non-inferior to those induced by 7vPnC or 7vPnC reference[a] measured 1 month after the infant series. Assess the non-inferiority of antigen-specific response (Dip, HBV, Hib) 1 month after dose 3 of PnC and concomitant vaccine in the 13vPnC group relative to the 7vPnC group.	13vPnC or 7vPnC (2, 3, 4, 11-12)	Infanrix hexa (2, 3, 4, 11-12)	13vPnC: 300 7vPnC: 303

Table 5-1: Overview of 13vPnC Clinical Studies

Study	Country	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
Formulation Bridging Trial					
6096A1-009	Poland	Demonstrate that the immune response to 13 serotypes after administration of 13vPnC+P80 is non-inferior relative to 13vPnC-P80 measured 1 month after the infant series.	13vPnC+P80 or 13vPnC-P80 (2, 3, 4, 12)	Pentaxim (2, 3, 4) Engerix-B (2) Priorix (12)	13vPnC+P80: 250 13vPnC-P80: 250
Manufacturing Scale Bridging Trials					
6096A1-3000	Poland	Assess the PnC response induced by manufacturing (man) scale 13vPnC relative to pilot scale 13vPnC measured 1 month after the infant series. (Immunogenicity was not assessed for the toddler dose.)	13vPnC pilot lot or 13vPnC man lot (2, 3, 4, 12)	Pentaxim (2, 3, 4) Engerix-B (2) Priorix (12)	13vPnC pilot: 134 13vPnC man: 134
6096A1-3005	United States	Demonstrate that the immune responses induced by 3 lots of 13vPnC are equivalent at 1 month after the infant series. Demonstrate the non-inferiority of immune response induced by Pediarix given with 13vPnC relative to Pediarix given with 7vPnC 1 month after the infant series (antigens assessed: Tet; poliovirus types 1, 2, 3; HBV).	13vPnC pilot lot 1, 13vPnC pilot lot 2, or 13vPnC man lot or 7vPnC (2, 4, 6, 12)	Pediarix (2, 4, 6) ActHIB (2, 4, 6) MMR II and Varivax (12) Havrix (12)	13vPnC pilot 1: 486 13vPnC pilot 2: 484 13vPnC man: 485 7vPnC: 244

Table 5-1: Overview of 13vPnC Clinical Studies

Study	Country	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
Additional Vaccine Schedules and Concomitant Vaccine Immunogenicity Trials					
6096A1-007	United Kingdom	Evaluate the immune response after NeisVac-C (MnC using SBA) and 13vPnC relative to NeisVac-C and 7vPnC measured 1 month after the infant series. Evaluate the immune response after Pediacel (antigens assessed: PT, FHA, PRN, FIM, Hib) and 13vPnC relative to Pediacel and 7vPnC measured 1 month after the infant series. PnC objectives: Assess the immune response (IgG) to 13vPnC measured 1 month after the infant series and before and 1 month after the toddler dose.	13vPnC or 7vPnC (2, 4, 12)	NeisVac-C (2, 4) Pediacel (2, 3, 4) Menitorix (12)	13vPnC: 139 7vPnC: 139

Table 5-1: Overview of 13vPnC Clinical Studies

Study	Country	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
6096A1-008	France	Demonstrate that the immune responses after Pentavac (antigens assessed: PT, FHA, Hib, Dip, Tet, poliovirus types 1, 2, 3) and 13vPnC are non-inferior to the response after Pentavac and 7vPnC measured 1 month after the infant series. PnC objectives: Assess immune responses to 13vPnC measured 1 month after the infant series. Assess PnC responses, 1 month after the toddler dose, to the following (infant series/toddler dose) sequences: 13vPnC/13vPnC and 7vPnC/13vPnC relative to 7vPnC/7vPnC. Posttoddler dose pneumococcal responses induced by 13vPnC/13vPnC relative to 7vPnC/13vPnC were also assessed.	13vPnC or 7vPnC (2, 3, 4, 12)	Pentavac (2, 3, 4, 12)	13vPnC: 302 7vPnC: 309
6096A1-011	India	Assess the immune response after Easyfive, i.e., DTP-Hib-HBV vaccine (antigens assessed: PT, FHA, PRN) and 13vPnC relative to DTP-Hib-HBV and 7vPnC measured 1 month after the infant series. PnC objective: Assess the PnC immune response after 13vPnC relative to 7vPnC measured 1 month after the infant series.	13vPnC or 7vPnC (6, 10, 14 weeks, 12 months)	Easyfive (6, 10, 14 weeks) Biopolio (6, 10, 14 weeks)	13vPnC: 178 7vPnC: 175

Table 5-1: Overview of 13vPnC Clinical Studies

Study	Country	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
6096A1-500	Italy	Demonstrate that the immune response after Infanrix hexa (antigen assessed: HBV) and 13vPnC is non-inferior to the response after Infanrix hexa and 7vPnC measured 1 month after the toddler dose. PnC objectives: Assess the immune response to 13vPnC measured 1 month after the infant series and just before the toddler dose. Assess the immune responses induced by 13vPnC relative to 7vPnC measured 1 month after the toddler dose.	13vPnC or 7vPnC (3, 5, 11)	Infanrix hexa (3, 5, 11)	13vPnC: 302 7vPnC: 302
6096A1-501	Spain	Demonstrate that the immune response after Meningitec (antigen assessed: MnC by SBA) and 13vPnC is non-inferior to response after Meningitec and 7vPnC measured 1 month after a 2-dose Meningitec infant series. Assess the non-inferiority of antigen-specific response to PT, FHA, PRN, Dip, Tet, and poliovirus types 1, 2, 3 after Infanrix hexa and 13vPnC relative to Infanrix hexa and 7vPnC. PnC objectives: Assess the immune responses to 13vPnC measured 1 month after dose 2 and 1 month after dose 3 of the infant series and 1 month after the toddler dose.	13vPnC or 7vPnC (2, 4, 6, 15)	Infanrix hexa (2, 4, 6) Meningitec (2, 4, 15) Infanrix-IPV+Hib (15) MMR II (12)	13vPnC: 314 7vPnC: 302

Table 5-1: Overview of 13vPnC Clinical Studies

Study	Country	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
6096A1-3007	Spain	Demonstrate the non-inferiority of immune response after NeisVac-C and 13vPnC relative to NeisVac-C (antigen assessed: MnC using SBA) and 7vPnC measured 1 month after a 2-dose NeisVac-C infant series. Demonstrate the non-inferiority of immune response after Infanrix hexa (antigens assessed: Dip, Tet) and 13vPnC relative to Infanrix hexa and 7vPnC measured 1 month after a 3-dose infant series. PnC objectives: Assess the immune responses to 13vPnC measured 1 month after dose 2 and 1 month after dose 3 of the infant series.	13vPnC or 7vPnC (2, 4, 6, 15)	Infanrix hexa (2, 4, 6) NeisVac-C (2, 4, 15) Priorix (12) Infanrix-IPV+Hib (15)	13vPnC: 218 7vPnC: 226
6096A1-3008	Canada	Demonstrate non-inferiority of immune responses induced by NeisVac-C (antigen assessed: MnC using SBA) given with 13vPnC relative to responses induced by NeisVac-C given with 7vPnC when measured 1 month after dose 2 of the NeisVac-C infant series. Demonstrate non-inferiority of immune responses induced by Pentacel (antigens assessed: Hib, PT, FHA, PRN, FIM) given with 13vPnC relative to responses induced by Pentacel given with 7vPnC measured 1 month after the 3-dose infant series. PnC objective: Assess immune response (IgG) to 13vPnC measured 1 month	13vPnC or 7vPnC (2, 4, 6, 12)	NeisVac-C (2, 6, 12) Pentacel (2, 4, 6) MMR II (12) Varicella (12)	13vPnC: 300 7vPnC: 303

Table 5-1: Overview of 13vPnC Clinical Studies

Study	Country	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
		after the 3-dose infant series.			
Trial in Older Infants and Young Children					
6096A1-3002	Poland	Assess the PnC response induced by 13vPnC when measured 1 month after the last scheduled dose in each age group.	13vPnC: Group 1: (3 doses) 7 to <12 months, 1 month later, and 12-16 months Group 2: (2 doses) 12 to <24 months and 56 to 70 days later Group 3: (1 dose) 24 to <72 months	NA	Group 1: 90 Group 2: 112 Group 3: 152
Phase 1-2 Trials					
6096A1-002	United States	(NOTE: Immunogenicity was a secondary objective in this study.) Assess the postvaccination responses to the 13 pneumococcal serotypes in 13vPnC. Obtain sera to be used as reagents for further development, validation, and standardization of pneumococcal assays.	Single dose of 13vPnC or 23vPS	NA	23vPS: 15 13vPnC: 15
6096A1-003	United States	Compare the percentages of subjects achieving a predefined antibody level to each of the 7 common serotypes after 3 doses of 13vPnC relative to 3 doses of 7vPnC.	13vPnC or 7vPnC (2, 4, 6, 12-15)	Pediarix (2, 4, 6) ActHIB (2, 4, 6, 12-15)	13vPnC: 121 7vPnC: 126

Table 5-1: Overview of 13vPnC Clinical Studies

Study	Country	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)

Abbreviations: 13vPnC+P80 = 13vPnC formulated with polysorbate 80; 13vPnC-P80 = 13vPnC formulated without polysorbate 80; 23vPS = 23-valent pneumococcal polysaccharide vaccine; Dip = diphtheria; FHA = filamentous hemagglutinin; FIM = fimbrial agglutinogens; HBV = hepatitis B virus vaccine; Hib = Haemophilus influenzae type b; man = manufacturing; MnC = meningococcal C; NA = not applicable; OPV = oral poliovirus vaccine; PnC = pneumococcal conjugate vaccine; PRN = pertactin; PT = pertussis toxoid; SBA = serum bactericidal assay; Tet = tetanus.

Components of vaccines by trade name: ActHIB = Hib; Biopolio = OPV; Easyfive = DTP (whole cell pertussis), Hib, and HBV; Engerix-B = HBV; Havrix = HAV; Infanrix hexa = DTaP, Hib, HBV, and IPV; Infanrix-IPV+Hib = DTaP, IPV, and Hib; Meningitec = meningococcal C vaccine; Menitorix = Hib and meningococcal C vaccine; MMR II = measles, mumps, and rubella vaccine; NeisVac-C = meningococcal C vaccine; Pediacel = DTaP, Hib, and IPV; Pediarix = DTaP, HBV, and IPV; PedvaxHIB = Hib; Pentavac = DTaP, Hib, and IPV; Pentaxim = DTaP, Hib, and IPV; Priorix = MMR; ProQuad = MMR and varicella vaccine; VAQTA = HAV; Varivax = varicella vaccine.

a. In studies 004 and 006, values for the additional serotypes in the 13vPnC group are compared with the 7vPnC reference value, defined as the lowest value among the 7 common serotypes in the 7vPnC group.

Adapted from: ID: 20 Jan 2009.

5.1 Non-inferiority Trials for Pneumococcal Conjugated Antigens

The 13vPnC phase 3 clinical program includes 2 non-inferiority trials (study 004 in US infants and study 006 in German infants). The 004 trial, designed as the pivotal non-inferiority trial to support licensure of 13vPnC in the U.S., conforms to a 2, 4, 6, 12-15 month U.S. vaccination schedule, and includes concomitant vaccines licensed and recommended in the U.S. Study 006 is a pivotal trial for European, but not U.S. licensure. The 006 study is not intended to satisfy non-inferiority evaluation for U.S. licensure as it conforms to a 2, 3, 4, 12 month regime and includes a concomitant vaccine not licensed in the US (Infanrix hexa). However, in study 006, the age at which the 3 dose primary series is administered in infants and the short intervals between doses permits a particularly stringent assessment of comparative immune response. Both studies were double-blind, controlled, randomized trials, which thereby permitted direct comparison of the immunogenicity of 13vPnC with that of 7vPnC. The trials, involving approximately 300 infants per group, were powered to demonstrate the non-inferiority of the pneumococcal IgG antibody responses elicited by 13vPnC when compared with those elicited by 7vPnC.

A primary criterion for non-inferiority for each of the 7 serotypes common to both vaccines (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) is the comparison of the proportion of infants demonstrating an IgG ELISA concentration ≥0.35 μg/mL measured 1 month after the infant series.

Immune responses to the additional serotypes contained in 13vPnC (serotypes 1, 3, 5, 6A, 7F, and 19A) were evaluated by comparing the proportion of responders at an IgG ELISA concentration ≥0.35 μg/mL with the lowest response value exhibited by any of the common serotypes among the 7vPnC recipients. This approach was proposed because Prevnar is highly effective against all of the common serotypes, and therefore, one may extrapolate that all of the additional serotypes should be at least as immunogenic as the least immunogenic of the common serotypes. However, this provides an incomplete picture of the potential benefit imparted by 13vPnC with regard to the additional serotypes. Therefore, the responses elicited by 13vPnC to the additional serotypes were also evaluated with respect to the actual responses (if any) elicited to these serotypes by 7vPnC. This latter assessment provides further information related to the likely benefit conferred by the 6 additional serotypes and is formally included among the additional criteria for evaluation.

The pivotal trials were designed to have an overall 90% power to demonstrate non-inferiority using the proportion of responders at IgG concentrations ≥0.35 µg/mL. This was based on sample size calculations assuming a minimum reference response level for each serotype. However, understanding that the responses can be variable, thereby resulting in an unintended lower statistical power for a given serotype, a series of additional predefined criteria (described in section 4.1.2) were established to permit a broader basis for comparison between the 2 vaccines. These criteria are consistent with the recommendation from WHO TRS document 927, Annex 2.[42] The first of these, for the 7 common serotypes, involved comparison of the geometric mean IgG ELISA antibody concentrations (GMCs). For each of the additional 6 serotypes, the IgG GMCs would be similarly compared with the lowest GMC response among the 7 common serotypes. The GMC comparisons after the toddler dose were co-primary endpoints for the 004 U.S. study and GMC comparisons were secondary endpoints for the 004 study after the primary series and the 006 German study after the primary series and the toddler dose. Additional criteria included the following assessments: relative margin of failure for percent responders at the 0.35ug/mL endpoint (e.g., -11% non-inferiority is of less concern than -50%), non-inferiority using the IgG ELISA threshold of 0.15 µg/mL, elicitation of specific OPA antibody, immune responses following the toddler dose, review and comparison of the reverse cumulative distribution curves (RCDCs) embodying the overall antibody response distribution across the entire study population (all evaluated population), for the 6 additional serotypes, comparison of the proportion of responders at ≥0.35 µg/mL, GMCs, and OPA antibody titers to the actual responses elicited by 7vPnC against these serotypes, providing a more comprehensive assessment of potential benefit.

5.1.1 US Pivotal Non-inferiority Study 6096A1-004

This section discusses overall comparative results within study 004 between 13vPnC and 7vPnC across all serotypes. However, given that the nature of the responses to each serotype is unique, it is appropriate to consider the responses to each serotype individually across all of the phase 3 trials. These individual serotype discussions are presented in section 5.3. In study 004, vaccinations were given at 2, 4, 6, and 12 to 15 months of age. Either 13vPnC or 7vPnC was injected into the anterolateral muscle of the left thigh, and the other routine vaccines (Pediarix and ActHIB) were concomitantly injected into the anterolateral muscle of the right thigh during the infant series.

5.1.1.1 Immune Responses Following the Infant Series

At the primary endpoint, the proportion of responders with an antibody concentration ≥0.35 µg/mL 1 month after dose 3, the non-inferiority criterion was met for 10 of the 13 serotypes (Table 5-2 and Table 5-3). The exceptions included the common serotypes 6B and 9V, and the additional serotype 3. For serotypes 6B and 9V, the differences at the lower bound of the 95% CI were not substantial. The difference for serotype 3 was much greater, but this was in comparison with the lowest response among the common serotypes in the 7vPnC recipients; when compared with the serotype 3 response directly elicited by 7vPnC, 13vPnC exhibited an approximately 10-fold greater number of serotype 3 responders (Table 5-4).

Twelve (12) of the 13 serotypes, including all 7 of the common serotypes, met the GMC ratio non-inferiority criterion when comparing the IgG ELISA GMCs between the 2 vaccine groups (Table 5-2 and Table 5-3). The only exception was serotype 3 and, again, this was due to comparison with the lowest GMC among the common serotypes in the 7vPnC recipients; 13vPnC elicited an IgG GMC value for serotype 3 that was 10-fold greater than that elicited directly by 7vPnC (Table 5-4).

The non-inferiority criterion was met for all 13 serotypes when the proportion of responders at the antibody concentration of 0.15 µg/mL was compared (Table 5-2 and Table 5-3).

There were no differences in the proportion of infants exhibiting a functional OPA titer ≥1:8 for the 7 common serotypes, with response rates of at least 90.4% and 92.6% in the 13vPnC and 7vPnC groups, respectively. Ratios of OPA GMTs (13vPnC/7vPnC) ranged from 0.67 to 1.24. Importantly, the proportion of subjects with OPA titers ≥ 1:8 linked with protective efficacy for serotypes 6B and 9V were 98.9% and 100% respectively, and the 95% CI demonstrated nearly complete overlap with 7vPnC responses.

For the 6 additional serotypes, much higher 13vPnC/7vPnC ratios of OPA GMTs were noted, ranging from 9.76 to 74.17 (Table 5-2 and Table 5-3). Notably, the proportion of subjects with OPA responses ≥ 1:8 to serotype 3 was 96.8% in the 13vPnC group compared to 21.3 in the 7vPnC group and corresponding OPA GMTs were 120.67 compared to 6.70. Hence despite the failure of serotype 3 to meet the IgG non-inferiority criteria when compared to the lowest response among the common serotypes in the 7vPnC recipients, there is ample functional antibody response that is likely to be associated with protection.

5.1.1.2 Immune Responses Following the Toddler Dose

At 1 month after the toddler dose, all non-inferiority criteria were met for 12 of the 13 serotypes (Table 5-5 and Table 5-6). The only exception was serotype 3 and, again, this was due to the nature of the comparison with the lowest responses seen among the common serotypes in the 7vPnC group. However, direct comparison with the serotype 3 responses in the latter showed that 13vPnC elicited a notably greater response to this serotype, both in terms of IgG ELISA antibodies and functional OPA antibodies (Table 5-7). 97.8% of children demonstrated OPA responses ≥ 1:8 after 13vPnC compared to 43.8%, and OPA titers were over 30 times greater (380.41 vs. 11.81), consistent with a high degree of protection likely to be afforded by 13vPnC that is not present after 7vPnC.

Table 5-2: Postinfant Series Immunogenicity Data for Study 6096A1-004 – Common Serotypes – Evaluable Infant Immunogenicity Population

Test	Vaccine Group	4	95% CI	6B	95% CI	9V	95% CI	14	95% CI	18C	95% CI	19F	95% CI	23F	95% CI
% Resp ≥0.35 µg/mL	13v	94.4	90.9, 96.9	87.3	82.5, 91.1	90.5	86.2, 93.8	97.6	94.9, 99.1	96.8	93.8, 98.6	98.0	95.4, 99.4	90.5	86.2, 93.8
	7v	*98.0*	*95.4, 99.4*	*92.8*	*88.9, 95.7*	*98.4*	*96.0, 99.6*	*97.2*	*94.4, 98.9*	*98.4*	*96.0, 99.6*	*97.6*	*94.9, 99.1*	*94.0*	*90.4, 96.6*
	Diff[a]	-3.6	-7.3, -0.1	-5.5	-10.9, -0.1	-7.9	-12.4, -4	0.4	-2.7, 3.5	-1.6	-4.7, 1.2	0.4	-2.4, 3.4	-3.6	-8.5, 1.2
% Resp ≥0.15 µg/mL	13v	99.2	97.2, 99.9	94.0	90.4, 96.6	99.2	97.2, 99.9	98.8	96.5, 99.8	99.2	97.2, 99.9	100.0	98.5, 100.0	97.2	94.4, 98.9
	7v	*99.6*	*97.8, 100.0*	*97.6*	*94.8, 99.1*	*99.6*	*97.8, 100.0*	*99.6*	*97.8, 100.0*	*100.0*	*98.5, 100.0*	*98.4*	*96.0, 99.6*	*99.2*	*97.2, 99.9*
	Diff[a]	-0.4	-2.5, 1.5	-3.6	-7.4, 0.0	-0.4	-2.5, 1.5	-0.8	-3.1, 1.1	-0.8	-2.8, 0.7	1.6	0.0, 4.0	-2.0	-4.9, 0.4
GMC µg/mL	13v	1.31	1.19, 1.45	2.10	1.77, 2.49	0.98	0.89, 1.08	4.74	4.18, 5.39	1.37	1.24, 1.52	1.85	1.69, 2.04	1.33	1.17, 1.51
	7v	*1.93*	*1.75, 2.13*	*3.14*	*2.64, 3.74*	*1.40*	*1.27, 1.55*	*5.67*	*5.02, 6.40*	*1.79*	*1.63, 1.96*	*2.24*	*2.01, 2.50*	*1.90*	*1.68, 2.15*
	Ratio[b]	0.68	0.59, 0.78	0.67	0.52, 0.85	0.70	0.61, 0.80	0.84	0.70, 1.00	0.77	0.67, 0.88	0.83	0.72, 0.96	0.70	0.59, 0.84
OPA GMT[c]	13v	359.32	276.04, 467.72	1054.65	817.34, 1360.87	4035.40	2932.68, 5552.75	1240.41	934.93, 1645.69	275.59	210.33, 361.10	54.42	40.20, 73.65	791.07	604.96, 1034.44
	7v	*535.68*	*421.13, 681.37*	*1513.66*	*1206.64, 1898.81*	*3259.01*	*2288.43, 4641.25*	*1480.55*	*1133.40, 1934.02*	*375.64*	*291.68, 483.75*	*44.92*	*33.90, 59.52*	*923.56*	*708.59, 1203.74*
	Ratio[b]	0.67	0.47, 0.96	0.70	0.50, 0.98	1.24	0.77, 1.99	0.84	0.57, 1.23	0.73	0.51, 1.06	1.21	0.80, 1.83	0.86	0.59, 1.25
OPA Titer[c] ≥1:8	13v	97.8	92.4, 99.7	98.9	94.2, 100.0	100.0	96.1, 100.0	100.0	96.2, 100.0	100.0	96.2, 100.0	90.4	82.6, 95.5	98.9	94.2, 100.0
	7v	*98.9*	*94.1, 100.0*	*100.0*	*96.2, 100.0*	*98.9*	*94.2, 100.0*	*100.0*	*96.2, 100.0*	*100.0*	*96.2, 100.0*	*92.6*	*85.3, 97.0*	*98.9*	*94.2, 100.0*

Note: N, or the number of subjects with evaluable and determinate IgG antibody concentrations, ranged from 250 to 252 for the common serotypes. The number of subjects with determinate antibody titers (OPA) ranged from 92 to 94 for the common serotypes.

Abbreviations: 7v = 7vPnC; 13v = 13vPnC; CI = confidence interval; Diff = difference; GMC = geometric mean concentration; GMT = geometric mean titer; OPA = opsonophagocytic activity (assay); Resp = responders.

a. Difference in proportions, 13vPnC – 7vPnC, and exact 2-sided CIs for the difference are expressed as percentages.

b. Ratio of GMCs or GMTs: 13vPnC to 7vPnC. 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 – 7vPnC).

c. The OPA titer is defined as the reciprocal of the serum dilution with at least 50% killing of the bacteria, when compared with the average bacterial count in the HL60 control wells.

ID: 6 Oct 2008.

Table 5-3: Postinfant Series Immunogenicity Data for Study 6096A1-004 – Additional Serotypes – Evaluable Infant Immunogenicity Population

Test	Vaccine Group	1	95% CI	3	95% CI	5	95% CI	6A	95% CI	7F	95% CI	19A	95% CI
% Resp[a] ≥0.35 µg/mL	13v	95.6	92.3, 97.8	63.5	57.1, 69.4	89.7	85.2, 93.1	96.0	92.8, 98.1	98.4	96.0, 99.6	98.4	96.0, 99.6
	7v	*92.8*	*88.9, 95.7*	*92.8*	*88.9, 95.7*	*92.8*	*88.9, 95.7*	*92.8*	*88.9, 95.7*	*92.8*	*88.9, 95.7*	*92.8*	*88.9, 95.7*
	Diff[b]	2.8	-1.3, 7.2	-29.3	-36.2, -22.4	-3.1	-8.3, 1.9	3.2	-0.8, 7.6	5.6	1.9, 9.7	5.6	1.9, 9.7
% Resp[a] ≥0.15 µg/mL	13v	98.8	96.6, 99.8	92.4	88.3, 95.3	98.4	96.0, 99.6	98.4	96.0, 99.6	98.8	96.6, 99.8	100.0	98.5, 100.0
	7v	*97.6*	*94.8, 99.1*	*97.6*	*94.8, 99.1*	*97.6*	*94.8, 99.1*	*97.6*	*94.8, 99.1*	*97.6*	*94.8, 99.1*	*97.6*	*94.8, 99.1*
	Diff[b]	1.2	-1.4, 4.1	-5.2	-9.5, -1.3	0.8	-1.9, 3.7	0.8	-1.9, 3.7	1.2	-1.4, 4.1	2.4	0.7, 5.2
IgG GMC[a] µg/mL	13v	2.03	1.78, 2.32	0.49	0.43, 0.55	1.33	1.18, 1.50	2.19	1.93, 2.48	2.57	2.28, 2.89	2.07	1.87, 2.30
	7v	*1.40*	*1.27, 1.55*	*1.40*	*1.27, 1.55*	*1.40*	*1.27, 1.55*	*1.40*	*1.27, 1.55*	*1.40*	*1.27, 1.55*	*1.40*	*1.27, 1.55*
	Ratio[c]	1.45	1.23, 1.71	0.35	0.30, 0.41	0.95	0.81, 1.11	1.56	1.33, 1.83	1.83	1.57, 2.13	1.48	1.28, 1.71
OPA GMT[a,d]	13v	51.83	38.84, 69.16	120.67	92.38, 157.62	90.86	67.10, 123.02	979.68	783.04, 1225.71	9493.77	7339.13, 12280.98	151.94	105.16, 219.52
	7v	*4.41*	*4.06, 4.80*	*6.70*	*5.27, 8.52*	*4.15*	*3.94, 4.38*	*100.35*	*66.22, 152.08*	*128.00*	*79.55, 205.97*	*6.53*	*5.01, 8.50*
	Ratio[c]	11.75	8.72, 15.83	18.00	12.60, 25.72	21.88	16.17, 29.61	9.76	6.11, 15.61	74.17	43.68, 125.93	23.28	14.83, 36.52
OPA Titer[a,d] ≥1:8	13v	98.9	94.1, 100.0	96.8	91.0, 99.3	92.3	84.8, 96.9	100.0	96.2, 100.0	100.0	96.2, 100.0	91.4	83.8, 96.2
	7v	*9.8*	*4.6, 17.8*	*21.3*	*13.5, 30.9*	*2.2*	*0.3, 7.6*	*77.7*	*67.9, 85.6*	*76.4*	*66.2, 84.8*	*16.3*	*9.4, 25.5*

Note: N, or the number of subjects with evaluable and determinate IgG antibody concentrations, ranged from 197 to 252 for the additional serotypes. The number of subjects with determinate antibody titers (OPA) ranged from 89 to 94 for the additional serotypes.

Abbreviations: 7v = 7vPnC; 13v = 13vPnC; CI = confidence interval; Diff = difference; GMC = geometric mean concentration; GMT = geometric mean titer; OPA = opsonophagocytic activity (assay); Resp = responders.

a. For percentage of responders at ≥0.35 µg/mL and at ≥0.15 µg/mL and for IgG GMCs, the comparator for the additional serotypes is 7vPnC reference, i.e., the lowest proportion of responders among the 7 common serotypes in the 7vPnC group. For the OPA assay results, the 7vPnC comparator for the additional serotypes is the actual value for each serotype elicited by the vaccine (7vPnC).

b. Difference in proportions, 13vPnC – 7vPnC reference, expressed as a percentage. The exact 2-sided CI is for the difference in proportions.

c. Ratio of GMCs (13vPnC to 7vPnC reference) or of GMTs (13vPnC to 7vPnC). 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 – 7vPnC reference).

d. The OPA titer is defined as the reciprocal of the serum dilution with at least 50% killing of the bacteria, when compared with the average bacterial count in the HL60 control wells.

ID: 6 Oct 2008

Table 5-4: Antibody Response to Pneumococcal Serotype 3 After the Infant Series – Evaluable Infant Immunogenicity Population

Study	Vaccine Group	ELISA Results N[a]	ELISA Results % Responders[b] at ≥0.35 µg/mL (95% CI)	ELISA Results IgG GMC (µg/mL) (95% CI)	ELISA Results % Responders[b] at ≥0.15 µg/mL (95% CI)	OPA Assay Results N[a]	OPA Assay Results OPA GMT[c] (95% CI)	OPA Assay Results % Responders[b] at ≥1:8 Titer[c] (95% CI)
2, 4, 6 months								
6096A1-004	13vPnC	249	63.5 (57.1, 69.4)	0.49 (0.43, 0.55)	92.4 (88.3, 95.3)	94	120.67 (92.38, 157.62)	96.8 (91.0, 99.3)
	7vPnC	*241*	*4.6 (2.3, 8.0)*	*0.04 (0.03, 0.04)*	*7.9 (4.8, 12.0)*	*94*	*6.70 (5.27, 8.52)*	*21.3 (13.5, 30.9)*

Extracted from 2.7.3 SCE-US, Table 3-49

a. Number of subjects with determinate antibody concentration or titer to the given serotype and denominator for percentages.
b. Percentage achieving the prespecified pneumococcal concentrations or titers.
c. The OPA titer is defined as the reciprocal of the serum dilution with at least 50% killing of the bacteria, when compared with the average bacterial count in the HL60 control wells.

Table 5-5: Posttoddler Dose Immunogenicity Data for Study 6096A1-004 – Common Serotypes – Evaluable Toddler Immunogenicity Population

Test	Vaccine Group	4	95% CI	6B	95% CI	9V	95% CI	14	95% CI	18C	95% CI	19F	95% CI	23F	95% CI
% Resp ≥0.35 µg/mL	13v	99.1	97.0, 99.9	99.6	97.6, 100.0	99.1	96.9, 99.9	98.7	96.3, 99.7	98.7	96.3, 99.7	100.0	98.4,100.0	99.6	97.6, 100.0
	7v	*100.0*	*98.4, 100.0*	*100.0*	*98.4, 100.0*	*99.6*	*97.5, 100.0*	*99.1*	*96.8, 99.9*	*100.0*	*98.4, 100.0*	*98.7*	*96.1, 99.7*	*100.0*	*98.4, 100.0*
	Diff[a]	-0.9	-3.1, 0.8	-0.4	-2.4, 1.3	-0.4	-2.6, 1.7	-0.4	-2.9, 2.1	-1.3	-3.7, 0.4	1.3	-0.3, 3.9	-0.4	-2.4, 1.3
% Resp ≥0.15 µg/mL	13v	100.0	98.4, 100.0	100.0	98.4, 100.0	100.0	98.4, 100.0	100.0	98.4, 100.0	99.6	97.7, 100.0	100.0	98.4, 100.0	100.0	98.4, 100.0
	7v	*100.0*	*98.4, 100.0*	*100.0*	*98.4, 100.0*	*100.0*	*98.4, 100.0*	*100.0*	*98.4, 100.0*	*100.0*	*98.4, 100.0*	*99.1*	*96.8, 99.9*	*100.0*	*98.4, 100.0*
	Diff[a]	0.0	-1.6, 1.7	0.0	-1.6, 1.7	0.0	-1.6, 1.7	0.0	-1.6, 1.7	-0.4	-2.3, 1.2	0.9	-0.7, 3.2	0.0	-1.6, 1.7
GMC µg/mL	13v	3.73	3.28, 4.24	11.53	9.99, 13.30	2.62	2.34, 2.94	9.11	7.95, 10.45	3.20	2.82, 3.64	6.60	5.85, 7.44	5.07	4.41, 5.83
	7v	*5.49*	*4.91, 6.13*	*15.63*	*13.80, 17.69*	*3.63*	*3.25, 4.05*	*12.72*	*11.22, 14.41*	*4.70*	*4.18, 5.28*	*5.60*	*4.87, 6.43*	*7.84*	*6.91, 8.90*
	Ratio[b]	0.68	0.57, 0.80	0.74	0.61, 0.89	0.72	0.62, 0.85	0.72	0.60, 0.86	0.68	0.57, 0.81	1.18	0.98, 1.41	0.65	0.54, 0.78
OPA GMT[c]	13v	1179.98	847.34, 1643.20	3099.51	2337.02, 4110.79	11856.03	8809.85, 15955.49	2002.23	1452.54, 2759.93	993.27	754.08, 1308.33	199.65	144.22, 276.38	2723.25	1960.67, 3782.41
	7v	*1492.46*	*1114.40, 1998.78*	*4066.22*	*3243.42, 5097.76*	*18032.33*	*14124.99, 23020.53*	*2365.87*	*1870.56, 2992.34*	*1722.16*	*1326.59, 2235.67*	*167.20*	*121.35, 230.37*	*4981.68*	*3885.71, 6386.76*
	Ratio[b]	0.79	0.51, 1.22	0.76	0.53, 1.09	0.66	0.45, 0.96	0.85	0.57, 1.25	0.58	0.40, 0.84	1.19	0.76, 1.88	0.55	0.36, 0.82
OPA Titer[c] ≥1:8	13v	98.9	93.8, 100.0	98.9	94.1, 100.0	98.9	94.0, 100.0	100.0	96.1, 100.0	98.9	94.0, 100.0	96.7	90.8, 99.3	98.9	94.0, 100.0
	7v	*98.9*	*94.1, 100.0*	*100.0*	*96.2, 100.0*	*100.0*	*96.2, 100.0*	*100.0*	*96.2, 100.0*	*100.0*	*96.2, 100.0*	*94.8*	*88.3, 98.3*	*100.0*	*96.1, 100.0*

Note: N, or the number of subjects with evaluable and determinate IgG antibody concentrations, ranged from 220 to 236 for the common serotypes. The number of subjects with determinate antibody titers (OPA) ranged from 88 to 96 for the common serotypes.

Abbreviations: 7v = 7vPnC; 13v = 13vPnC; CI = confidence interval; Diff = difference; GMC = geometric mean concentration; GMT = geometric mean titer; OPA = opsonophagocytic activity (assay); Resp = responders.

a. Difference in proportions, 13vPnC – 7vPnC, and exact 2-sided CIs for the difference are expressed as percentages.

b. Ratio of GMCs or GMTs: 13vPnC to 7vPnC. 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 – 7vPnC).

c. The OPA titer is defined as the reciprocal of the serum dilution with at least 50% killing of the bacteria, when compared with the average bacterial count in the HL60 control wells.

ID: 6 Oct 2008

Table 5-6: Posttoddler Dose Immunogenicity Data for Study 6096A1-004 – Additional Serotypes – Evaluable Toddler Immunogenicity Population

Test	Vaccine Group	1	95% CI	3	95% CI	5	95% CI	6A	95% CI	7F	95% CI	19A	95% CI
% Resp[a] ≥0.35 µg/mL	13v	100.0	98.4,100.0	90.5	86.0, 94.0	99.6	97.7, 100.0	100.0	98.4, 100.0	99.6	97.7,100.0	100.0	98.4,100.0
	7v	*98.7*	*96.1, 99.7*	*98.7*	*96.1, 99.7*	*98.7*	*96.1, 99.7*	*98.7*	*96.1, 99.7*	*98.7*	*96.1, 99.7*	*98.7*	*96.1, 99.7*
	Diff[b]	1.3	-0.3, 3.9	-8.1	-12.8, -4.0	0.9	-1.2, 3.5	1.3	-0.3, 3.9	0.9	-1.2, 3.5	1.3	-0.3, 3.9
% Resp[a] ≥0.15 µg/mL	13v	100.0	98.4, 100.0	97.4	94.5, 99.0	100.0	98.4, 100.0	100.0	98.4, 100.0	100.0	98.4, 100.0	100.0	98.4, 100.0
	7v	*99.1*	*96.8, 99.9*	*99.1*	*96.8, 99.9*	*99.1*	*96.8, 99.9*	*99.1*	*96.8, 99.9*	*99.1*	*96.8, 99.9*	*99.1*	*96.8, 99.9*
	Diff[b]	0.9	-0.7, 3.2	-1.7	-4.7, 0.9	0.9	-0.7, 3.2	0.9	-0.7, 3.2	0.9	-0.7, 3.2	0.9	-0.7, 3.2
GMC µg/mL[a]	13v	5.06	4.43, 5.80	0.94	0.83, 1.05	3.72	3.31, 4.18	8.20	7.30, 9.20	5.67	5.01, 6.42	8.55	7.64, 9.56
	7v	*3.63*	*3.25, 4.05*	*3.63*	*3.25, 4.05*	*3.63*	*3.25, 4.05*	*3.63*	*3.25, 4.05*	*3.63*	*3.25, 4.05*	*3.63*	*3.25, 4.05*
	Ratio[c]	1.40	1.17, 1.66	0.26	0.22, 0.30	1.03	0.87, 1.20	2.26	1.93, 2.65	1.56	1.32, 1.85	2.36	2.01, 2.76
OPA GMT[a,d]	13v	164.23	113.83, 236.93	380.41	300.19, 482.08	300.41	229.39, 393.40	2241.79	1706.71, 2944.63	11629.44	9053.62, 14938.11	1024.00	774.12, 1354.54
	7v	*5.01*	*4.22, 5.96*	*11.81*	*8.68, 16.08*	*4.69*	*3.99, 5.51*	*538.54*	*374.83, 773.75*	*267.84*	*164.49, 436.11*	*28.65*	*18.58, 44.17*
	Ratio[c]	32.75	21.99, 48.78	32.20	21.82, 47.52	64.07	47.08, 87.20	4.16	2.65, 6.55	43.42	25.15, 74.97	35.74	21.34, 59.85
OPA Titer[a,d] ≥1:8	13v	98.9	93.9, 100.0	97.8	92.3, 99.7	98.9	94.0, 100.0	98.9	94.1, 100.0	100.0	96.0, 100.0	97.8	92.3, 99.7
	7v	*12.0*	*6.1, 20.4*	*43.8*	*33.6, 54.3*	*5.2*	*1.7, 11.7*	*94.8*	*88.3, 98.3*	*80.4*	*70.9, 88.0*	*53.2*	*42.6, 63.6*

Note: N, or the number of subjects with evaluable and determinate IgG antibody concentrations, ranged from 223 to 236 for the additional serotypes. The number of subjects with determinate antibody titers (OPA) ranged from 89 to 96 for the additional serotypes.

Abbreviations: 7v = 7vPnC; 13v = 13vPnC; CI = confidence interval; Diff = difference; GMC = geometric mean concentration; GMT = geometric mean titer; OPA = opsonophagocytic activity (assay): Resp = responders.

a. For the percentage of responders at ≥0.35 µg/mL and at ≥0.15 µg/mL and for IgG GMC, the comparator for the additional serotypes is 7vPnC reference, i.e., the lowest proportion of responders among the 7 common serotypes in the 7vPnC group. For the OPA assay results, the 7vPnC comparator for the additional serotypes is the actual value for each serotype elicited by the vaccine (7vPnC).

b. Difference in proportions, 13vPnC – 7vPnC, and exact 2-sided CIs for the difference are expressed as percentages.

c. Ratio of GMCs or GMTs: 13vPnC to 7vPnC reference. 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 – 7vPnC reference).

d. The OPA titer is defined as the reciprocal of the serum dilution with at least 50% killing of the bacteria, when compared with the average bacterial count in the HL60 control wells.

ID: 6 Oct 2008

Table 5-7: Antibody Response to Pneumococcal Serotype 3 After the Toddler Dose – Evaluable Toddler Immunogenicity Population

		ELISA Results				OPA Assay Results		
Study and Vaccine Group	**Time Point**	**N[a]**	**% Responders[b] at ≥0.35 µg/mL (95% CI)**	**IgG GMC (µg/mL) (95% CI)**	**% Responders[b] at ≥0.15 µg/mL (95% CI)**	**N[a]**	**OPA GMT[c] (95% CI)**	**% Responders[b] at ≥1:8 Titer[c] (95% CI)**
6096A1-004 13vPnC	Pretoddler	224	16.1 (11.5, 21.5)	0.15 (0.13, 0.17)	45.1 (38.5, 51.9)	NA	NA	NA
13vPnC	Posttoddler	232	90.5 (86.0, 94.0)	0.94 (0.83, 1.05)	97.4 (94.5, 99.0)	91	380.41 (300.19, 482.08)	97.8 (92.3, 99.7)
7vPnC	*Pretoddler*	*198*	*6.6 (3.5, 11.0)*	*0.05 (0.04, 0.06)*	*16.7 (11.8, 22.6)*	*NA*	*NA*	*NA*
7vPnC	*Posttoddler*	*215*	*10.7 (6.9, 15.6)*	*0.07 (0.05, 0.08)*	*20.5 (15.3, 26.5)*	*96*	*11.81 (8.68, 16.08)*	*43.8 (33.6, 54.3)*

Extracted from 2.7.3 SCE-US, Table 3-50.

a. Number of subjects with determinate antibody concentration or titer to the given serotype and denominator for percentages. Ns were identical for % responders and IgG GMCs except in study 007. For GMCs N=85 pretoddler; N=85 posttoddler.

b. Percentage achieving the prespecified pneumococcal concentrations or titers.

c. The OPA titer is defined as the reciprocal of the serum dilution with at least 50% killing of the bacteria, when compared with the average bacterial count in the HL60 control wells.

5.1.1.3 Conclusions of the 6096A1-004 Study

For the 7 common serotypes, the non-inferiority primary criterion was met for the large majority of serotypes, and, for all serotypes using the GMC ratio criterion and the additional criterion (proportion of responders with an antibody concentration ≥ 0.15 μg/mL). Similar opsonophagocytic antibody titers were elicited and 90% or more of subjects had OPA antibody responses ≥ 1:8 for all 7 serotypes after the infant dose. Higher antibody levels, IgG ELISA and OPA, were achieved after the toddler dose, compared with after the infant series. Although 13vPnC elicited slightly lower antibody levels than Prevnar, the observed differences are unlikely to affect the vaccine's effectiveness, and, even more unlikely after the toddler dose, because 13vPnC-induced antibody levels are higher than those associated with protection against IPD.

For the 6 additional serotypes, all postinfant series non-inferiority criteria were met, except for serotype 3. In study 004, 96.8% of subjects demonstrated OPA antibody ≥1:8 threshold for serotype 3, consistent with a high likelihood of protection. Antibody responses elicited by 13vPnC to the 6 additional serotypes, as determined by both IgG ELISA and OPA titers, are substantially greater than those elicited by 7vPnC.

5.2 Immunogenicity of Manufacturing Scale and Consistency Series Vaccine Lots and Comparison of 13vPnC Manufactured Product to 7vPnC

Different lots of 13vPnC produced using the commercial process and including the vaccine's final formulation were tested in 2 separate studies (6096A1-3000 in Poland) and (6096A1-3005 in the U.S.) to demonstrate consistency of the manufacturing process and comparability of scale.. Although not an original objective of study 3005, an additional comparison from this trial provided direct evidence of non-inferiority of 13vPnC manufactured product to 7vPnC.

5.2.1 Consistency of Manufacturing Scale Lots (Study 6096A1-3005)

The 3005 consistency lot study was required for U.S. licensure and will be described here. All conjugates contained in the manufacturing-scale vaccine lot were made at manufacturing scale. Two (2) vaccine lots were filled in pilot facilities at one-tenth of manufacturing scale and 1 lot was filled at a manufacturing facility at the intended commercial scale. Of the common serotypes, serotype 19F has undergone process changes for 13vPnC compared with 7vPnC (as

described in section 3). The remaining common serotype conjugates have not undergone process changes and, accordingly, have previously been demonstrated to be clinically equivalent as part of the original 7vPnC approval process.

The US study 3005 was conducted using a 2-, 4-, and 6-month infant series. Two (2) pilot lots (pilot lots 1 and 2) and 1 manufacturing lot were assessed for equivalency of the immune response. In this study, lots were tested by pair-wise comparisons of all 3 lots (pilot lot 1 to manufacturing lot, pilot lot 2 to manufacturing lot, and pilot lot 1 to pilot lot 2). To be considered equivalent, the GMCs needed to be within 2-fold (the lower limit of the 2-sided 95% CI for the GMR greater than 0.5 and the upper limit less than 2.0). Using these criteria, equivalent responses were demonstrated across all serotypes irrespective of the specific lot comparisons (Table 5-8 and 5-9). These observations provide immunologic evidence of the ability to produce 13vPnC at manufacturing scale which consistently produces an equivalent immune response after immunization of infants. GMCs after the toddler dose were higher than those after the infant series for all serotypes and responses remained equivalent between lots (Table 5-10).

5.2.2 Comparison of Pneumococcal IgG responses after Manufacturing Scale 13vPnC to those after 7vPnC (Study 6096A1-3005)

Although not an initial objective of the study, the presence of the 7vPnC arm in study 3005 provided the opportunity to compare immune responses elicited by 13vPnC (in its final formulation) to those elicited by 7vPnC. Given the established equivalence of the three lots of 13vPnC vaccine in this study, the data from the three 13vPnC groups were combined and compared with the 7vPnC responses. Combining data from the three 13vPnC groups increases the power of non-inferiority comparisons to 7vPnC by increasing the total number of evaluable subjects, particularly for serotype responses that are lower after both 13vPnC and 7vPnC vaccine (Tables 5-11 to 5-17). This analysis showed that, for each of the common serotypes after the infant series, the 13vPnC (final formulation) responses are non-inferior to the responses elicited by 7vPnC, i.e. the values at the lower bound of the 95% confidence interval exceeded -10%, and met the formal non-inferiority criterion used in the pivotal studies (Table 5-11). In addition, the geometric mean ratios (GMRs) of the anti-polysaccharide IgG responses, comparing each 13vPnC group with the 7vPnC group, likewise met the formal non-inferiority criterion as used in the pivotal studies.

Responses for the 6 additional serotypes were compared to the proportion of responders at ≥ 0.35ug/mL or GMCs for the common serotype with the lowest antibody response, as used for non-inferiority comparisons in the pivotal studies. All additional serotypes satisfied this stringent criterion, except for serotype 3 (Table 5-11 and 5-12), which nonetheless exhibited responses that were substantially greater than those elicited by 7vPnC. Supplementary analyses were performed, and all serotypes including type 3 exceeded -10% criteria for percent responders at 0.15ug/mL after the infant series (Table 5-13). This value is relevant because it reflects the protective antibody threshold established with the current ELISA in the Northern California population using sera from the original Prevnar NCKP efficacy trial. Therefore, 0.15 µg/mL is considered an appropriate secondary endpoint comparator predictive of efficacy for populations with socioeconomic and epidemiologic features similar to those in the NCKP study. Notably, responses to serotype 3 in 13vPnC recipients were considerably higher (73.3% ≥ 0.35ug/mL, GMC 0.56) than the actual responses after 7vPnC (3.0% ≥ 0.35ug/mL, GMC 0.04), indicating that 13vPnC is likely to provide some measure of protection against serotype 3 that is not provided by 7vPnC (Table 5-14).

After the toddler dose, comparisons performed with regard to proportion of responders at ≥ 0.35 µg/mL and with regard to GMRs showed that the responses in the 13vPnC group (3 lots combined) are non-inferior to those in the 7vPnC group, except for serotype 3, which failed to meet the -10% criteria compared to the 7vPnC serotype with the lowest antibody response in study 3005. (Tables 5-15 and 5-16). However, responses for the additional serotypes including serotype 3 (Table 5-17) were considerably higher than the actual responses after 7vPnC. As after the infant dose, IgG cross reactive antibody was seen for serotypes 5, 6A, and 19A. Based on experience from other trials, antibody response to serotype 5 is not accompanied by OPA response after 7vPnC, and OPA responses to 6A and 19A after 13vPnC are substantially greater than those after 7vPnC, consistent with a higher level of expected protection. (See sections 5.1.1, 5.3, and 6.0)

13vPnC recipients of manufactured lots demonstrated equivalent responses across the three lots of vaccine in study 6096A1-3005, and demonstrated non-inferior responses to 7vPnC vaccine, using a set of predefined criteria used for the 6096A1-004 and 6096A1-006 non-inferiority trials. Therefore, it is expected that manufactured 13vPnC will provide protection against the 7 common serotypes that is non-inferior to 7vPnC and will also provide protection against the 6 additional serotypes in the vaccine.

Table 5-8: Postinfant Series Immunogenicity Data for US Pilot to Manufacturing Study 6096A1-3005 – Common Serotypes – Evaluable Infant Immunogenicity Population

Test	Vaccine Group	4	95% CI	6B	95% CI	9V	95% CI	14	95% CI	18C	95% CI	19F	95% CI	23F	95% CI
% Resp ≥ 0.35 µg/mL	13v Pilot Lot 1	97.6	95.6, 98.8	94.9	92.3, 96.8	95.4	92.9, 97.2	99.2	97.8, 99.8	97.8	95.9, 99.0	97.8	95.9, 99.0	91.2	88.1, 93.8
	13v Pilot Lot 2	95.5	93.0, 97.3	89.5	86.1, 92.3	95.5	93.0, 97.3	99.0	97.4, 99.7	95.8	93.3, 97.5	97.5	95.4, 98.8	88.1	84.5, 91.1
	13v Man Lot	98.5	96.7, 99.4	94.4	91.7, 96.5	96.5	94.1, 98.1	98.2	96.3, 99.3	98.0	96.1, 99.1	99.2	97.8, 99.8	87.2	83.5, 90.3
Difference[a]	13v Pilot Lot 1 vs 13v Pilot Lot 2	2.0	-0.51, 4.75	5.3	1.55, 9.19	-0.2	-3.13, 2.83	0.3	-1.27, 1.95	2.1	-0.38, 4.74	0.3	-1.93, 2.60	3.2	-1.03, 7.46
	13v Pilot Lot 1 vs 13v Man Lot	-0.9	-3.09, 1.10	0.4	-2.77, 3.66	-1.1	-3.97, 1.73	1.1	-0.60, 3.01	-0.2	-2.33, 1.99	-1.5	-3.46, 0.28	4.0	-0.27, 8.39
	13v Pilot Lot 2 vs 13v Man Lot	-2.9	-5.58, -0.58	-4.9	-8.82, -1.10	-0.9	-3.81, 1.88	0.8	-1.04, 2.76	-2.2	-4.89, 0.23	-1.8	-3.87, 0.02	0.8	-3.75, 5.46
GMC[b] µg/mL	13v Pilot Lot 1	1.33	1.24, 1.43	2.89	2.58, 3.23	1.05	0.98, 1.12	4.97	4.59, 5.37	1.30	1.22, 1.38	1.85	1.71, 1.99	1.24	1.13, 1.36
	13v Pilot Lot 2	1.34	1.25, 1.44	2.15	1.91, 2.42	1.11	1.04, 1.19	5.13	4.70, 5.59	1.34	1.24, 1.44	2.07	1.92, 2.24	1.27	1.15, 1.40
	13v Man Lot	1.75	1.63, 1.88	2.54	2.27, 2.85	1.11	1.04, 1.19	5.18	4.72, 5.69	1.48	1.38, 1.58	2.59	2.40, 2.78	1.03	0.94, 1.14
Equivalence[c]	13v Pilot Lot 1 vs 13v Pilot Lot 2	-0.01	-0.11, 0.09	0.30	0.13, 0.46	-0.06	-0.16, 0.04	-0.03	-0.15, 0.09	-0.03	-0.13, 0.07	-0.11	-0.22, -0.01	-0.03	-0.16, 0.11
	13v Pilot Lot 1 vs 13v Man Lot	-0.27	-0.38, -0.17	0.13	-0.04, 0.29	-0.06	-0.16, 0.04	-0.04	-0.16, 0.08	-0.13	-0.23, -0.03	-0.34	-0.44, -0.23	0.18	0.04, 0.31
	13v Pilot Lot 2 vs 13v Man Lot	-0.27	-0.37, -0.16	-0.17	-0.33, -0.01	0.00	-0.10, 0.10	-0.01	-0.13, 0.11	-0.10	-0.20, -0.00	-0.22	-0.33, -0.11	0.20	0.07, 0.34

Note: N, or the number of subjects with evaluable and determinate IgG antibody concentrations, ranged from 387 to 413 across common serotypes.
Abbreviations: 13v = 13vPnC; CI = confidence interval; GMC = geometric mean concentration, Man = manufacturing; Resp = responders.

a. Difference in proportions, lot 1 – lot 2, lot 1 – manufacturing lot, lot 2 – manufacturing lot, and exact 2-sided CIs for the difference are expressed as percentages.
b. GMCs were calculated using all subjects with evaluable data for the specified blood draw. CIs for GMCs are back-transformations of CIs based on the Student t distribution for the mean.
c. The 3 lots are considered equivalent if the 95% CI for the difference on the natural-log scale between any 2 lots is less than 0.693 and greater than -0.693 for all 13 serotypes.

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Table 5-9: Postinfant Series Immunogenicity Data for US Pilot to Manufacturing Study 6096A1-3005 – Additional Serotypes – Evaluable Infant Immunogenicity Population

Test	Vaccine Group	1	95% CI	3	95% CI	5	95% CI	6A	95% CI	7F	95% CI	19A	95% CI
% Resp ≥ 0.35 µg/mL	13v Pilot Lot 1	97.8	95.9, 99.0	68.5	63.7, 73.0	94.2	91.5, 96.2	98.1	96.2, 99.2	99.8	98.7, 100.0	98.1	96.2, 99.2
	13v Pilot Lot 2	97.0	94.9, 98.5	72.4	67.7, 76.8	90.3	87.0, 93.0	95.5	93.0, 97.3	99.0	97.5, 99.7	99.0	97.5, 99.7
	13v Man Lot	98.5	96.7, 99.4	79.1	74.8, 83.0	94.4	91.6, 96.5	98.2	96.4, 99.3	99.7	98.6, 100.0	98.7	97.1, 99.6
Difference[a]	13v Pilot Lot 1 vs 13v Pilot Lot 2	0.8	-1.48, 3.18	-3.9	-10.27, 2.45	3.9	0.15, 7.69	2.5	0.12, 5.23	0.8	-0.47, 2.30	-1.0	-2.91, 0.80
	13v Pilot Lot 1 vs 13v Man Lot	-0.7	-2.78, 1.34	-10.7	-16.80, -4.57	-0.2	-3.52, 3.09	-0.2	-2.22, 1.86	0.0	-1.12, 1.18	-0.7	-2.69, 1.19
	13v Pilot Lot 2 vs 13v Man Lot	-1.5	-3.77, 0.67	-6.8	-12.76, -0.74	-4.1	-7.92, -0.36	-2.7	-5.39, -0.27	-0.7	-2.30, 0.52	0.3	-1.40, 2.04
GMC[b] µg/mL	**13v Pilot Lot 1**	1.62	1.50, 1.76	0.52	0.48, 0.55	1.35	1.24, 1.47	2.40	2.21, 2.61	2.54	2.37, 2.71	1.85	1.71, 2.00
	13v Pilot Lot 2	1.81	1.66, 1.98	0.56	0.52, 0.61	1.05	0.96, 1.14	2.10	1.92, 2.29	2.52	2.35, 2.70	2.00	1.85, 2.16
	13v Man Lot	1.91	1.76, 2.07	0.61	0.57, 0.66	1.35	1.25, 1.47	2.12	1.96, 2.30	2.67	2.50, 2.85	1.88	1.74, 2.02
Equivalence[c]	13v Pilot Lot 1 vs 13v Pilot Lot 2	-0.11	-0.23, 0.01	-0.09	-0.19, 0.02	0.25	0.13, 0.37	0.14	0.02, 0.25	0.01	-0.09, 0.10	-0.08	-0.19, 0.03
	13v Pilot Lot 1 vs 13v Man Lot	-0.16	-0.28, -0.04	-0.18	-0.28, -0.07	0.00	-0.12, 0.12	0.12	0.01, 0.24	-0.05	-0.14, 0.04	-0.02	-0.12, 0.09
	13v Pilot Lot 2 vs 13v Man Lot	-0.05	-0.17, 0.06	-0.09	-0.19, 0.02	-0.25	-0.37, -0.13	-0.01	-0.13, 0.11	-0.06	-0.15, 0.04	0.06	-0.05, 0.17

Note: N, or the number of subjects with evaluable and determinate IgG antibody concentrations, ranged from 393 to 413 across additional serotypes.
Abbreviations: 13v = 13vPnC; CI = confidence interval; GMC = geometric mean concentration; Man = manufacturing; Resp = responders.

a. Difference in proportions, lot 1 – lot 2, lot 1 – manufacturing lot, lot 2 – manufacturing lot, and exact 2-sided CIs for the difference are expressed as percentages.
b. GMCs were calculated using all subjects with evaluable data for the specified blood draw. CIs for GMCs are back-transformations of CIs based on the Student t distribution for the mean.
c. The 3 lots are considered equivalent if the 95% CI for the difference on the natural-log scale between any 2 lots is less than 0.693 and greater than -0.693 for all 13 serotypes.

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Table 5-10: Pneumococcal IgG GMCs and Equivalency Assessment (µg/mL) for Each 13vPnC Group After the Toddler Dose – Study 6096A1-3005 Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)											
	13vPnC Pilot Lot 1			13vPnC Pilot Lot 2			13vPnC Manufacturing Lot			Difference (95% CI) in Log-Transformed Geometric Means		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13vPnC Pilot Lot 1 - Pilot Lot 2	13vPnC Pilot Lot 1 - Manufacturing Lot	13vPnC Pilot Lot 2 - Manufacturing Lot
7vPnC												
4	364	2.29	(2.11, 2.48)	342	2.25	(2.07, 2.44)	355	3.06	(2.79, 3.35)	0.02 (-0.10, 0.13)	-0.29 (-0.41, -0.17)	-0.31 (-0.43, -0.19)
6B	368	11.14	(10.24, 12.11)	341	9.33	(8.55, 10.19)	357	9.92	(9.15, 10.75)	0.18 (0.06, 0.30)	0.12 (-0.00, 0.23)	-0.06 (-0.18, 0.06)
9V	368	1.91	(1.76, 2.06)	342	1.95	(1.80, 2.10)	357	1.99	(1.84, 2.15)	-0.02 (-0.13, 0.09)	-0.04 (-0.15, 0.07)	-0.02 (-0.13, 0.09)
14	366	6.61	(6.06, 7.22)	344	7.05	(6.42, 7.74)	358	6.91	(6.32, 7.56)	-0.06 (-0.19, 0.06)	-0.04 (-0.17, 0.08)	0.02 (-0.11, 0.15)
18C	362	1.95	(1.78, 2.12)	341	2.20	(2.01, 2.41)	354	2.48	(2.27, 2.71)	-0.12 (-0.25, 0.00)	-0.24 (-0.37, -0.12)	-0.12 (-0.25, 0.01)
19F	362	4.51	(4.05, 5.03)	342	4.67	(4.23, 5.14)	353	6.51	(5.91, 7.18)	-0.03 (-0.18, 0.11)	-0.37 (-0.51, -0.22)	-0.33 (-0.47, -0.20)
23F	362	3.35	(3.02, 3.71)	340	3.46	(3.14, 3.82)	353	3.10	(2.81, 3.43)	-0.03 (-0.17, 0.11)	0.08 (-0.07, 0.22)	0.11 (-0.03, 0.25)
Additional												
1	367	2.75	(2.53, 2.99)	344	2.95	(2.68, 3.24)	357	3.01	(2.75, 3.30)	-0.07 (-0.20, 0.06)	-0.09 (-0.21, 0.03)	-0.02 (-0.15, 0.11)
3	366	0.75	(0.69, 0.81)	343	0.71	(0.65, 0.77)	356	0.80	(0.74, 0.87)	0.06 (-0.06, 0.18)	-0.07 (-0.18, 0.04)	-0.13 (-0.25, -0.01)

Table 5-10: Pneumococcal IgG GMCs and Equivalency Assessment (µg/mL) for Each 13vPnC Group After the Toddler Dose – Study 6096A1-3005 Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)											
	13vPnC Pilot Lot 1			13vPnC Pilot Lot 2			13vPnC Manufacturing Lot			Difference (95% CI) in Log-Transformed Geometric Means		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13vPnC Pilot Lot 1 - Pilot Lot 2	13vPnC Pilot Lot 1 - Manufacturing Lot	13vPnC Pilot Lot 2 - Manufacturing Lot
5	368	3.11	(2.87, 3.37)	343	2.63	(2.42, 2.87)	357	2.80	(2.60, 3.02)	0.17 (0.05, 0.28)	0.10 (-0.00, 0.21)	-0.06 (-0.17, 0.05)
6A	366	7.52	(6.93, 8.17)	342	6.97	(6.41, 7.59)	355	6.83	(6.30, 7.41)	0.08 (-0.04, 0.19)	0.10 (-0.02, 0.21)	0.02 (-0.10, 0.14)
7F	366	4.35	(4.01, 4.72)	343	4.24	(3.86, 4.66)	358	4.58	(4.21, 4.98)	0.03 (-0.10, 0.15)	-0.05 (-0.17, 0.07)	-0.08 (-0.20, 0.05)
19A	362	8.41	(7.73, 9.14)	341	8.32	(7.66, 9.04)	353	8.60	(7.91, 9.36)	0.01 (-0.11, 0.13)	-0.02 (-0.14, 0.10)	-0.03 (-0.15, 0.08)

a. n = 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 (CIs) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_GMC_13V_EQUIV.SAS. Runtime ID: 07MAY2009 16:53
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/Immuno_6MAY09.zip/imm_pnc_elisa_gmc_equiv_13v_eval_tp.htm

Table 5-11: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Dose 3 of Infant Series – Study 6096A1-3005 Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	1216	1182	97.2	(96.1, 98.1)	165	163	98.8	(95.7, 99.9)	-1.6	(-3.2, 1.4)
6B	1209	1124	93.0	(91.4, 94.3)	165	160	97.0	(93.1, 99.0)	-4.0	(-6.6, -0.1)
9V	1212	1161	95.8	(94.5, 96.9)	158	156	98.7	(95.5, 99.8)	-2.9	(-4.7, 0.2)
14	1175	1161	98.8	(98.0, 99.3)	163	162	99.4	(96.6, 100.0)	-0.6	(-1.7, 2.1)
18C	1214	1180	97.2	(96.1, 98.1)	165	163	98.8	(95.7, 99.9)	-1.6	(-3.2, 1.4)
19F	1208	1186	98.2	(97.3, 98.9)	165	161	97.6	(93.9, 99.3)	0.6	(-1.3, 4.0)
23F	1214	1079	88.9	(87.0, 90.6)	165	157	95.2	(90.7, 97.9)	-6.3	(-9.5, -1.8)
Additional										
1	1212	1185	97.8	(96.8, 98.5)	165	157	95.2	(90.7, 97.9)	2.6	(-0.3, 6.9)
3	1193	875	73.3	(70.7, 75.8)	165	157	95.2	(90.7, 97.9)	-21.8	(-25.6, -16.9)
5	1210	1125	93.0	(91.4, 94.4)	165	157	95.2	(90.7, 97.9)	-2.2	(-5.2, 2.3)
6A	1216	1183	97.3	(96.2, 98.1)	165	157	95.2	(90.7, 97.9)	2.1	(-0.8, 6.4)
7F	1213	1207	99.5	(98.9, 99.8)	165	157	95.2	(90.7, 97.9)	4.4	(1.7, 8.6)
19A	1214	1197	98.6	(97.8, 99.2)	165	157	95.2	(90.7, 97.9)	3.4	(0.6, 7.7)

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 - 7vPnC reference, expressed as a percentage. For the 7vPnC serotypes, the reference value is the corresponding proportion in the 7vPnC group. For the additional serotypes, the reference value is serotype 23F from the 7vPnC group.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC - 7vPnC reference, expressed as a percentage.

Table 5-11: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Dose 3 of Infant Series – Study 6096A1-3005 Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])

Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_RESP_POP.SAS. Runtime ID: 30JUN2009 10:44
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/EXP FDA REQ 30JUN09.doc

Table 5-12: Pneumococcal IgG GMCs and Equivalency Assessment (µg/mL) Using GMRs After the Infant Series – Study 6096A1-3005 Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized)						
	13vPnC			7vPnC			Geometric Mean Ratio[d] (95% CI[e])
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13vPnC / 7vPnC
7vPnC							
4	1216	1.46	(1.40, 1.52)	165	1.95	(1.73, 2.19)	0.75 (0.66, 0.85)
6B	1209	2.52	(2.36, 2.69)	165	2.93	(2.47, 3.48)	0.86 (0.71, 1.04)
9V	1212	1.09	(1.05, 1.14)	158	1.35	(1.23, 1.49)	0.81 (0.72, 0.90)
14	1175	5.10	(4.85, 5.36)	163	6.21	(5.40, 7.14)	0.82 (0.71, 0.95)
18C	1214	1.37	(1.32, 1.43)	165	1.61	(1.44, 1.80)	0.85 (0.76, 0.95)
19F	1208	2.15	(2.06, 2.25)	165	2.30	(2.02, 2.61)	0.94 (0.83, 1.07)
23F	1214	1.18	(1.11, 1.25)	165	1.71	(1.48, 1.97)	0.69 (0.59, 0.81)
Additional							
1	1212	1.78	(1.70, 1.87)	158	1.35	(1.23, 1.49)	1.32 (1.15, 1.51)
3	1193	0.56	(0.54, 0.59)	158	1.35	(1.23, 1.49)	0.42 (0.37, 0.47)
5	1210	1.24	(1.19, 1.31)	158	1.35	(1.23, 1.49)	0.92 (0.80, 1.06)
6A	1216	2.21	(2.11, 2.32)	158	1.35	(1.23, 1.49)	1.64 (1.42, 1.88)
7F	1213	2.58	(2.48, 2.68)	158	1.35	(1.23, 1.49)	1.91 (1.70, 2.13)
19A	1214	1.91	(1.83, 2.00)	158	1.35	(1.23, 1.49)	1.41 (1.24, 1.60)

a. n = 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 (CIs) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs. For the 7vPnC serotypes, the reference value is the corresponding geometric mean concentration in the 7vPnC group. For the additional serotypes, the reference value is serotype 9V from the 7vPnC group.
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.

Table 5-12: Pneumococcal IgG GMCs and Equivalency Assessment (µg/mL) Using GMRs After the Infant Series – Study 6096A1-3005 Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized)						
	13vPnC			7vPnC			Geometric Mean Ratio[d] (95% CI[c])
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13vPnC / 7vPnC

Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_GMR_COMB_13V_MIN.SAS. Runtime ID: 30JUN2009 07:34
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/EXP FDA REQ 30JUN09.doc

Table 5-13: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.15 µg/mL After Dose 3 of Infant Series – Study 6096A1-3005 Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	1216	1212	99.7	(99.2, 99.9)	165	165	100.0	(97.8, 100.0)	-0.3	(-0.9, 1.7)
6B	1209	1191	98.5	(97.7, 99.1)	165	163	98.8	(95.7, 99.9)	-0.3	(-1.6, 2.7)
9V	1212	1205	99.4	(98.8, 99.8)	158	158	100.0	(97.7, 100.0)	-0.6	(-1.3, 1.6)
14	1175	1174	99.9	(99.5, 100.0)	163	163	100.0	(97.8, 100.0)	-0.1	(-0.6, 2.0)
18C	1214	1208	99.5	(98.9, 99.8)	165	164	99.4	(96.7, 100.0)	0.1	(-0.8, 2.6)
19F	1208	1200	99.3	(98.7, 99.7)	165	163	98.8	(95.7, 99.9)	0.5	(-0.7, 3.4)
23F	1214	1184	97.5	(96.5, 98.3)	165	162	98.2	(94.8, 99.6)	-0.7	(-2.4, 2.6)
Additional										
1	1212	1209	99.8	(99.3, 99.9)	165	162	98.2	(94.8, 99.6)	1.6	(0.1, 4.7)
3	1193	1169	98.0	(97.0, 98.7)	165	162	98.2	(94.8, 99.6)	-0.2	(-1.9, 3.1)
5	1210	1199	99.1	(98.4, 99.5)	165	162	98.2	(94.8, 99.6)	0.9	(-0.6, 4.2)
6A	1216	1210	99.5	(98.9, 99.8)	165	162	98.2	(94.8, 99.6)	1.3	(-0.2, 4.5)
7F	1213	1213	100.0	(99.7, 100.0)	165	162	98.2	(94.8, 99.6)	1.8	(0.4, 5.2)
19A	1214	1212	99.8	(99.4, 100.0)	165	162	98.2	(94.8, 99.6)	1.7	(0.1, 4.9)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.15 µg/mL for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC - 7vPnC reference, expressed as a percentage. For the 7vPnC serotypes, the reference value is the corresponding proportion in the 7vPnC group. For the additional serotypes, the reference value is serotype 23F from the 7vPnC group.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC - 7vPnC reference, expressed as a percentage.
Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_RESP_POP15.SAS. Runtime ID: 30JUN2009 13:00

Table 5-13: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.15 µg/mL After Dose 3 of Infant Series – Study 6096A1-3005 Evaluable Pneumococcal Infant Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])

Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/EXP FDA REQ 30JUN09.doc

Table 5-14: Antibody Response to Pneumococcal Serotype 3 After the Infant Series – Evaluable Infant Immunogenicity Population 6096A1-3005

Study	Vaccine Group	N[a]	ELISA Results: % Responders at ≥0.35 µg/mL (95% CI)[b]	ELISA Results: IgG GMC[c] (µg/mL) (95% CI)[d]
2, 4, 6 months				
6096A1-3005	13vPnC	1193	73.3 (70.7, 75.8)	.0.56 (0.54, 0.59)
	7vPnC	*164*	*3.0 (1.0, 7.0)*	*0.04 (0.03, 0.05)*

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Exact 2-sided confidence interval based on the observed proportion of subjects.
c. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
d. Confidence intervals (CIs) are back transforms of confidence levels based on the student + distribution for the mean logarithm of the concentrations.

Source: Extracted from Submission to IND BB11673 on July 15, 2009 (#0079 SN0219)

Table 5-15: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35 µg/mL Using Combined 13v Lots After the Toddler Dose – Study 6096A1-3005 Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7vPnC										
4	1061	1055	99.4	(98.8, 99.8)	173	172	99.4	(96.8, 100.0)	0.0	(-0.9, 2.4)
6B	1066	1066	100.0	(99.7, 100.0)	173	173	100.0	(97.9, 100.0)	0.0	(-0.5, 2.1)
9V	1067	1062	99.5	(98.9, 99.8)	172	171	99.4	(96.8, 100.0)	0.1	(-0.8, 2.5)
14	1068	1067	99.9	(99.5, 100.0)	173	173	100.0	(97.9, 100.0)	-0.1	(-0.6, 1.9)
18C	1057	1046	99.0	(98.1, 99.5)	173	172	99.4	(96.8, 100.0)	-0.5	(-1.6, 2.1)
19F	1057	1045	98.9	(98.0, 99.4)	173	170	98.3	(95.0, 99.6)	0.6	(-1.0, 3.6)
23F	1055	1044	99.0	(98.1, 99.5)	173	172	99.4	(96.8, 100.0)	-0.5	(-1.6, 2.1)
Additional										
1	1068	1062	99.4	(98.8, 99.8)	173	170	98.3	(95.0, 99.6)	1.2	(-0.3, 4.2)
3	1065	898	84.3	(82.0, 86.5)	173	170	98.3	(95.0, 99.6)	-13.9	(-16.7, -10.4)
5	1068	1064	99.6	(99.0, 99.9)	173	170	98.3	(95.0, 99.6)	1.4	(-0.1, 4.4)
6A	1063	1062	99.9	(99.5, 100.0)	173	170	98.3	(95.0, 99.6)	1.6	(0.1, 4.7)
7F	1067	1063	99.6	(99.0, 99.9)	173	170	98.3	(95.0, 99.6)	1.4	(-0.1, 4.4)
19A	1056	1056	100.0	(99.7, 100.0)	173	170	98.3	(95.0, 99.6)	1.7	(0.4, 5.0)

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.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC - 7vPnC reference, expressed as a percentage. For the 7vPnC serotypes, the reference value is the corresponding proportion in the 7vPnC group. For the additional serotypes, the reference value is serotype 19F from the 7vPnC group.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC - 7vPnC reference, expressed as a percentage.

Table 5-15: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥ 0.35 µg/mL Using Combined 13v Lots After the Toddler Dose – Study 6096A1-3005 Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)									
	13vPnC				7vPnC					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])

Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_RESP_POP.SAS. Runtime ID: 30JUN2009 12:47
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/EXP FDA REQ 30JUN09.doc

Table 5-16: Pneumococcal IgG GMCs and Equivalency Assessment (µg/mL) Using GMRs After the Toddler Dose – Study 6096A1-3005 Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)						
	13vPnC			7vPnC			Geometric Mean Ratio[d] (95% CI[e])
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13vPnC / 7vPnC
7vPnC							
4	1061	2.50	(2.38, 2.63)	173	2.79	(2.45, 3.18)	0.90 (0.79, 1.03)
6B	1066	10.12	(9.64, 10.63)	173	9.47	(8.26, 10.86)	1.07 (0.94, 1.22)
9V	1067	1.95	(1.86, 2.04)	172	1.97	(1.77, 2.19)	0.99 (0.88, 1.12)
14	1068	6.85	(6.51, 7.22)	173	8.19	(7.31, 9.18)	0.84 (0.73, 0.96)
18C	1057	2.20	(2.09, 2.31)	173	2.33	(2.05, 2.65)	0.94 (0.82, 1.08)
19F	1057	5.16	(4.86, 5.47)	173	3.31	(2.87, 3.81)	1.56 (1.33, 1.82)
23F	1055	3.30	(3.12, 3.50)	173	4.49	(3.86, 5.23)	0.74 (0.63, 0.86)
Additional							
1	1068	2.90	(2.75, 3.05)	172	1.97	(1.77, 2.19)	1.47 (1.29, 1.69)
3	1065	0.75	(0.72, 0.79)	172	1.97	(1.77, 2.19)	0.38 (0.34, 0.43)
5	1068	2.85	(2.72, 2.98)	172	1.97	(1.77, 2.19)	1.45 (1.28, 1.63)
6A	1063	7.11	(6.78, 7.46)	172	1.97	(1.77, 2.19)	3.61 (3.18, 4.10)
7F	1067	4.39	(4.18, 4.61)	172	1.97	(1.77, 2.19)	2.23 (1.96, 2.54)
19A	1056	8.44	(8.05, 8.86)	172	1.97	(1.77, 2.19)	4.29 (3.78, 4.87)

a. n = 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 (CIs) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs. For the 7vPnC serotypes, the reference value is the corresponding geometric mean concentration in the 7vPnC group. For the additional serotypes, the reference value is serotype 9V from the 7vPnC group.
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.

Table 5-16: Pneumococcal IgG GMCs and Equivalency Assessment (µg/mL) Using GMRs After the Toddler Dose – Study 6096A1-3005 Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)						
	13vPnC			7vPnC			Geometric Mean Ratio[d] (95% CI[e])
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13vPnC / 7vPnC

Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_GMR_COMB_13V_MIN.SAS. Runtime ID: 30JUN2009 07:34
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/EXP FDA REQ 30JUN09.doc

Table 5-17: Antibody Response to Pneumococcal Serotype 3 After the Toddler Dose – Evaluable Infant Immunogenicity Population 6096A1-3005

Study	Vaccine Group	N[a]	ELISA Results % Responders at ≥0.35 µg/mL (95% CI)[b]	ELISA Results IgG GMC[c] (µg/mL) (95% CI)[d]
2, 4, 6 months				
6096A1-3005	13vPnC	1065	84.3 (82.0, 86.5)	0.75 (0.72, 0.79)
	7vPnC	*173*	*6.9 (3.6, 11.8)*	*0.07 (0.05, 0.08)*

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Exact 2-sided confidence interval based on the observed proportion of subjects.
c. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
d. Confidence intervals (CIs) are back transforms of confidence levels based on the student + distribution for the mean logarithm of the concentrations.

Source: Extracted from Submission to IND BB11673 on July 15, 2009 (#0079 SN0219)

5.3 Review of Vaccine Immunogenicity by Serotype

This section will further describe immune responses to individual serotypes in the U.S. 004 and 3005 studies. For a description of percent responders and GMCs across all studies in the 13vPnC U.S. dossier, the reader is referred to Tables 5-20 through 5-23 at the end of this section.

5.3.1 Antibody responses to the Common Serotypes in U.S. trials

5.3.1.1 Serotypes 4, 9, 14, 18C, 19F, and 23F

The immunogenicity of the common serotypes 4, 14, 18C, 19F and 23F were consistently demonstrated in all of the 13vPnC phase 3 trials (Table 5-20 through Table 5-23). The immune

responses met the primary criterion of non-inferiority in study 004 (Table 5-2). Non-inferiority criteria were met when comparing the IgG ELISA GMC values and assessing the proportion of responders at IgG concentrations ≥ 0.15 µg/mL. In study 004, the non-inferiority criterion was narrowly missed for 9V, as the difference at the lower bound of the 95% CI was only -12.4 (Table 5-2). Although the primary non-inferiority criterion was not achieved in study 004, the proportion of responders with an antibody concentration ≥ 0.35µg/mL to serotype 9V in the 13vPnC group was greater than 90%, and the non-inferiority criteria were met when comparing the IgG ELISA GMC values and assessing the proportion of responders at IgG concentrations ≥ 0.15 µg/mL.

Data from the manufacturing scale lot and consistency series study 3005 showed that over 95% (serotype 4), 95% (serotype 9V), 98% (serotype 14), 95% (serotype 18C), 97% (serotype 19F), and 88% (serotype 23F) of infants receiving a 3-dose infant series of the final 13vPnC formulation responded with IgG ELISA antibody concentrations ≥0.35 µg/mL (Table 5-8). The proportion of responders and the GMC values for all 6 serotypes observed in study 3005 (after 3 doses at 2, 4, and 6 months) are consistent with historical responses elicited by Prevnar. In addition, although not an original objective of the 3005 trial, 95.8% of 13vPnC recipients of the final manufactured formulation responded with 9V serotype specific IgG ≥ 0.35 µg/mL compared to 98.7% of 7vPnC recipients, the difference of which was non-inferior according to a -10% criterion (- 4.7% , 95% lower CI for 13vPnC-7vPnC) (Table 5-11).

When comparing pre- and posttoddler data, an approximate 3- to 10-fold rise in IgG ELISA GMCs depending on serotype was noted following the toddler dose. Higher IgG ELISA GMCs were achieved after the toddler dose (Table 5-16), compared with those achieved at 1 month after the infant series, suggesting the induction of immunologic memory by the vaccine for these serotypes.

Both pivotal non-inferiority studies demonstrated for each of these 6 serotypes the opsonic activity of 13vPnC induced antibody; the 13vPnC/7vPnC ratios of OPA GMTs were within 2-fold. Good correlations between OPA titers and IgG ELISA GMCs were noted for both vaccines, supporting the conclusion that polysaccharide-binding IgG antibodies after 13vPnC vaccination are biologically relevant (See also sections 4.2.2 and 6.0).

In conclusion, compared with Prevnar, 13vPnC elicits good levels of anticapsular polysaccharide IgG-binding and functional opsonic antibodies in a high proportion of infants for serotypes 4, 9V, 14, 18C, 19F, and 23F. All non-inferiority criteria for these serotypes were met in the study 004, except for serotype 9V; functional opsonic antibody response for serotype 9V were within 2-fold in 004 and IgG-binding antibody response rates were non-inferior in 3005. Accordingly, 13vPnC is highly likely to provide the same degree of effectiveness against overall pneumococcal disease caused by these 6 serotypes as that conferred by 7vPnC.

5.3.1.2 Serotype 6B

The immunogenicity of serotype 6B was evaluated in all of the 13vPnC phase 3 trials (Table 5-20 through Table 5-23). For US study 004, the responder proportions with IgG ELISA concentration ≥ 0.35 μg/mL were 87.3% and 92.8%, for the 13vPnC and 7vPnC groups, respectively, following the infant series at 2, 4, and 6 months of age (Table 5-2). Thus, the non-inferiority primary endpoint was missed by a small margin (difference -5.5%, 2-sided 95% CI: -10.9%, -0.1%), i.e. the lower 95% CI was slightly lower than the predetermined CI limit of -10%. However, the non-inferiority criteria were met for study 004 when the IgG ELISA GMC values were compared. Study 004 satisfied non-inferiority criteria when the proportion of responders at IgG concentrations ≥ 0.15 μg/mL was assessed.

Data from the consistency series study in the United States (study 3005), in which the final formulation was used, yielded responder proportions of 89.5% and 94.9% at ≥ 0.35 μg/mL for the 2 pilot scale groups and 94.4% for the manufacturing scale group (Table 5-8). These proportions, as well as the GMC values seen in study 3005, are consistent with historical anti-serotype 6B responses elicited by Prevnar. In addition, although not an original objective of the 3005 trial, 93.0% of 13vPnC recipients of a final manufactured formulation responded with 6B serotype specific IgG ≥ 0.35 μg/mL compared to 97% of 7vPnC recipients, the difference of which was non-inferior according to a -10% criterion (- 6.6% , 95% lower CI for 13vPnC-7vPnC) (Table 5-11).

When comparing pre- and posttoddler data, a greater than 10-fold rise in IgG ELISA GMCs following the toddler dose was noted, compared to the pre-toddler value. Substantially higher IgG ELISA GMCs were achieved after the toddler dose (10.12ug/mL, 95%CI: 9.64-10.63 μg/mL) (Table 5-16), compared with those achieved at 1 month after the infant series (2.52

µg/mL, 95%CI:2.36-2.69) (Table 5-12), reflecting the induction of immunologic memory by the vaccine for this serotype.

The 004 pivotal non-inferiority study demonstrated the opsonic activity of 13vPnC-induced antibody. The proportion of infants exhibiting positive OPA titers (≥ 1:8, see Table 5-2) was 98.9%, and this proportion were comparable with that exhibited by 7vPnC recipients. Good correlations between OPA titers and IgG ELISA GMCs were noted for both vaccines, supporting the conclusion that anticapsular polysaccharide-binding IgG antibodies after 13vPnC vaccination are biologically relevant (Sections 4.2.2 and 6.0).

In conclusion, 13vPnC elicits anti-serotype 6B IgG polysaccharide binding and functional opsonic antibodies. Although somewhat lower than the responses elicited by 7vPnC in study 004, all of the secondary non-inferiority criteria were met. These differences are not likely to be biologically significant with regard to overall high vaccine effectiveness against serotype 6B pneumococcal disease.

Given these observations, and the data from the final formulation manufacturing consistency series (study 3005) trial, which demonstrated responders with an antibody concentration ≥ 0.35 µg/mL of >94.9%, within the historic range for serotype 6B in Prevnar and non-inferior to the 7vPnC group in 3005 by a -10% 95% CI difference criterion, it is highly likely that 13vPnC will mediate effective protection against serotype 6B pneumococcal disease. This is even more likely given the booster response after the toddler dose resulting in a responder proportion of approximately 99%.

5.3.2 Antibody responses to the Additional Serotypes

5.3.2.1 Serotype 1

The immunogenicity of serotype 1 was consistently demonstrated in all of the 13vPnC phase 3 trials (Table 5-20 through Table 5-23). The immune responses to serotype 1 met the primary criterion of non-inferiority in pivotal U.S. study 004 (Table 5-3). Data from the manufacturing scale and consistency series studies 3005 showed that 97.0% to 98.5%of infants receiving 3 infant doses of the final 13vPnC formulation responded with IgG ELISA antibody concentrations ≥ 0.35 μg/m (Table 5-9).

When comparing pre- and posttoddler data, an approximate 10-fold rise in IgG ELISA GMCs following the toddler dose was noted. Substantially higher IgG ELISA GMCs were achieved after the toddler dose, compared with those achieved at 1 month after the infant series, reflecting the induction of immunologic memory by the vaccine for this serotype (Table 5-3, Table 5-6, Table 5-12, Table 5-16).

The 004 pivotal non-inferiority study demonstrated the opsonic activity of vaccine-induced antibody, with 13vPnC/7vPnC ratios of OPA GMTs greater than 10 after the infant series, and greater than 32 after the toddler dose. The proportion of infants exhibiting positive OPA titers (≥ 1:8, Table 5-3) was 98.9% (study 004). Good correlations between OPA titers and IgG ELISA GMCs were noted, supporting the conclusion that polysaccharide-binding IgG antibodies after 13vPnC vaccination are biologically relevant (Sections 4.2.2 and 6.0).

In conclusion, compared with 7vPnC, 13vPnC elicits substantial levels of anti-serotype 1 IgG polysaccharide binding and functional opsonic antibodies in a high proportion of infants. Based on similar immune responses elicited by the effective 7vPnC against the 7 common serotypes, the immune responses elicited against serotype 1 by 13vPnC are likely to be effective for the prevention of pneumococcal disease caused by this serotype.

Two (2) efficacy trials in African infants with 9vPnC that included 2 μg of CRM_{197} conjugated serotype 1 capsular polysaccharide have yielded mixed results. A trial in the Gambia noted a lack of efficacy for IPD caused by serotype 1 (4 and 2 cases, among vaccine and control recipients, respectively).[57] New data on nasopharyngeal carriage of *S. pneumoniae* from children in this trial is encouraging.[58] 4 placebo subjects were noted to carry serotype 1 when sampled at either 9-15

months of age or 21-27 months of age compared to 0 subjects in the 9vPnC vaccine groups, but this did not achieve statistical significance. A trial in South Africa suggested a trend for effectiveness against serotype 1, with 4 cases among controls compared with 1 case in infants immunized with 9vPnC; during the long-term follow-up trial, efficacy was supported by observations of a total of 1 and 5 cases of serotype 1 IPD among vaccine and control recipients, respectively.[59] Because of the limited number of cases in each of the 2 trials, these observations should be interpreted with caution.

Overall, studies providing serotype-specific outcomes of IPD are scant in the literature. The effectiveness of 23vPS has been recently evaluated in adult Alaskan natives. In this study, efficacy of 23vPS against serotype 1 invasive disease was demonstrated.[60] The anti-serotype 1 IgG ELISA responses seen in this study were similar to those seen in infants following administration of 13vPnC. These findings further support the potential effectiveness of 13vPnC against disease caused by serotype 1.

5.3.2.2 Serotype 3

The immunogenicity of serotype 3 was demonstrated across all of the 13vPnC phase 3 trials (Tables 5-20 through 5-23). In study 004, the criteria were not met either for the proportion of responders exhibiting IgG antibody concentrations ≥ 0.35 μg/mL or for the comparative IgG GMC (Table 5-3). However, these latter analyses were performed using the lowest respective responses among the common serotypes in the 7vPnC group as comparator values. When compared with the actual anti-serotype 3 responses elicited by 7vPnC, substantially higher specific polysaccharide-binding antibody levels were exhibited by 13vPnC, just not as high as type 6B in 7vPnC (Table 5-4) .

The inability of the serotype 3 response to meet the non-inferiority criteria in study 004, reflected the relatively low response level to this serotype seen in this study, which was the lowest of the 13 serotypes. The responses to serotype 3 for all 3 lots of 13vPnC used in the vaccine consistency series trial (study 3005) were also the lowest among the 13 serotypes. Although not an original objective of the consistency lot trial, responses to serotype 3 in 13vPnC recipients (combined results to 3 final formulation vaccine lots) were considerably higher (73.3% ≥ 0.35ug/mL, GMC 0.56) than the actual responses after 7vPnC (3.0% ≥ 0.35ug/mL, GMC 0.04) after the infant series (Table 5-14), indicating that 13vPnC is likely to provide some measure of protection against serotype 3 that is not provided by 7vPnC . Both the 004 and 3005 studies were performed in a US infant population, and 13vPnC in its final P80-containing formulation was used in the consistency series. The proportions of 13vPnC responders with an antibody concentration ≥0.35 μg/mL for these 2 studies ranged from 63.5% to 79.1%. Although lower than anticipated, these responses are notably more robust than those that would be elicited by 7vPnC against serotype 3.

The anti-serotype 3 responses met the predefined alternative non-inferiority criterion at the additional comparison level of ≥0.15 μg/mL in study 004. Of particular note, the specific polysaccharide-binding IgG antibody levels elicited by 13vPnC were at least 10 fold higher than the actual serotype 3 antibody response elicited by 7vPnC (Table 5-4 and Table 5-14).

Importantly, functional antibody against serotype 3 elicited by 13vPnC was assessed in an OPA assay using a type 3 strain (WU2) that is typical of serotype 3 clinical isolates. The WU2 strain expresses a characteristic type 3 capsule. Also, as is typical for type 3, the bacterium sheds

considerable quantities of non-cell wall associated polysaccharide into the assay medium. Given this phenomenon, and the bacterium's large capsule, the overall anti-type 3 OPA titers are expected to be lower in comparison to other serotypes. Since each serotype-specific OPA assay was independently developed and as there is no external reference, the clinical significance of absolute OPA titers cannot be determined. However, a "positive" OPA response (defined as a titer ≥1:8) is likely to reflect a clinically meaningful potential for protection against invasive disease.

In all studies where OPA was assessed, including both pivotal non-inferiority studies, the anti-type 3 opsonophagocytic activity of 13vPnC-induced antibody was clearly demonstrated. The proportion of subjects with OPA titers ≥1:8 ranged from 96.8% to 100% after the infant series and from 97.8% to 100% after the toddler dose. The 13vPnC/7vPnC ratios of OPA GMTs ranged from 17 to 40 after the infant series. OPA GMTs were similar or higher after the toddler dose compared with the postinfant OPA response. Studies included in the U.S. dossier with both OPA and IgG ELISA responses are shown in Table 5-18. Good correlations between OPA and IgG ELISA responses were noted, supporting the conclusion that type 3 polysaccharide-binding IgG antibodies after 13vPnC vaccination are biologically relevant (Figure 6-9, Sections 4.2.2 and 6.0).

Table 5-18: Antibody Response to Serotype 3: Selected Studies With Both ELISA and OPA Data

Study	Vaccination schedule (months)	Assay	Postinfant Series		Pretoddler Dose		Posttoddler Dose	
			% ≥0.35µg/mL % ≥1/8	GMC /GMT	% ≥0.35µg/mL % ≥1/8	GMC/ GMT	% ≥0.35µg/mL % ≥1/8	GMC/ GMT
004	2, 4, 6, 12	ELISA	63.5	0.49	16.1	0.15	90.5	0.94
		OPA	96.8	121	NA	NA	97.8	380
006	2, 3, 4, 12	ELISA	98.2	1.55	34.2	0.25	91.0	1.02
		OPA	99	251	NA	NA	98	188
500	3, 5, 11	ELISA	92.8	1.15	30.8	0.25	93.9	1.22
		OPA	99	176	NA	NA	100	505
3000[a]	2, 3, 4, 12	ELISA	93.7	1.20	NA	NA	NA	NA
		OPA	98	77	NA	NA	NA	NA

a. Manufacturing lot.

Source:extracted from /CLINICAL R&D/REGULATORY SUBMISSION SUMMARIES/6096A1 13vPnC Infant/13vPnC Infant EU MAA/Module 2/Module 2.7/2.7.3 Summary of Clinical Efficacy (Immunogenicity)/13vPnC Summary of Clinical Efficacy (Immunogenicity) (Table 3-47, Table 3-48).
CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/Europe Questions/APR09/007 ELISA/007_ELISA.zip
CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/Europe Questions/APR09/007 OPA/007_OPA.zip

As with most of the other serotypes, the anti-type 3 response levels decline from after the infant series to before the toddler boost. Following the toddler inoculation, the anti-type 3 responses were boosted to levels (GMC ranges of 0.94 to1.22 μg/mL) that were similar to, and overlapped, those seen after the infant series (GMC ranges of 0.49 to 1.62 μg/mL) (Table 5-20 through Table 5-23). In study 004, in which the postinfant responses were relatively lower than those seen in the other studies, the toddler dose resulted in an increased posttoddler response to levels similar to those seen across the remaining studies. Newly acquired data from study 3005 which evaluated 3 lots of the final 13vPnC formulation in the U.S. also showed an increase in type 3 anti-polysaccharide responses following the toddler boost compared with postinfant levels (Tables 5-8 through 5-17). This increase was consistently noted for all three 13vPnC groups. The proportion of responders at ≥ 0.35 μg/mL increased from 68.5% to 83.6%, 72.4% to 80.8%, and 79.1% to 88.5% from postinfant to posttoddler timepoints, respectively. The GMCs increased from 0.52 μg/mL to 0.75 μg/mL, 0.56 μg/mL to 0.71 μg/mL, and 0.61 μg/mL to 0.80 μg/mL, respectively.

As noted above, the posttoddler serotype 3 OPA responses after the toddler dose ranged from 97.8% to 100%, with associated increases in OPA GMTs for 3 of 4 studies for studies shown in Table 5-18. Recently, toddler OPA data have become available for the additional serotypes, including serotype 3, in the 7vPnC/13vPnc and 13vPnC/13vPnC groups of the 008 trial (see also Tables 7-8 and 7-9). The proportion of toddlers with an OPA titer of at least 1:8 were similarly high in the two study groups, 100% after a 4th dose of 13vPnC versus 97.8% after the first dose of 13vPnC. OPA GMTs were 428.88 (95%CI: 346.69, 530.56) in toddlers who received 13vPnC for the first time, compared to 345.33 (95%CI: 296.06, 402.80) in those receiving a 4th dose of 13vPnC. The 95%CI of the OPA GMTs overlap indicating that these estimates are not significantly different.

While the pattern for serotype 3 is different from that seen with the other serotypes in that the postbooster anti-polysaccharide responses are not strikingly higher than the postinfant responses, the levels achieved after the toddler dose are: (1) similar to the postinfant levels, (2) similar across studies, and (3) similar to the levels seen in toddlers who have received only a single 13vPnC dose.

In study 3002, 13vPnC was assessed in older children who had not previously received a PnC vaccine. Although the observed anti-serotype 3 responses were higher in this study (Table 7-2),

this reflects a general pattern across serotypes of enhanced 13vPnC immunogenicity in older children.

In conclusion, compared with 7vPnC, 13vPnC elicits significant levels of anti-serotype 3 IgG polysaccharide binding and functionally opsonophagocytic antibodies in a high proportion of infants after the primary series and after the toddler dose. Anti-polysaccharide antibody levels are similar after the toddler dose whether or not the subjects received a priming series of 13vPnC. These responses support the perspective that the 13vPnC vaccine elicits an anti-type 3 response that is capable of being boosted following subsequent vaccination or following natural exposure to the bacterium. The increase in OPA responses seen in 3 of the 4 studies in which OPA responses were also assessed suggest a maturation of the functional immune response upon boosting. Such responses have the potential to confer protection against type 3-mediated disease; particularly given that the elicited OPA activity was measured using a clinically relevant serotype 3 strain.

5.3.2.3 Serotype 5

The immunogenicity of serotype 5 was consistently demonstrated in all of the 13vPnC phase 3 trials (Table 5-20 through Table 5-23). The immune responses to serotype 5 met the primary criterion of non-inferiority in pivotal non-inferiority study 004 (Table 5-3). Data from the manufacturing scale and consistency series study 3005 showed that 90% to 94% of infants receiving 3 infant doses of the final 13vPnC formulation responded with IgG ELISA antibody concentrations ≥ 0.35 μg/mL (Table 5-9).

When comparing pre- and posttoddler data, an approximate 5-fold rise in IgG ELISA GMCs following the toddler dose was noted. Substantially higher IgG ELISA GMCs were achieved after the toddler dose, compared with those achieved at 1 month after the infant series, reflecting the induction of immunologic memory by the vaccine for this serotype (Table 5-3, Table 5-6, Table 5-12, Table 5-16).

Both pivotal non-inferiority studies demonstrated the opsonic activity of vaccine-induced antibody, with 13vPnC/7vPnC ratios of OPA GMTs greater than 20 after the infant series, and greater than 60 after the toddler dose. The proportion of infants exhibiting positive OPA titers (≥ 1:8, see also sections 4.2.2 and 6.0) was 98.9% in study 004.

Interestingly, 7vPnC also appeared to elicit moderate levels of IgG ELISA antibodies to serotype 5. However, these antibodies did not demonstrate opsonic activity, unlike those elicited by 13vPnC. In fact, after vaccination with 7vPnC, a correlation between IgG-binding antibodies and OPA responses could not be demonstrated (Figure 6-10, section 4.2.2 and 6.0). By contrast, good correlations between OPA titers and IgG ELISA GMCs were noted after administration of 13vPnC, supporting the conclusion that polysaccharide-binding IgG antibodies after 13vPnC vaccination are biologically relevant.

Compared with 7vPnC, 13vPnC elicits substantial levels of anti-serotype 5 IgG polysaccharide binding and functional opsonic antibodies in a high proportion of infants. Based on similar immune responses elicited by the effective 7vPnC against the 7 common serotypes, the immune responses elicited against serotype 5 by 13vPnC are likely to be effective for the prevention of pneumococcal disease caused by this serotype. This conclusion is supported by data from a Gambian efficacy study of 9vPnC that contained an equivalent amount of CRM_{197} conjugated

serotype 5 polysaccharide.[57, 59] In this study, the 9-valent vaccine demonstrated 88% efficacy against IPD caused by serotype 5 and the IgG ELISA antibody responses in the trial were similar to those seen in the current 13vPnC trials.

5.3.2.4 Serotype 6A

The immunogenicity of serotype 6A was consistently demonstrated in all of the 13vPnC phase 3 trials (Table 5-20 through Table 5-23). The immune responses to serotype 6A met the primary criterion of non-inferiority in the U.S. pivotal non-inferiority study 004 (Table 5-3). Data from the manufacturing consistency series study 3005 showed that 95% to 98% of infants receiving 3 infant doses of the final 13vPnC formulation responded with IgG ELISA antibody concentrations ≥ 0.35 μg/mL Table 5-9).

When comparing pre- and posttoddler data, a 5- to 10- fold rise in IgG ELISA GMCs following the toddler dose was noted. Substantially higher IgG ELISA GMCs were achieved after the toddler dose, compared with those achieved at 1 month after the infant series, reflecting the induction of immunologic memory by the vaccine for this serotype (Tables 5-3, Table 5-6, Table 5-12, Table 5-16).

The 004 pivotal non-inferiority study demonstrated the opsonic activity of vaccine-induced antibody, with 13vPnC/7vPnC ratios of OPA GMTs of approximately 10 after the infant series, and approximately 4 after the toddler dose (Table 5-3). The proportion of infants exhibiting positive OPA titers (≥ 1:8, see also sections 4.2.2 and 6.0) was 98.9% in study 004.

7vPnC also elicited high levels of IgG ELISA antibodies to serotype 6A. These antibodies exhibited a certain level of opsonic activity, in agreement with the observation that 7vPnC affords a degree of protection against 6A-specific IPD.[61] However, 13vPnC gives rise to notably greater OPA titers (GMT fold rise of approximately 10). Good correlations between OPA titers and IgG ELISA GMCs were seen after administration of 13vPnC, supporting the conclusion that polysaccharide-binding IgG antibodies after 13vPnC vaccination are biologically relevant (Figure 6-11, Section 4.2.2 and 6.0).

Compared with 7vPnC, 13vPnC elicits substantially higher levels of anti-serotype 6A IgG polysaccharide binding and functional opsonic antibodies in infants. Based on similar immune responses elicited by the effective 7vPnC against the 7 common serotypes, the immune responses elicited against serotype 6A by 13vPnC are very likely to be effective for the prevention of pneumococcal disease caused by this serotype. This is particularly likely to be the case given the already partial effectiveness against serotype 6A mediated by 7vPnC as a result of the ability of serotype 6B in this vaccine to elicit cross-reactive opsonic antibody.

5.3.2.5 Serotype 7F

The immunogenicity of serotype 7F was consistently demonstrated in all of the 13vPnC phase 3 trials (Table 5-20 through Table 5-23). The immune responses to serotype 7F met the primary criterion of non-inferiority in study 004. Data from the manufacturing consistency series study 3005 showed that over 99% of infants receiving 3 infant doses of the final 13vPnC formulation responded with IgG ELISA antibody concentrations ≥ 0.35 μg/mL.

When comparing pre- and posttoddler data, a 4- to 7-fold rise in IgG ELISA GMCs following the toddler dose was noted. Substantially higher IgG ELISA GMCs were achieved after the toddler dose, compared with those achieved at 1 month after the infant series, reflecting the induction of immunologic memory by the vaccine for this serotype (Table 5-3, Table 5-6, Table 5-12, Table 5-16).

The 004 non-inferiority study demonstrated opsonic activity of vaccine-induced antibody, with 13vPnC/7vPnC ratios of OPA GMTs ranging from 74 after the infant series to greater than 40 after the toddler dose. Some opsonic activity was noted in sera from 7vPnC recipients. This latter observation may be an artifact of the apparent high sensitivity of the serotype 7F OPA assay. Nonetheless, the OPA GMT ratios clearly demonstrate the substantially greater level of functional opsonic activity elicited by 13vPnC. In fact, after vaccination with 7vPnC, a correlation between IgG binding antibodies and OPA responses could not be demonstrated (Figure 6-12, sections 4.2.2 and 6.0). By contrast, good correlations between OPA titers and IgG ELISA GMCs were noted after administration of 13vPnC, supporting the conclusion that polysaccharide-binding IgG antibodies after 13vPnC vaccination are biologically relevant. Also, given that 7vPnC is known not to afford protection against disease caused by type 7F, a clinically meaningful OPA titer value (1:2048) was defined for the assessment of "positive" OPA responders (see section 4.2.2, Table 5-19). Using this conservative value, the proportion of infants exhibiting positive OPA responses was 90.4% in study 004 and response rates were considerably higher than those after 7vPnC, at 13.5%.

Compared with 7vPnC, 13vPnC elicits substantial levels of anti-serotype 7F IgG polysaccharide binding and functional opsonic antibodies in a high proportion of infants. Based on similar immune responses elicited by the effective 7vPnC against the 7 common serotypes, the immune

responses elicited against serotype 7F by 13vPnC are likely to be effective for the prevention of pneumococcal disease caused by this serotype.

Table 5-19: Comparison of Subjects Achieving an OPA Antibody Titer ≥ 1:2048 After Dose 3 of the Infant Series – Evaluable Infant Immunogenicity Population (6096A1-004)

	Vaccine Group (as Randomized)							
	13vPnC N[a]=94			7vPnC N[a]=89				
Serotype	n[b]	%	(95% CI[c])	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
7F	85	90.4	(82.6, 95.5)	12	13.5	(7.2, 22.4)	76.9	(66.0, 85.2)

a. N = number of subjects with a determinate OPA antibody titer to the given serotype.
b. n = Number of subjects with an antibody titer ≥1:2048 for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC – 7vPnC reference, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC – 7vPnC reference, expressed as a percentage.
Program ID: Study 6096A1-ISE/CP IMM_COMPARE_RESP_POP.SAS. Runtime ID: 10JUN2009 09:14

5.3.2.6 Serotype 19A

The immunogenicity of serotype 19A was consistently demonstrated in all of the 13vPnC phase 3 trials (Table 5-20 through Table 5-23). The immune responses to serotype 19A met the primary criterion of non-inferiority in study 004. Data from the 3005 consistency series study 3005 showed that over 98% of infants receiving 3 infant doses of the final 13vPnC formulation responded with IgG ELISA antibody concentrations ≥ 0.35 µg/mL.

When comparing pre- and posttoddler data, an approximate 10-fold rise in IgG ELISA GMCs following the toddler dose was noted. Substantially higher IgG ELISA GMCs were achieved after the toddler dose, compared with those achieved at 1 month after the infant series, reflecting the induction of immunologic memory by the vaccine for this serotype.

The pivotal 004 non-inferiority studies demonstrated the opsonic activity of vaccine-induced antibody, with 13vPnC/7vPnC ratios of OPA GMTs greater than 23 after the infant series to greater than 35 after the toddler dose. The proportion of infants exhibiting positive OPA titers (≥ 1:8, see sections 4.2.2 and 6.0) was 91.4% in study 004 after the infant series and 97.8% after the toddler dose.

Evaluation of anti-serotype 19A IgG ELISA responses elicited by 7vPnC demonstrates that this vaccine gives rise to a substantial level of specific polysaccharide binding antibodies. However, these binding antibodies do not exhibit opsonic activity as previously reported.[63] These results are concordant with epidemiological studies showing that 7vPnC has no effectiveness against serotype 19A-specific pneumococcal disease.61 By contrast, the antibodies elicited by 13vPnC demonstrate substantial levels of OPA. In fact, after vaccination with 7vPnC, a correlation between IgG-binding antibodies and OPA responses could not be demonstrated (Figure 6-13, sections 4.2.2 and 6.0). However, good correlations between OPA titers and IgG ELISA GMCs were noted after administration of 13vPnC, supporting the conclusion that polysaccharide-binding IgG antibodies after 13vPnC vaccination are biologically relevant.

In conclusion, compared with 7vPnC, 13vPnC elicits substantial levels of anti-serotype 19A IgG polysaccharide binding and functional opsonic antibodies in a high proportion of infants. Based on similar immune responses elicited by the effective 7vPnC against the 7 common serotypes,

the immune responses elicited against serotype 19A by 13vPnC are likely to be effective for the prevention of pneumococcal disease caused by this serotype.

Table 5-20: Proportion of Subjects in the 13vPnC Group Achieving Pneumococcal IgG Antibody Concentrations ≥0.35 µg/mL After the Final Dose of the Infant Series – Evaluable Infant Immunogenicity Population

Study and Groups	Country	Common Serotypes % Responders							Additional Serotypes % Responders					
		4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A
2-Dose Schedule														
2, 4 months														
6096A1-007	United Kingdom	95.3	40.2	85.6	92.5	92.8	93.6	66.7	97.2	86.0	89.3	79.2	94.4	92.7
3, 5 months														
6096A1-500	Italy	96.6	58.4	94.7	94.2	92.4	95.1	68.6	96.6	92.8	91.6	86.5	98.5	98.5
3-Dose Schedule														
2, 3, 4 months														
6096A1-006	Germany	98.2	77.5	98.6	98.9	97.2	95.8	88.7	96.1	98.2	93.0	91.9	98.6	99.3
6096A1-008	France	91.4	72.6	92.9	94.9	90.5	97.9	82.8	90.8	96.3	84.0	85.6	97.5	97.5
6096A1-009	Poland													
+P80		93.3	60.9	97.1	94.5	97.9	95.8	86.1	95.8	97.9	94.1	86.6	98.7	98.7
-P80		94.1	66.4	97.5	97.5	97.9	98.3	92.4	92.4	99.2	92.4	86.1	99.6	100.0
6096A1-3000 (+P80)	Poland													
Pilot		96.9	74.0	96.2	94.5	93.1	97.7	81.7	90.8	95.4	88.5	86.3	100.0	99.2
Man		97.7	77.3	98.4	92.9	96.1	98.4	82.8	93.0	93.7	90.6	85.2	100.0	99.2
2, 4, 6 months														
6096A1-004	United States	94.4	87.3	90.5	97.6	96.8	98.0	90.5	95.6	63.5	89.7	96.0	98.4	98.4
6096A1-501	Spain													
Postdose 2		96.7	57.3	91.9	98.5	91.8	97.8	68.1	96.3	88.0	87.4	84.4	98.5	91.1
Postdose 3		98.9	98.5	99.3	97.4	98.1	99.3	94.6	99.3	90.3	97.3	97.4	100.0	99.6

Table 5-20: Proportion of Subjects in the 13vPnC Group Achieving Pneumococcal IgG Antibody Concentrations ≥0.35 µg/mL After the Final Dose of the Infant Series – Evaluable Infant Immunogenicity Population

Study and Groups	Country	Common Serotypes % Responders							Additional Serotypes % Responders					
		4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A
6096A1-3007	Spain													
Postdose 2		92.5	27.9	89.9	91.0	88.9	100.0	55.8	96.0	73.8	86.4	80.8	94.5	92.9
Postdose 3		98.5	94.9	97.0	97.0	99.0	99.0	93.0	98.5	86.2	96.0	99.0	100.0	99.5
6096A1-3005 (+P80)	United States													
Pilot 1		97.6	94.9	95.4	99.2	97.8	97.8	91.2	97.8	68.5	94.2	98.1	99.8	98.1
Pilot 2		95.5	89.5	95.5	99.0	95.8	97.5	88.1	97.0	72.4	90.3	95.5	99.0	99.0
Man		98.5	94.4	96.5	98.2	98.0	99.2	87.2	98.5	79.1	94.4	98.2	99.7	98.7
6096A1-3008	Canada	97.1	93.1	95.3	98.2	96.4	98.5	90.2	95.7	79.6	87.0	96.4	98.6	97.8
6, 10, 14 Weeks														
6096A1-011	India	97.0	80.4	89.0	87.7	94.0	92.7	88.8	96.1	79.4	87.6	88.5	96.0	99.0

Abbreviations: 13v = 13vPnC; Man = manufacturing; +P80 = formulated with polysorbate 80; -P80 = formulated without polysorbate 80.
Note: For number of subjects with determinate antibody concentration for the specified serotype, see tables by individual serotype.
ID: 10 Nov 2008

Table 5-21: Pneumococcal IgG Geometric Mean Concentrations (µg/mL) in the 13vPnC Group After the Final Dose of the Infant Series – Evaluable Infant Immunogenicity Population

		Common Serotypes GMC							Additional Serotypes GMC					
Study and Groups	**Country**	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**	**1**	**3**	**5**	**6A**	**7F**	**19A**
2-Dose														
Schedule														
2, 4 months														
6096A1-007	United Kingdom	1.37	0.26	0.87	1.83	1.37	2.38	0.53	1.69	0.63	0.95	0.86	2.14	1.90
3, 5 months														
6096A1-500	Italy	2.38	0.41	1.68	2.84	1.72	3.42	0.61	2.30	1.15	1.27	1.17	2.06	2.87
3-Dose														
Schedule														
2, 3, 4 months														
6096A1-006	Germany	2.18	0.98	1.65	4.14	1.94	1.73	1.26	1.83	1.55	1.31	1.33	2.59	3.26
6096A1-008	France	1.29	0.74	1.15	2.74	1.42	1.55	0.92	1.21	1.25	0.93	0.94	1.93	2.10
6096A1-009	Poland													
+P80		1.47	0.51	1.46	2.37	1.84	1.46	0.93	1.39	1.50	1.26	0.99	1.98	2.68
-P80		1.53	0.57	1.51	2.48	1.87	1.75	1.11	1.48	1.62	1.30	1.04	1.89	2.94
6096A1-3000	Poland													
Pilot (+P80)		1.55	0.83	1.21	2.30	1.51	1.64	0.92	1.29	1.21	1.00	1.05	2.14	2.31
Man (+P80)		2.09	0.80	1.28	2.15	1.60	1.60	0.82	1.42	1.20	0.96	0.87	2.00	2.19
2, 4, 6 months														
6096A1-004	United States	1.31	2.10	0.98	4.74	1.37	1.85	1.33	2.03	0.49	1.33	2.19	2.57	2.07
6096A1-501	Spain													
Postdose 2		1.89	0.42	1.49	3.83	1.59	2.86	0.54	1.91	0.79	1.00	1.08	1.85	2.35
Postdose 3		2.33	3.88	1.71	6.17	2.29	2.63	2.14	3.04	0.97	1.93	3.16	4.03	3.09
6096A1-3007	Spain													
Postdose 2		1.55	0.21	1.15	1.94	1.30	2.98	0.40	1.87	0.54	0.88	0.81	1.51	1.52
Postdose 3		2.32	2.59	1.51	4.51	1.86	2.46	1.67	2.95	0.85	1.83	3.08	3.41	2.50
6096A1-3005	United States													
13v Pilot 1		1.33	2.89	1.05	4.97	1.30	1.85	1.24	1.62	0.52	1.35	2.40	2.54	1.85

Table 5-21: Pneumococcal IgG Geometric Mean Concentrations (µg/mL) in the 13vPnC Group After the Final Dose of the Infant Series – Evaluable Infant Immunogenicity Population

		Common Serotypes GMC							Additional Serotypes GMC					
Study and Groups	**Country**	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**	**1**	**3**	**5**	**6A**	**7F**	**19A**
13v Pilot 2		1.34	2.15	1.11	5.13	1.34	2.07	1.27	1.81	0.56	1.05	2.10	2.52	2.00
13v Man		1.75	2.54	1.11	5.18	1.48	2.59	1.03	1.91	0.61	1.35	2.12	2.67	1.88
6096A1-3008	Canada	1.46	2.16	1.12	5.43	1.37	2.18	1.15	1.82	0.63	0.90	1.92	2.26	2.00
6, 10, 14 Weeks														
6096A1-011	India	2.01	1.57	1.26	2.32	1.45	1.93	1.33	1.99	0.60	1.10	1.55	2.26	2.43

Abbreviations: 13v = 13vPnC; GMC = geometric mean concentration; Man = manufacturing; +P80 = formulated with polysorbate 80; -P80 = formulated without polysorbate 80.

Note: For number of subjects with determinate antibody concentration for the specified serotype, see tables by individual serotype.

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Table 5-22: Proportion of Subjects in the 13vPnC Group Achieving Pneumococcal IgG Antibody Concentrations ≥0.35 µg/mL Before or After the Toddler Dose – Evaluable Toddler Immunogenicity Population

	Common Serotypes % Responders							Additional Serotypes % Responders					
Study and Groups	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**	**1**	**3**	**5**	**6A**	**7F**	**19A**
2-Dose Schedule													
3, 5 months													
6096A1-007													
Pretoddler	24.7	74.4	44.0	92.0	13.2	67.0	37.1	50.0	12.6	78.4	79.1	71.4	86.8
Posttoddler	99.0	98.0	98.0	100.0	97.1	98.1	98.1	100.0	88.2	100.0	98.0	100.0	100.0
6096A1-500													
Pretoddler	66.9	76.3	70.5	94.4	53.0	92.4	32.3	83.4	30.8	87.3	86.4	90.7	96.2
Posttoddler	100.0	100.0	100.0	99.6	99.2	98.8	99.2	99.6	93.9	100.0	99.6	99.6	100.0
3-Dose Schedule													
2, 3, 4 months													
6096A1-006													
Pretoddler	63.9	88.7	66.4	94.9	48.0	83.7	48.7	72.9	34.2	82.5	84.1	92.4	95.3
Posttoddler	99.3	99.3	100.0	98.9	99.6	98.6	98.2	98.9	91.0	100.0	98.2	98.9	100.0
6096A1-008[a]													
Pretoddler	45.6	91.1	61.9	94.5	34.7	77.0	36.7	64.4	20.3	82.2	85.7	89.5	92.0
Posttoddler (13v/13v)	100.0	99.6	100.0	99.6	99.6	97.9	99.6	100.0	94.8	100.0	100.0	100.0	100.0
Pretoddler	62.7	87.0	63.6	94.1	50.8	66.1	47.5	2.6	7.0	58.9	51.7	7.7	79.5
Posttoddler (7v/13v)	99.1	98.1	100.0	99.1	98.2	97.3	99.1	95.5	93.8	90.1	89.9	100.0	100.0

Table 5-22: Proportion of Subjects in the 13vPnC Group Achieving Pneumococcal IgG Antibody Concentrations ≥0.35 µg/mL Before or After the Toddler Dose – Evaluable Toddler Immunogenicity Population

	Common Serotypes % Responders							Additional Serotypes % Responders					
Study and Groups	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**	**1**	**3**	**5**	**6A**	**7F**	**19A**
6096A1-009													
Pretoddler													
+P80	44.1	72.5	49.8	92.9	41.0	80.4	29.9	72.7	14.3	80.1	66.2	89.4	91.1
-P80	51.7	78.6	56.7	94.5	44.1	86.5	34.3	71.8	15.8	81.2	76.8	89.5	90.3
Posttoddler													
+P80	99.6	99.6	99.6	99.6	100.0	99.1	98.7	100.0	95.1	99.6	99.6	100.0	100.0
-P80	99.6	99.2	100.0	99.6	99.6	98.7	99.6	99.2	94.5	100.0	100.0	100.0	100.0
2, 4, 6 months													
6096A1-004													
Pretoddler	46.7	80.8	56.8	93.0	45.9	79.0	54.1	79.5	16.1	83.8	90.4	89.9	85.6
Posttoddler	99.1	99.6	99.1	98.7	98.7	100.0	99.6	100.0	90.5	99.6	100.0	99.6	100.0
6096A1-501													
Posttoddler	99.2	99.6	100.0	100.0	99.6	99.6	99.1	98.7	92.2	99.1	99.1	98.8	100.0

Abbreviations: +P80 = formulated with polysorbate 80; -P80 = formulated without polysorbate 80; 13v/13v=13vPnC for the infant series and for the toddler dose; 7v/13v=7vPnC for the infant series and 13vPnC for the toddler dose.

Note: For number of subjects with determinate antibody concentration for the specified serotype, see tables by individual serotype.

a. Subjects in study 008 who received 13vPnC at the toddler dose received either 13vPnC or 7vPnC for the infant series.

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Table 5-23: Pneumococcal IgG Geometric Mean Concentrations (µg/mL) in the 13vPnC Group Before or After the Toddler Dose – Evaluable Toddler Immunogenicity Population

	Common Serotypes GMC							Additional Serotypes GMC					
Study and Groups	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**	**1**	**3**	**5**	**6A**	**7F**	**19A**
2-Dose Schedule													
3, 5 months													
6096A1-007[a]													
Pretoddler	0.21	0.77	0.29	1.34	0.20	0.60	0.24	0.39	0.14	0.59	0.81	0.56	1.01
Posttoddler	3.52	7.67	2.46	11.32	2.14	7.25	3.13	5.60	0.98	3.68	6.31	4.06	11.33
6096A1-500[a]													
Pretoddler	0.53	0.61	0.48	2.03	0.35	0.94	0.26	0.68	0.25	0.88	0.81	0.76	1.20
Posttoddler	4.77	10.00	3.02	10.30	2.83	9.01	3.43	5.76	1.22	3.59	6.78	4.31	9.81
3-Dose Schedule													
2, 3, 4 months													
6096A1-006[a]													
Pretoddler	0.46	0.97	0.46	2.20	0.33	0.68	0.33	0.52	0.25	0.74	0.76	0.99	1.28
Posttoddler	4.16	9.14	2.75	8.34	2.79	5.99	3.36	4.25	1.02	3.56	5.88	4.79	9.58
6096A1-008[a,b]													
Pretoddler	0.3	1.0	0.4	2.0	0.3	0.7	0.3	0.4	0.2	0.8	0.9	0.8	1.5
Posttoddler (13v/13v)	4.2	9.0	2.6	9.5	2.3	5.2	3.0	4.1	1.0	3.3	6.1	4.5	9.5
Pretoddler	0.5	0.9	0.4	2.4	0.3	0.6	0.3	0.0	0.1	0.4	0.4	0.1	0.9
Posttoddler (7v/13v)	4.0	10.3	2.3	7.8	2.4	3.7	3.1	1.8	1.3	1.1	2.6	3.7	5.3

Table 5-23: Pneumococcal IgG Geometric Mean Concentrations (µg/mL) in the 13vPnC Group Before or After the Toddler Dose – Evaluable Toddler Immunogenicity Population

	Common Serotypes GMC							Additional Serotypes GMC					
Study and Groups	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**	**1**	**3**	**5**	**6A**	**7F**	**19A**
6096A1-009[a]													
Pretoddler													
+P80	0.35	0.58	0.38	1.82	0.32	0.67	0.21	0.54	0.14	0.67	0.53	0.81	1.02
-P80	0.37	0.68	0.41	2.17	0.32	0.76	0.25	0.56	0.18	0.73	0.63	0.84	1.02
Posttoddler													
+P80	5.25	9.89	3.01	11.72	3.40	9.63	3.88	6.03	1.09	3.80	7.48	5.36	13.20
-P80	5.38	10.65	3.10	11.95	3.10	10.27	4.15	6.11	1.16	3.98	8.19	4.95	13.02
2, 4, 6 months													
6096A1-004[a]													
Pretoddler	0.35	0.78	0.39	1.89	0.34	0.73	0.38	0.64	0.15	0.77	0.83	0.83	0.92
Posttoddler	3.73	11.53	2.62	9.11	3.20	6.60	5.07	5.06	0.94	3.72	8.20	5.67	8.55
6096A1-501													
Posttoddler	4.97	11.88	3.44	11.37	3.96	8.04	5.07	4.79	1.07	3.90	7.07	5.78	11.64

Abbreviations: GMC = geometric mean concentration; +P80 = formulated with polysorbate 80; -P80 = formulated without polysorbate 80.
Note: For number of subjects with determinate antibody concentration for the specified serotype, see tables by individual serotype.
a. Population includes only those subjects with determinate antibody concentrations at the pretoddler and posttoddler dose time points.
b. Subjects in study 008 who received 13vPnC at the toddler dose received either 13vPnC or 7vPnC for the infant series.
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6.0 INTERPRETATION OF THE RELATIONSHIP BETWEEN IgG ELISA AND FUNCTIONAL OPA RESPONSES

WHO TRS 927 annex 2 states that: "Opsonophagocytic activity as measured by opsonophagocytic assay after a three-dose priming series is required to demonstrate the functionality of antibodies" as a part of dossier for licensure of a new conjugate vaccine. The relationship between the IgG ELISA and OPA responses elicited against the 7 common serotypes by 7vPnC has been established for some time.[46, 47] In infants, following immunization, a relationship exists between antipolysaccharide IgG-binding antibody and functional OPA antibody for each of these types. Hence, binding IgG antibody concentrations reflect biologically significant activity.

However, this relationship has not yet been established for the additional 6 serotypes present in 13vPnC. In fact, data from the phase 3 studies reported here show that 7vPnC elicits substantial levels of IgG ELISA responses to the added serotypes 5, 6A, and 19A. Surveillance data obtained after the introduction of 7vPnC suggests that this vaccine may exhibit partial effectiveness against serotype 6A, but not against serotypes 5 or 19A.[61]The basis for this observation may be found in the functional OPA antibody responses to these serotypes observed in recipients of 7vPnC.

ELISA/OPA Associations

The association between anticapsular polysaccharide IgG ELISA concentrations and functional OPA antibody levels are presented in Figures 6-1 through 6-13. Each panel presents data for a single 13vPnC serotype and incorporates data obtained after the infant series in studies 003, 004, 006, 500 and 3000, using all samples for which both IgG concentrations and OPA titers were determined. Each symbol represents data from a single study subject, either a recipient of 7vPnC (red circles) or a recipient of 13vPnC (green triangles). IgG concentration values are plotted on the x-axis and OPA titers are on the y-axis on the log(e)-scale. The vertical line designates the anti-polysaccharide IgG concentrations of 0.35 µg/mL used as the primary comparator point for assessment of immune responses between the 2 vaccines. The horizontal line represents the OPA titer that is the cut-off for a positive OPA response. This value is 1:8 for all serotypes, except serotype 7F for which the cut-off is a titer of 1:2048 (see section 4.2.2).

Although 7vPnC elicits some functional activity against serotype 6A, the OPA elicited against serotypes 5 and 19A is negligible. In contrast to the immune responses against the 7 common serotypes seen after vaccination with 7vPnC, there is only a partial association between IgG ELISA and OPA responses for serotype 6A, and there is no association between polysaccharide-binding IgG antibody and OPA antibody for each of the remaining 5 additional serotypes.

On the other hand, 13vPnC elicits substantially greater levels of opsonic antibody activity against the 6 additional serotypes compared with 7vPnC. The OPA GMTs are approximately 10- to 100-fold greater for these serotypes after both the infant series and the toddler dose. Importantly, a clear association is apparent between IgG ELISA responses and OPA responses following vaccination with 13vPnC for each of the 6 additional serotypes, as well as for the 7 common serotypes. Therefore, the conclusions and observations reported in the following sections are based on both IgG ELISA and OPA antibody data. The demonstrated association between anticapsular polysaccharide IgG ELISA and OPA responses for all 13 serotypes after 13vPnC vaccination supports the concept that the IgG concentrations, measured against each serotype following administration of 13vPnC, represent biologically active antipneumococcal antibodies.

Common Serotypes

Figure 6-1: ELISA:OPA Association for Serotype 4

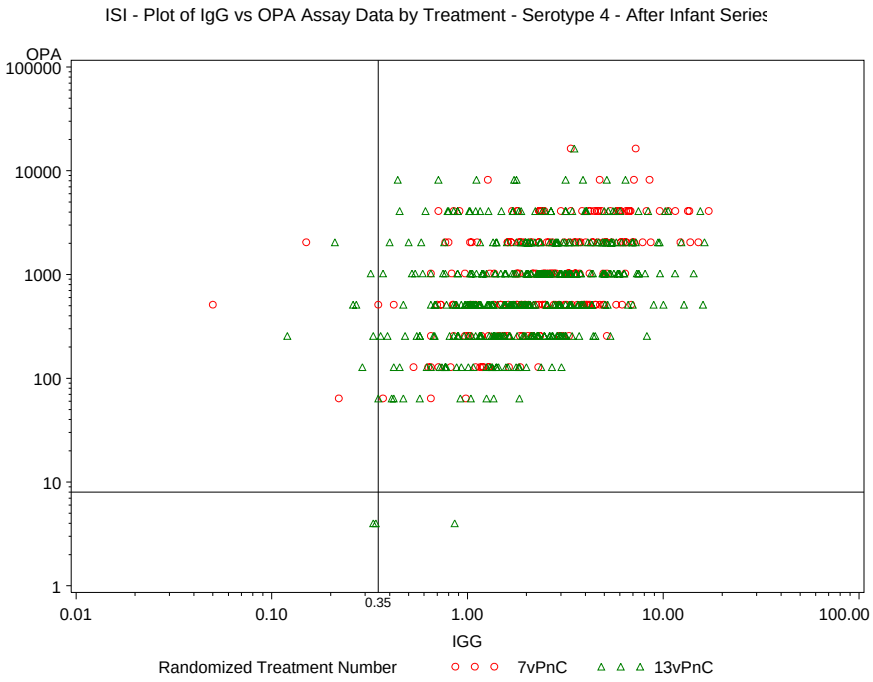


Figure 6-2: ELISA:OPA Association for Serotype 6B

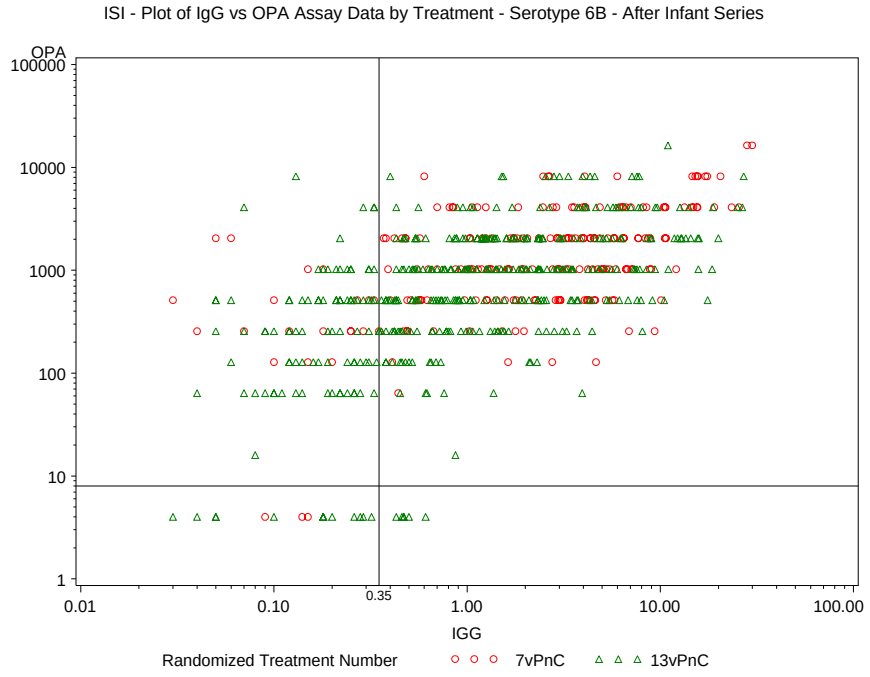


Figure 6-3: ELISA:OPA Association for Serotype 9V

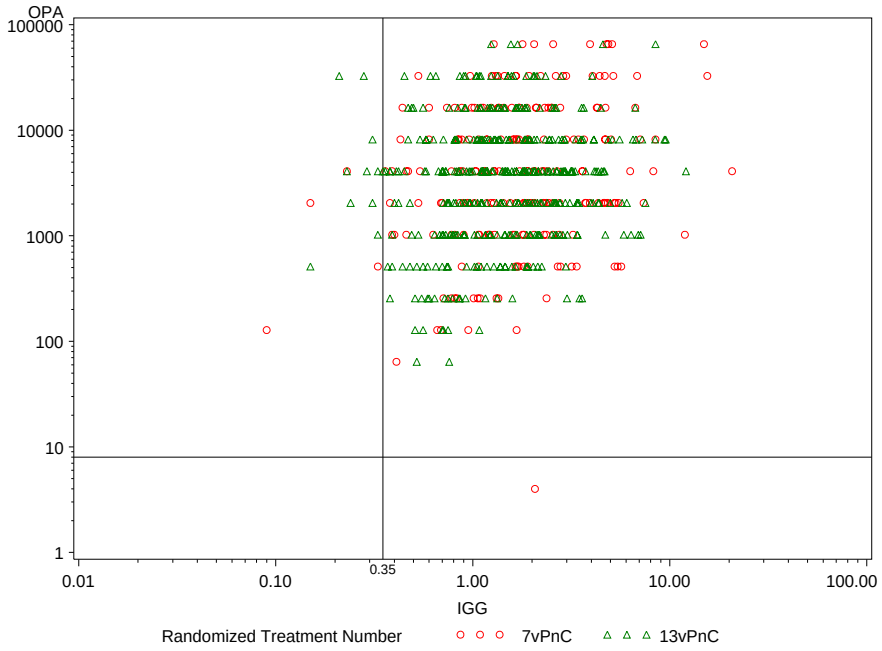


Figure 6-4: ELISA:OPA Association for Serotype 14

Figure 6-5: ELISA:OPA Association for Serotype 18C

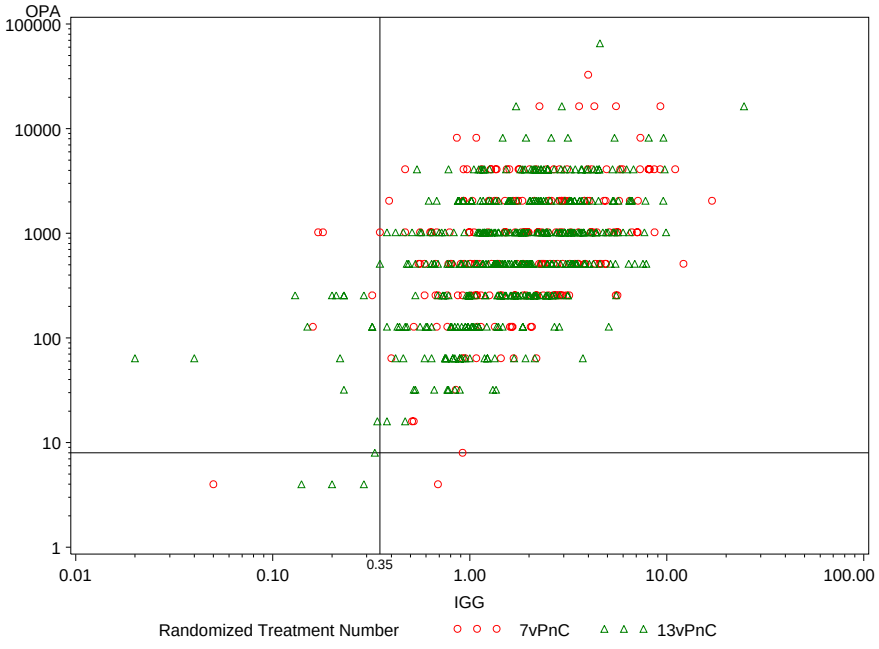


Figure 6-6: ELISA:OPA Association for Serotype 19F

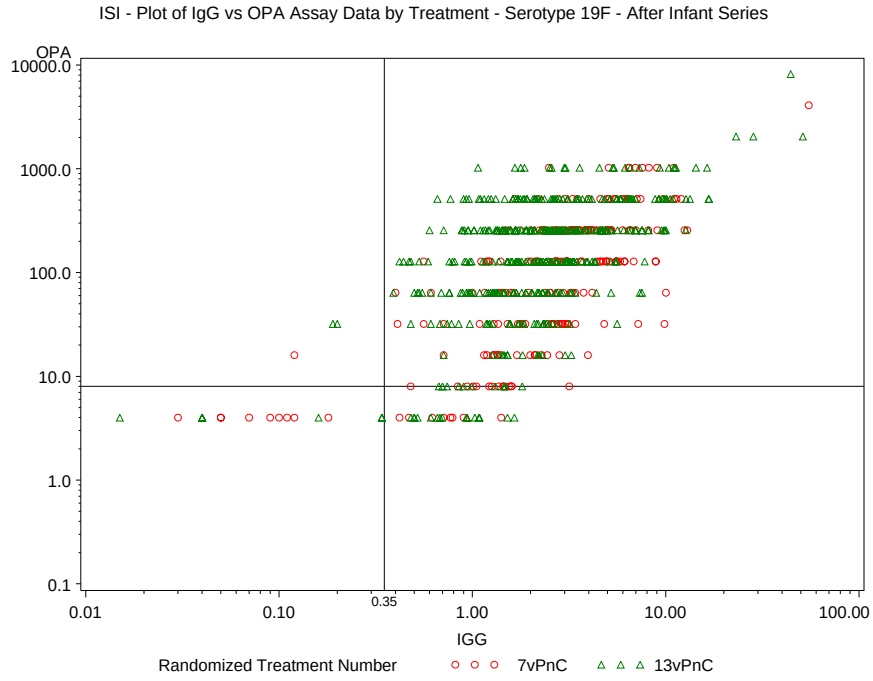
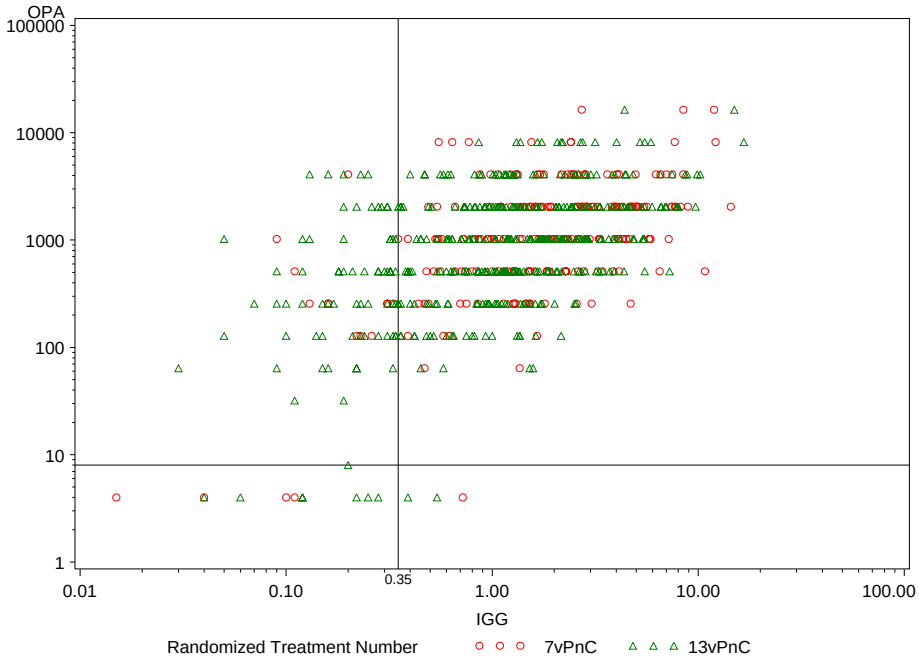


Figure 6-7: ELISA:OPA Association for Serotype 23F



Additional Serotypes

Figure 6-8: ELISA:OPA Association for Serotype 1

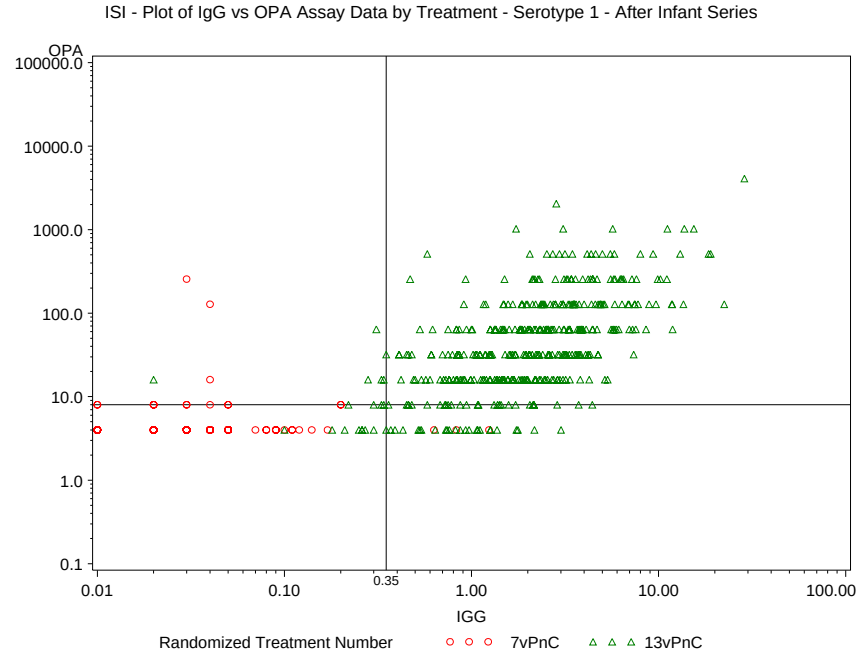


Figure 6-9: ELISA:OPA Association for Serotype 3

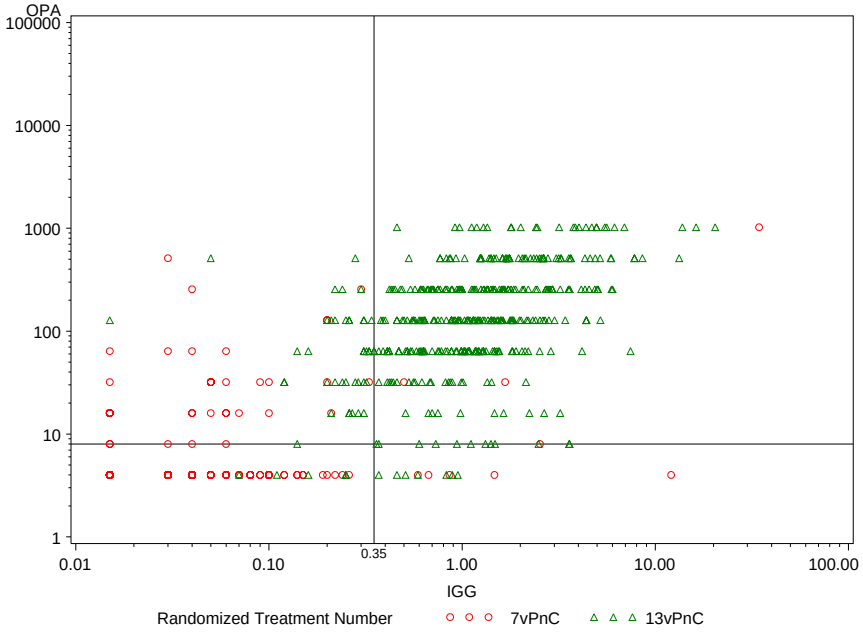


Figure 6-10: ELISA:OPA Association for Serotype 5

ISI - Plot of IgG vs OPA Assay Data by Treatment - Serotype 5 - After Infant Series

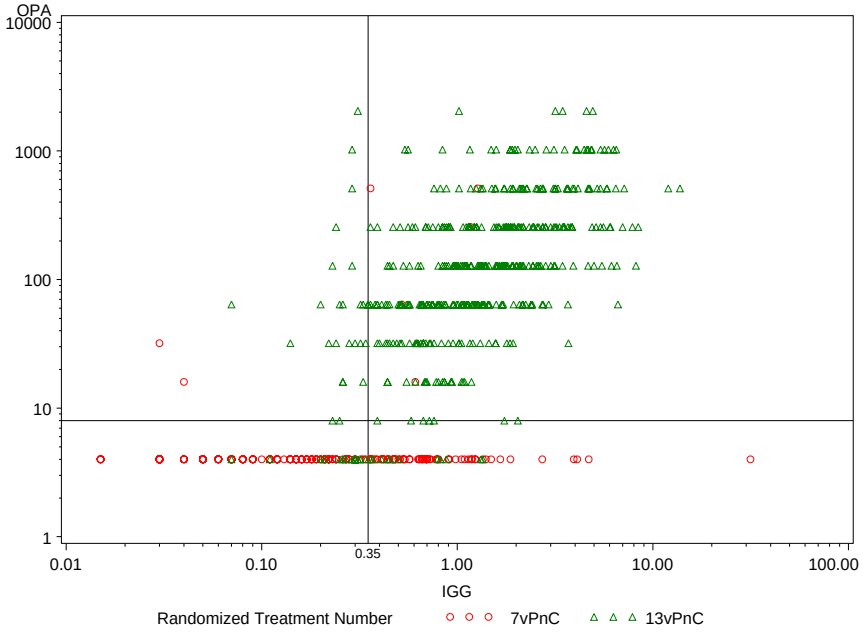


Figure 6-11: ELISA:OPA Association for Serotype 6A

ISI - Plot of IgG vs OPA Assay Data by Treatment - Serotype 6A - After Infant Series

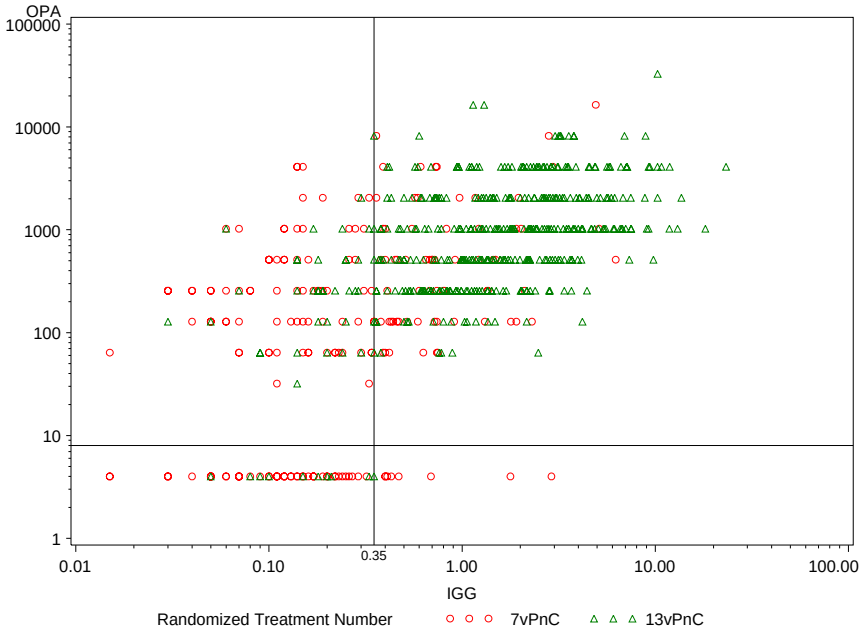
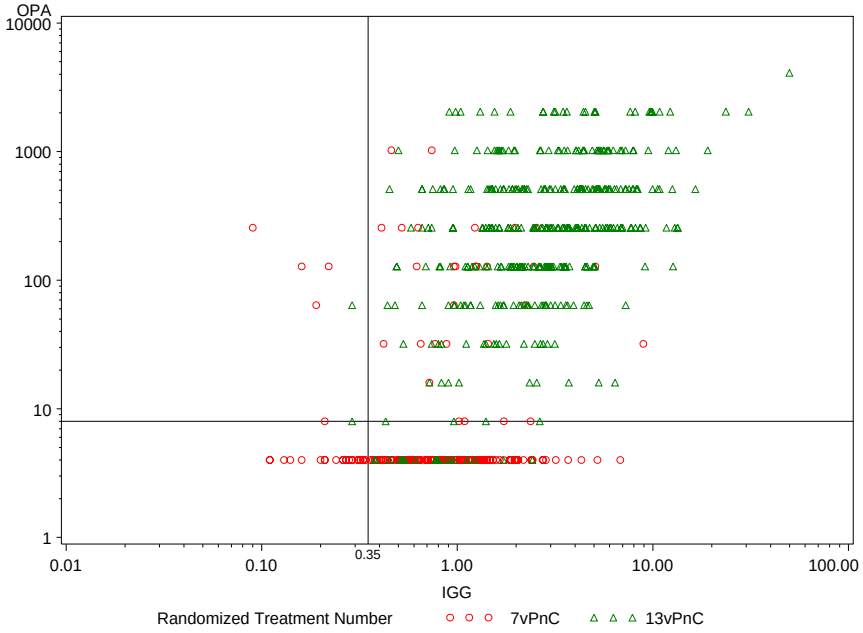


Figure 6-12: ELISA:OPA Association for Serotype 7F

Figure 6-13: ELISA:OPA Association for Serotype 19A



From the ELISA:OPA plots, it can be concluded that there is positive association of serotype specific ELISA with the OPA assay in the case of 13vPnC subjects across all 13 serotypes, and also for 7vPnC subjects for the original 7 serotypes.

To further assess the association between clinically meaningful anti-polysaccharide IgG responses and functional OPA responses, we evaluated the pattern in evaluable ELISA and OPA responses following the infant series for all available data from studies 003, 004, 006, 500, and 3000. As can be noted from the data in Table 6-1, most subjects exhibited a positive response to vaccination following the infant series for both ELISA and OPA for each of the 7 common serotypes. As expected, 13vPnC is comparable to 7vPnC in this respect, for the common serotypes.

(Note that, for serotypes 6B and 23F, a proportion of individuals in both vaccine groups that exhibit OPA activity, do not exhibit positive polysaccharide-binding ELISA antibody responses. Given that this observation is similar between the 2 vaccine groups, it can be concluded that the OPA assay for these serotypes [using the 1:8 titer responder cut-off] is a clinically more sensitive assay and correspondingly the IgG level associated with protection could be lower than other serotypes.)

Table 6-1: Frequencies of Positive Pneumococcal IgG and OPA Responders After the Infant Series for the Common Serotypes – Evaluable Infant Immunogenicity Population

		Positive ELISA (≥0.35 µg/mL)			
		13vPnC		7vPnC	
Serotype	Positive OPA[a]	Yes n (%)	No n (%)	Yes n (%)	No n (%)
4	Yes	**400 (97.6)**	7 (1.7)	**215 (98.6)**	3 (1.4)
	No	1 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)
6B	Yes	**310 (74.3)**	88 (21.1)	**196 (89.9)**	19 (8.7)
	No	6 (1.4)	13 (3.1)	0 (0.0)	3 (1.4)
9V	Yes	**395 (97.5)**	10 (2.5)	**205 (97.6)**	4 (1.9)
	No	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
14	Yes	**391 (95.4)**	19 (4.6)	**208 (97.7)**	5 (2.3)
	No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18C	Yes	**400 (95.7)**	15 (3.6)	**212 (97.2)**	4 (1.8)
	No	0 (0.0)	3 (0.7)	1 (0.5)	1 (0.5)
19F	Yes	**389 (94.2)**	2 (0.5)	**194 (91.5)**	1 (0.5)
	No	15 (3.6)	7 (1.7)	8 (3.8)	9 (4.2)
23F	Yes	**337 (80.8)**	71 (17.0)	**196 (92.0)**	12 (5.6)
	No	2 (0.5)	7 (1.7)	1 (0.5)	4 (1.9)

a. Titer ≥ 1:8.

Program ID: Study 6096A1-ISE/CP IMM_PNEUM_IGG_OPA_COMP_FREQ.SAS. Runtime ID: 18MAR2009 13:56 (Modified)

Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/Europe Questions/MAR09/SWE Q42 & BEL Q104-106/Q42_1.zip

The pattern in responses following the infant series for the additional 6 serotypes is more complex (Table 6-2). For the 13vPnC group, most subjects had a positive response to vaccination following the infant series for both anti-polysaccharide IgG ELISA and OPA.

For serotype 6A, the OPA responses in 7vPnC vaccinated subjects are not unexpected given the known ability of serotype 6B to elicit a cross-reactive functional antibody response to type 6A.[62] However, the pattern of ELISA and OPA responses is shifted toward a pattern of joint ELISA:OPA responses in the 13vPnC group, likely due to the type 6A immunogen contained in the 13-valent vaccine (Table 6-2 and Figure 6-11 and section 5.3.4) .

For serotype 19A, 71% of subjects vaccinated with 7vPnC exhibited an ELISA response, but without an associated OPA response (Table 6-2 and Figure 6-13 and section 5.3.6). This is likely due to a known non-functional cross-reactive anti-19A polysaccharide-binding response elicited by type 19F.[63] By contrast, the 13vPnC elicits antibodies that are both polysaccharide-binding and have functional OPA activity.

Of interest, these ELISA and OPA findings for 6A and 19A are also consistent with the post-marketing matched case-control studies and CDC ABC surveillance where Prevnar showed statistically significant protection against 6A but not against 19A IPD. [37, 38, 39, 64]
Finally, for serotype 5, 32% of subjects exhibited an ELISA response in the 7vPnC vaccinated group; however this response was without functional OPA activity in contrast to the functional activity exhibited by the 13vPnC recipients (Table 6-2 and Figure 6-10 and section 5.3.3).

Table 6-2: Frequencies of Positive Pneumococcal IgG and OPA Responders After the Infant Series for the Additional Serotypes – Evaluable Infant Immunogenicity Population

		Positive ELISA (≥ 0.35 µg/mL)			
		13vPnC		7vPnC	
Serotype	Positive OPA[a]	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Additional					
1	Yes	**370 (89.8)**	9 (2.2)	**0 (0.0)**	15 (7.0)
	No	25 (6.1)	8 (1.9)	3 (1.4)	197 (91.6)
3	Yes	**362 (87.7)**	39 (9.4)	**4 (1.9)**	38 (18.0)
	No	7 (1.7)	5 (1.2)	5 (2.4)	164 (77.7)
5	Yes	**411 (89.3)**	24 (5.2)	**5 (2.6)**	2 (1.0)
	No	11 (2.4)	14 (3.0)	62 (32.0)	125 (64.4)
6A	Yes	**370 (89.4)**	34 (8.2)	**70 (33.3)**	81 (38.6)
	No	1 (0.2)	9 (2.2)	8 (3.8)	51 (24.3)
7F	Yes[b]	**373 (91.0)**	1 (0.2)	**0 (0.0)**	19 (9.2)
	No	35 (8.5)	1 (0.2)	4 (1.9)	184 (88.9)
19A	Yes	**374 (94.2)**	2 (0.5)	**29 (14.5)**	5 (2.5)
	No	21 (5.3)	0 (0.0)	141 (70.5)	25 (12.5)

a. Titer ≥ 1:8 (except for serotype 7F).
b. Positive OPA titer cut-off for type 7F is 1:2048.
Program ID: Study 6096A1-ISE/CP IMM_PNEUM_IGG_OPA_COMP_FREQ.SAS. Runtime ID: 20APR2009 16:59
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/ Europe Questions/MAR09/SWE Q42 & BEL Q104-106/Q42_5.zip

Similar patterns are observed when each study is examined individually (data not shown.)

The data analyses presented in these tables, along with the analyses of the ELISA:OPA plots (above), demonstrate that the anti-polysaccharide IgG ELISA responses are positively correlated with the functional OPA responses in 13vPnC recipients across all 13 serotypes, and in 7vPnC recipients for the 7 common serotypes.

7.0 APPROACHES TO THE TRANSITION FROM PREVNAR (7VPNC) TO 13VPNC

7.1 13vPnC vaccination of naïve older infants and young children

13vPnC was assessed for immunogenicity in populations of older infants and young children who had not previously been immunized with a pneumococcal vaccine. Study 3002 was designed to include 3 age groups to define the schedule for catch-up vaccination. The subjects in group 1 received 3 doses of the vaccine, with the first dose being administered at 7 to <12 months of age, the second dose 4 to 6 weeks later, and the third dose at 12 to 16 months of age (at least 28 days after dose 2). Subjects in group 2 received the initial dose at 12 to <24 months with a subsequent dose given 56 to 70 days later. Finally, subjects in group 3 were given only a single dose of the vaccine at 24 to <72 months of age. The immunogenicity data, obtained 1 month after the last dose for each of the "catch-up" vaccination regimens, showed good antibody responses to all vaccine serotypes, with GMCs at least comparable to those achieved after a 3-dose infant series (Table 7-1 and Table 7-2). Upon completion of vaccination, the proportion of responders at an IgG concentration ≥ 0.35 μg/mL was generally greater than 92% for all serotypes in all 3 study groups, with the sole exception of serotype 14 in group 3 (88.1%). The proportion of responders for serotype 6B exceeded 98% for all groups.
A proposed vaccination schedule for naïve older children is shown in Table 7-3.

Table 7-1: Immunogenicity Data in Older Populations (Study 6096A1-3002) – Common Serotypes – Evaluable Immunogenicity Populations

Test	Vaccine Group[a]	4	95% CI	6B	95% CI	9V	95% CI	14	95% CI	18C	95% CI	19F	95% CI	23F	95% CI
% Resp ≥0.35 µg/mL	13v Group 1	100.0	(95.7, 100.0)	98.8	(93.5, 100.0)	98.8	(93.5, 100.0)	100.0	(95.7, 100.0)	100.0	(95.7, 100.0)	97.6	(91.7, 99.7)	98.8	(93.5, 100.0)
	13v Group 2	100.0	(96.7, 100.0)	100.00	(96.7, 100.0)	99.0	(94.8, 100.0)	100.0	(96.6, 100.0)	100.0	(96.7, 100.0)	100.0	(96.7, 100.0)	92.7	(86.2, 96.8)
	13v Group 3	99.3	(96.4, 100.0)	99.3	(96.3, 100.0)	98.6	(95.2, 99.8)	88.1	(81.5, 93.1)	98.7	(95.3, 99.8)	98.0	(94.2, 99.6)	93.4	(88.2, 96.8)
GMC[b] µg/mL	13v Group 1	3.63	(3.11, 4.23)	4.77	(3.90, 5.84)	2.56	(2.21, 2.96)	8.04	(6.95, 9.30)	2.77	(2.39, 3.23)	2.88	(2.35, 3.54)	2.16	(1.82, 2.55)
	13v Group 2	4.28	(3.78, 4.86)	3.38	(2.81, 4.06)	3.08	(2.69, 3.53)	6.45	(5.48, 7.59)	3.71	(3.29, 4.19)	3.07	(2.68, 3.51)	1.98	(1.64, 2.39)
	13v Group 3	3.37	(2.95, 3.85)	3.41	(2.80, 4.16)	2.67	(2.32, 3.07)	2.24	(1.71, 2.93)	2.56	(2.17, 3.03)	2.53	(2.14, 2.99)	1.55	(1.31, 1.85)

Note: N, or the number of subjects with determinate IgG antibody concentrations, ranged from 83 to 84 in group 1, 104 to 110 in group 2, and 135 to 151 in group 3 for the common serotypes.

Abbreviations: 13v = 13vPnC; CI = confidence interval; GMC = geometric mean concentration; Resp = responders.

a. Vaccine administration per group was as follows: Group 1 – (3 doses) 7 to <12 months, 28 to 42 days after vaccination 1, and 12 to 16 months (at least 28 days after vaccination 2). Group 2 – (2 doses) 12 to <24 months and 56 to 70 days after vaccination 1. Group 3 – (1 dose) 24 to <72 months.

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. CIs for GMCs are back-transformations of CIs based on the Student t distribution for the mean logarithm of the concentrations.

ID: 6 Oct 2008

Table 7-2: Immunogenicity Data in Older Populations (Study 6096A1-3002) – Additional Serotypes – Evaluable Immunogenicity Population

Test	Vaccine Group[a]	1	95% CI	3	95% CI	5	95% CI	6A	95% CI	7F	95% CI	19A	95% CI
% Resp ≥0.35 µg/mL	13v Group 1	100.0	(95.7, 100.0)	98.8	(93.5, 100.0)	97.6	(91.7, 99.7)	100.0	(95.7, 100.0)	100.0	(95.7, 100.0)	100.0	(95.7, 100.0)
	13v Group 2	100.0	(96.6, 100.0)	100.0	(96.6, 100.0)	99.1	(94.9, 100.0)	98.2	(93.6, 99.8)	100.0	(96.6, 100.0)	100.0	(96.7, 100.0)
	13v Group 3	96.6	(92.3, 98.9)	97.3	(93.3, 99.3)	98.7	(95.3, 99.8)	100.0	(97.6, 100.0)	99.3	(96.1, 100.0)	100.0	(97.6, 100.0)
GMC[b] µg/mL	13v Group 1	2.88	(2.44, 3.39)	1.94	(1.68, 2.24)	2.85	(2.34, 3.46)	3.72	(3.12, 4.45)	5.30	(4.54, 6.18)	4.77	(4.28, 5.33)
	13v Group 2	2.74	(2.37, 3.16)	1.86	(1.60, 2.15)	2.16	(1.89, 2.47)	2.62	(2.25, 3.06)	5.99	(5.40, 6.65)	4.94	(4.31, 5.65)
	13v Group 3	1.78	(1.52, 2.08)	1.42	(1.23, 1.64)	2.33	(2.05, 2.64)	2.96	(2.52, 3.47)	4.92	(4.26, 5.68)	6.03	(5.22, 6.97)

Note: N, or the number of subjects with determinate IgG antibody concentrations, ranged from 83 to 84 in group 1, 107 to 110 in group 2, and 142 to 152 in group 3 for the additional serotypes.

Abbreviations: 13v = 13vPnC; CI = confidence interval; GMC = geometric mean concentration; Resp = responders.

a. Vaccine administration per group was as follows: Group 1 – (3 doses) 7 to <12 months, 28 to 42 days after vaccination 1, and 12 to 16 months (at least 28 days after vaccination 2). Group 2 – (2 doses) 12 to <24 months and 56 to 70 days after vaccination 1. Group 3 – (1 dose) 24 to <72 months.

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. CIs for GMCs are back-transformations of CIs based on the Student t distribution for the mean logarithm of the concentrations.

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Based on the findings of study 6096A1-3002, the following schedule of immunization is proposed for 13vPnC immunization of previously unvaccinated children ≥ 7 months of age:

Table 7-3: Vaccination Schedule for Unvaccinated Children ≥ 7 Months of Age

Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	**3***
12-23 months of age	**2†**
≥24 months through 5 years of age (prior to the 6th birthday)	**1**

* 2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months.
† 2 doses at least 2 months apart.

7.2 Transition from Prevnar (7vPnC) to 13vPnC in infants previously vaccinated with 3 or fewer doses of Prevnar

Given that the 7 common serotype conjugates are identical between the 2 vaccines, and given that the immunogenicity profile of 13vPnC has been shown to be similar to Prevnar for these serotypes, it can be recommended that switching to 13vPnC can occur at any time in the schedule for infants who have not completed the Prevnar series (infant series and toddler dose).

Based on accumulated experience with Prevnar and successor pneumococcal conjugate vaccines, antibody response after a three dose infant series represents the appropriate comparator for catch-up regimens, beyond the first year of life. At the time of the licensure of Prevnar (7vPnC), the catch-up immunization was assessed by comparing the antibody responses in children >7 months of age to the response in infants after three doses in the NCKP efficacy trial.[92] The basis for this comparison was demonstrated efficacy of 7vPnC in the pivotal efficacy trial where the per protocol efficacy was 97.4% but importantly the efficacy in partially vaccinated children was 85.7% (p=0.05) with a case split of 7:1 in favor of the vaccine. As a result of this analysis, the Prevnar label reads: "GMCs attained using the various schedules among older infants and children were comparable to the immune responses of children, who received concomitant DTaP, in the NCKP efficacy study (118-8) after 3 doses."

Since the original licensure of Prevnar, considerably more data have accumulated to suggest significant durable efficacy after 3 doses in infants. Two efficacy trials with an experimental 9-valent version of the vaccine, one in South Africa, and one in the Gambia,[45, 101] studied a 3-dose primary series without a booster dose. In the South Africa trial, the average follow up was around 850 days and the efficacy against IPD in HIV-negative children was 83% (95% CI: 39, 97). Persistent IgG antibody and efficacy (77.8%; 95% CI 34.4–92.5) against vaccine-serotype invasive pneumococcal disease has been demonstrated for over years of follow-up in HIV-negative children.[59] In the Gambia trial, the average follow up was 87 weeks in the per protocol analysis with efficacy against invasive disease of 77% (95% CI: 51, 90). Also in these two trials there was a significant efficacy against radiologically confirmed pneumonia, indicating that this schedule is also effective against non-invasive mucosal disease. Post-marketing effectiveness studies in the U.S. and Australia have also confirmed the efficacy of a 3-dose vaccination series without a booster dose.

In the U.S., Whitney et al performed a matched case-control analysis studying invasive disease in the U.S.[64] IPD cases were identified through the CDC's Active Bacterial Core surveillance (ABCs). Eligible children were those less than 2 years of age with onset of IPD between Jan. 1, 2001, and June 30, 2003, and children 2–4 years of age with onset between Jan. 1, 2001, and May 31, 2004. The data from this study suggest 96% effectiveness against IPD in children who received three doses of Prevnar at less than 7 months of age without a booster dose. Furthermore, the study authors noted that catch-up schedules were highly effective. This study reported 93% and 96% effectiveness for toddlers age 12 to 23 months who received 1 or 2 doses, respectively. Also, 94% effectiveness was observed for toddlers $\geq$ 24 months of age who received 1 dose. Finally, the effectiveness of 1 dose at 7–11 months of age, followed by 2 doses 12–16 months was 98%. In Australia, Prevnar was introduced into the national program in the non-indigenous population in January, 2005 as a 3-dose series in the first year of life without a booster dose. In the first two years after vaccine introduction, there was an approximate 90% reduction in IPD in children under 2 years of age and an 82% reduction in the 2-14 year old age group suggesting some indirect benefit as well.[65] Taken together, these studies demonstrate that a 3-dose primary series of Prevnar will induce a sufficient antibody response and immune memory to provide protection against invasive and noninvasive infections for at least the first two years of life. While a booster dose will likely extend protection and may increase the likelihood of a herd impact, efficacy without the booster dose is substantial and, therefore, immune responses after the primary series represent a reasonable comparator for catch-up programs.

The data above demonstrate that three doses of Prevnar in the first year of life can mediate significant protection and therefore the post-primary series antibody response represents a reasonable standard for comparing catch-up immunization programs.

In study 008 (France), subjects who received 7vPnC for the infant series at (2, 3 and 4 months of age) were randomly assigned to receive either 7vPnC or 13vPnC at the 12-month toddler dose. (See Tables 7-4 through 7-11 at end of this section)

The IgG data from children who received 3 doses of 7vPnC followed by a dose of 13vPnC in the second year of life demonstrated that the toddler dose of 13vPnC elicited immune responses to the 7 common serotypes that are comparable to those seen in subjects boosted with 7vPnC (Table 7-5). The 13vPnC toddler dose after an infant series with 7vPnC also elicited robust responses to the 6 additional serotypes that were comparable to the immune responses observed after a 3-dose infant series with 13vPnC (Table 7-4), although somewhat less than the toddler response seen in children who had completed the infant series with 13vPnC (Table 7-5, Table 7-6). (The post toddler responses to serotype 3 were comparable irrespective of whether the subjects had received 7vPnC or 13vPnC in the infant series). Table 7-7 shows that the geometric mean fold rises (GMFR) in IgG antibody responses were comparable for the 7 common serotypes, when 7vPnC or 13vPnC was used for the toddler dose. Table 7-8 shows the GMC titers after the third dose of the infant series in the group that received 3 doses of 13vPnC and a booster dose of 13vPnC. A comparison of the GMCs after the third dose of the infant series in the group that received 3 doses of 13vPnC and a booster dose of 13vPnC (Table 7-8) with the GMCs after the toddler dose in the group that received infant 3 doses of 7vPnC and 1 toddler dose of 13vPnC (in Table 7-7) shows that the GMCs are comparable for the additional 6 serotypes of 13vPnC, e.g. for serotype 1 (1.21, 1.8), serotype 3 (1.25, 1.3), serotype 5 (0.93, 1.1), serotype 6A (0.94, 2.6), serotype 7F (1.93, 3.7), and serotype 19A (2.10, 5.3).

Functional OPA antibody determinations were performed for the 6 additional serotypes after the toddler dose for the 2 groups in which the subjects received 13vPnC for this dose. (OPA determinations were not performed for the subjects in the 7vPnC only group, or for any of the common serotypes, as these responses have already been assessed in the context of the pivotal studies 006 and 004.) The proportions of OPA responders for each of these serotypes were very high and comparable between the subjects who received 13vPnC following an infant series with 7vPnC and the subjects who received 13vPnC following a 13vPnC infant series (Table 7-9).

The OPA GMTs were also comparable between the 2 study groups, encompassed within a 2-fold difference for each serotype (Table 7-10). There was no consistent pattern of a relatively greater response with either group.

Overall, both the anti-pneumococcal IgG and functional OPA antibody data discussed in this response indicate that only a single dose of 13vPnC is necessary when given after an infant series with 7vPnC to elicit appropriate levels of anti-pneumococcal antibodies against the 6 additional serotypes.

Given that the 7 common serotype conjugates are identical between the 2 vaccines, and given that the immunogenicity profile of 13vPnC has been shown to be similar to Prevnar for these serotypes, it can be recommended that switching to 13vPnC can occur at any time in the schedule for infants who have not completed the full 4 dose Prevnar series (infant series and toddler dose).

Comparison of catch-up regimens to a 4-dose infant and toddler series represents an alternative approach to define a catch-up regimen. From a practical perspective, comparison of catch-up schedules to a post-toddler dose in a 4-dose series will result in failure for some serotypes because the titers achieved after the booster dose are very high. This is true for both the original Prevnar serotypes as well as for the six new serotypes. The comparisons in study 3002 are identical to those used to originally approve the catch-up schedule for Prevnar. If the catch-up groups in 3002 had been compared to the toddler responses (see columns 2 and 3 in Table 7-11), one or (in some cases) two doses in naïve children would not achieve antibody titers that would be considered acceptable, in spite of the known effectiveness of these catch-up regimens for Prevnar. Similarly, children receiving one toddler dose of 13vPnC following an infant series with 7vPnC would not achieve antibody levels for the 6 additional serotypes as those seen in children who have been immunized with the complete 13vPnC series. Yet, the levels that are achieved are substantial and, importantly, comparable to the levels considered effective following the infant series.

These data indicate that only a single dose of 13vPnC is necessary when given after an infant 3 dose series with 7vPnC to elicit appropriate levels of anti-polysaccharide antibodies against the 6 additional serotypes.

Thus, there are three (3) transition scenarios that need to be considered at the time of the introduction of PCV13 for children who have received three or fewer doses of Prevnar (7vPnC). These define the substitution of 13vPnC in the Prevnar (7vPnC) immunization series at various points and lead to proposed regimens as follows:

2, 4 and 6 months			12-24 months	
7v	**7v**	**7v**	**13v**	--
7v	**7v**	**13v**	**13v**	--
7v	**13v**	**13v**	**13v**	

1. 7v 7v 7v / 13v

Based on experience from the 004 and 006 non-inferiority trials, and the comparisons of 13vPnC and 7vPnC in the 3005 lot consistency trial, this regimen should provide protection against the 7 common serotypes that is non-inferior to a four dose Prevnar regimen. Protection against the 7 common serotypes and 6 additional serotypes is further informed by 2 studies. The Polish 3002 study clearly shows that two doses at 12-24 months are sufficient. The French 008 study examined this regimen, and demonstrated that for the 7 PCV7 types, no more doses of 13v are needed. For the 6 new serotypes, the GMCs after one dose of 13v were comparable or greater than the response to three doses in PCV13 in infants. As noted above, three dose regimens have been associated with long term protection and this comparison was the basis of the approved catchup regimen for the Prevnar label.

2. **7v 7v 13v / 13v**

Based on experience from the 004 and 006 non-inferiority trials, and the comparisons of 13vPnC and 7vPnC in the 3005 lot consistency trial, this regimen should provide protection against the 7 common serotypes that is non-inferior to a four dose Prevnar regimen. There are no data on the

response to the 6 new serotypes after one dose of PCV13 in infants. Therefore, protection against the 6 new serotypes between 6 and 12 months of age is not known. However, a subsequent dose at 12 months should be as equivalent or better than only one dose at 12 months as seen in the French 008 study. Again, based on the Polish 3002 study, a second dose in the second year would certainly be sufficient.

3. 7v 13v 13v / 13v

Based on experience from the 004 and 006 non-inferiority trials, and the comparisons of 13vPnC and 7vPnC in the 3005 lot consistency trial, this regimen should provide protection against the 7 common serotypes that is non-inferior to a four dose Prevnar regimen. Based on the 2+1 studies in the UK and Italy, the response after the booster dose elicits immunity to the six additional serotypes that is well above the levels seen after the infant and quite comparable to the response after a four-dose regimen. Therefore, no further PCV13 dosing would be required.

7.3 Catch-up in children who have been fully vaccinated with Prevnar (7v 7v 7v / 7v 13v)

It is vitally important to provide physicians with information regarding what to do with children who have previously received 4 doses of 7vPnC, as soon as 13vPnC is available. As described above, the study in France (008) provides immunogenicity data indicating that only a single dose of 13vPnC is needed in children 12 to 15 months of age, who have received 3 doses of Prevnar, to elicit appropriate anti-polysaccharide antibody levels against the 6 additional serotypes. Study 3002 in Poland demonstrated that children 24 months or older only need 1 dose of 13vPnC to be protected against the additional serotypes in 13vPnC as well. Thus, children who are between 12 months and 5 years of age require only a single dose of 13vPnC. However, for children who have completed the entire 4-dose Prevnar series, an additional dose of 13vPnC would result in the administration of a total of 5 doses of conjugate vaccine. A theoretical concern exists with regard to safety; the most likely reason for a potential safety issue would be the total amount of CRM_{197} that a child would receive. However, 4 doses of 13vPnC contain approximately 135 µg of CRM_{197}, which is considerably more carrier protein than 4 doses of 7vPnC plus 1 dose of 13vPnC (4+1), which represents approximately 100 µg of CRM197. Hence, the total amount of carrier protein in such a scenario should not be of concern. In addition, study 6096A1-3011 is currently in progress and will address local and systemic reactions associated with administration

of 13vPnC to toddlers and children who have received a full 4 dose 7vPnC series (see Section 10.4.2 and 11)

7.4 Conclusions: Proposed transition from Prevnar (7vPnC) to 13vPnC

Results of studies and analysis provided in sections 7.2 and 7.3 lead to the following recommendation regarding transition form Prevnar (7vPnC) to 13vPnC:

Children who have begun immunization with Prevnar (7vPnC) may complete immunization by switching to 13vPnC at any point in the schedule. Children who have completed the infant series with Prevnar should receive a single dose of 13vPnC in the second year of life. Children 12 months through 5 years of age who have received 4 doses of Prevnar should receive one dose of 13vPnC.

Table 7-4: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Dose 3 of the Infant Series - Evaluable Infant Immunogenicity Population (Study 6096A1-008)

	Vaccine Group (as Randomized)			
	13vPnC			
Serotype	N[a]	n[b]	%	(95% CI[c])
7vPnC				
4	244	223	91.4	(87.1, 94.6)
6B	241	175	72.6	(66.5, 78.1)
9V	238	221	92.9	(88.8, 95.8)
14	236	224	94.9	(91.3, 97.3)
18C	242	219	90.5	(86.1, 93.9)
19F	241	236	97.9	(95.2, 99.3)
23F	244	202	82.8	(77.5, 87.3)
Additional				
1	240	218	90.8	(86.5, 94.2)
3	242	233	96.3	(93.1, 98.3)
5	243	204	84.0	(78.7, 88.3)
6A	243	208	85.6	(80.5, 89.8)
7F	238	232	97.5	(94.6, 99.1)
19A	244	238	97.5	(94.7, 99.1)

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 (CI) based upon the observed proportion of subjects.

Program ID: Study 6096A1-008/CB IMM-PNEUM_ELISA_RESP_I.SAS. Runtime ID: 17APR2008 14:42

Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/008/Reports, Tables, and Figures/Immunogenicity/6096-008 imm_pnc_elisa_resp_13_pt35_eval_i.htm

Table 7-5: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After the Toddler Dose - Evaluable Toddler Immunogenicity Population (Study 008)

	Vaccine Group (Sequence as Randomized)											
	13vPnC/13vPnC				7vPnC/7vPnC				7vPnC/13vPnC			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI)	N[a]	n[b]	%	(95% CI[c])
7vPnC												
4	233	233	100.0	(98.4, 100.0)	126	126	100.0	(97.1, 100.0)	111	110	99.1	(95.1, 100.0)
6B	233	232	99.6	(97.6, 100.0)	126	125	99.2	(95.7, 100.0)	108	106	98.1	(93.5, 99.8)
9V	232	232	100.0	(98.4, 100.0)	124	124	100.0	(97.1, 100.0)	109	109	100.0	(96.7, 100.0)
14	233	232	99.6	(97.6, 100.0)	125	125	100.0	(97.1, 100.0)	111	110	99.1	(95.1, 100.0)
18C	230	229	99.6	(97.6, 100.0)	125	124	99.2	(95.6, 100.0)	113	111	98.2	(93.8, 99.8)
19F	233	228	97.9	(95.1, 99.3)	126	123	97.6	(93.2, 99.5)	112	109	97.3	(92.4, 99.4)
23F	232	231	99.6	(97.6, 100.0)	123	122	99.2	(95.6, 100.0)	111	110	99.1	(95.1, 100.0)
Additional												
1	233	233	100.0	(98.4, 100.0)	119	1	0.8	(0.0, 4.6)	112	107	95.5	(89.9, 98.5)
3	233	221	94.8	(91.2, 97.3)	124	17	13.7	(8.2, 21.0)	113	106	93.8	(87.7, 97.5)
5	236	236	100.0	(98.4, 100.0)	111	81	73.0	(63.7, 81.0)	111	100	90.1	(83.0, 94.9)
6A	235	235	100.0	(98.4, 100.0)	124	111	89.5	(82.7, 94.3)	109	98	89.9	(82.7, 94.9)
7F	234	234	100.0	(98.4, 100.0)	124	9	7.3	(3.4, 13.3)	110	110	100.0	(96.7, 100.0)
19A	233	233	100.0	(98.4, 100.0)	127	127	100.0	(97.1, 100.0)	112	112	100.0	(96.8, 100.0)

a. N = number of subjects with assay results for the specified serotype.
b. n = Number of subjects with assay result ≥ the specified comparison level.
c. Exact 2-sided confidence interval (CI) based upon the observed proportion of subjects.
Program ID: Study 6096A1-008/CB IMM-PNEUM_ELISA_RESP_POST_T.SAS. Runtime ID: 17OCT2008 10:01.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/008/Reports, Tables, and Figures/Immunogenicity/6096-008 imm_pnc_elisa_resp_pt35_eval_t_post.htm.

Table 7-6: Comparisons of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After the Toddler Dose - Evaluable Toddler Immunogenicity Population (Study 008)

	Vaccine Group (Sequence as Randomized)		Summary Statistics							
			Group 1			Group 2				
Serotype	Group 1	Group 2	N_1[a]	n_1[b]	%	N_2[a]	n_2[b]	%	Difference[c]	(95% CI[d])
7vPnC										
4	13vPnC/13vPnC	7vPnC/7vPnC	233	233	100.0	126	126	100.0	0.0	(-1.7, 2.9)
	13vPnC/13vPnC	7vPnC/13vPnC	233	233	100.0	111	110	99.1	0.9	(-0.9, 4.9)
	7vPnC/13vPnC	7vPnC/7vPnC	111	110	99.1	126	126	100.0	-0.9	(-4.9, 2.1)
6B	13vPnC/13vPnC	7vPnC/7vPnC	233	232	99.6	126	125	99.2	0.4	(-1.8, 3.8)
	13vPnC/13vPnC	7vPnC/13vPnC	233	232	99.6	108	106	98.1	1.4	(-1.1, 5.9)
	7vPnC/13vPnC	7vPnC/7vPnC	108	106	98.1	126	125	99.2	-1.1	(-5.8, 2.7)
9V	13vPnC/13vPnC	7vPnC/7vPnC	232	232	100.0	124	124	100.0	0.0	(-1.7, 2.9)
	13vPnC/13vPnC	7vPnC/13vPnC	232	232	100.0	109	109	100.0	0.0	(-1.8, 3.3)
	7vPnC/13vPnC	7vPnC/7vPnC	109	109	100.0	124	124	100.0	0.0	(-3.3, 3.0)
14	13vPnC/13vPnC	7vPnC/7vPnC	233	232	99.6	125	125	100.0	-0.4	(-2.5, 2.4)
	13vPnC/13vPnC	7vPnC/13vPnC	233	232	99.6	111	110	99.1	0.5	(-1.8, 4.4)
	7vPnC/13vPnC	7vPnC/7vPnC	111	110	99.1	125	125	100.0	-0.9	(-4.9, 2.1)
18C	13vPnC/13vPnC	7vPnC/7vPnC	230	229	99.6	125	124	99.2	0.4	(-1.8, 3.8)
	13vPnC/13vPnC	7vPnC/13vPnC	230	229	99.6	113	111	98.2	1.3	(-1.1, 5.7)
	7vPnC/13vPnC	7vPnC/7vPnC	113	111	98.2	125	124	99.2	-1.0	(-5.5, 2.8)
19F	13vPnC/13vPnC	7vPnC/7vPnC	233	228	97.9	126	123	97.6	0.2	(-3.1, 4.7)
	13vPnC/13vPnC	7vPnC/13vPnC	233	228	97.9	112	109	97.3	0.5	(-2.9, 5.4)
	7vPnC/13vPnC	7vPnC/7vPnC	112	109	97.3	126	123	97.6	-0.3	(-5.5, 4.4)
23F	13vPnC/13vPnC	7vPnC/7vPnC	232	231	99.6	123	122	99.2	0.4	(-1.8, 3.9)
	13vPnC/13vPnC	7vPnC/13vPnC	232	231	99.6	111	110	99.1	0.5	(-1.9, 4.4)
	7vPnC/13vPnC	7vPnC/7vPnC	111	110	99.1	123	122	99.2	-0.1	(-4.1, 3.7)

Table 7-6: Comparisons of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After the Toddler Dose - Evaluable Toddler Immunogenicity Population (Study 008)

	Vaccine Group (Sequence as Randomized)		Summary Statistics							
			Group 1			Group 2				
Serotype	Group 1	Group 2	N_1[a]	n_1[b]	%	N_2[a]	n_2[b]	%	Difference[c]	(95% CI[d])
Additional										
1	13vPnC/13vPnC	7vPnC/7vPnC	233	233	100.0	126	123	97.6	2.4	(0.2, 6.8)
	13vPnC/13vPnC	7vPnC/13vPnC	233	233	100.0	112	107	95.5	4.5	(1.5, 10.1)
	7vPnC/13vPnC	7vPnC/7vPnC	112	107	95.5	126	123	97.6	-2.1	(-7.9, 3.0)
3	13vPnC/13vPnC	7vPnC/7vPnC	233	221	94.8	126	123	97.6	-2.8	(-6.9, 1.9)
	13vPnC/13vPnC	7vPnC/13vPnC	233	221	94.8	113	106	93.8	1.0	(-4.0, 7.4)
	7vPnC/13vPnC	7vPnC/7vPnC	113	106	93.8	126	123	97.6	-3.8	(-10.2, 1.5)
5	13vPnC/13vPnC	7vPnC/7vPnC	236	236	100.0	126	123	97.6	2.4	(0.2, 6.8)
	13vPnC/13vPnC	7vPnC/13vPnC	236	236	100.0	111	100	90.1	9.9	(5.1, 17.0)
	7vPnC/13vPnC	7vPnC/7vPnC	111	100	90.1	126	123	97.6	-7.5	(-14.8, -1.4)
6A	13vPnC/13vPnC	7vPnC/7vPnC	235	235	100.0	126	123	97.6	2.4	(0.2, 6.8)
	13vPnC/13vPnC	7vPnC/13vPnC	235	235	100.0	109	98	89.9	10.1	(5.1, 17.3)
	7vPnC/13vPnC	7vPnC/7vPnC	109	98	89.9	126	123	97.6	-7.7	(-15.1, -1.5)
7F	13vPnC/13vPnC	7vPnC/7vPnC	234	234	100.0	126	123	97.6	2.4	(0.2, 6.8)
	13vPnC/13vPnC	7vPnC/13vPnC	234	234	100.0	110	110	100.0	0.0	(-1.8, 3.3)
	7vPnC/13vPnC	7vPnC/7vPnC	110	110	100.0	126	123	97.6	2.4	(-0.9, 6.8)
19A	13vPnC/13vPnC	7vPnC/7vPnC	233	233	100.0	126	123	97.6	2.4	(0.2, 6.8)
	13vPnC/13vPnC	7vPnC/13vPnC	233	233	100.0	112	112	100.0	0.0	(-1.9, 3.2)
	7vPnC/13vPnC	7vPnC/7vPnC	112	112	100.0	126	123	97.6	2.4	(-1.0, 6.8)

a. N = number of subjects with assay results for the specified serotype.
b. n = Number of subjects with assay result greater than or equal to the specified comparison level.
c. Difference in proportions, group 1 – group 2, expressed as a percentage. For the 7vPnC serotypes, the reference value is the corresponding proportion in group 2. For the additional serotypes, the reference value when group 2 is 7vPnC/7vPnC is serotype 19F from the 7vPnC/7vPnC group.
d. Exact 2-sided confidence interval (CI) for the difference in proportions, group 1 – group 2, expressed as a percentage.
Program ID: Study 6096A1-008/CB IMM-PNEUM_ELISA_COMP_RESP_T.SAS. Runtime ID: 05DEC2008 9:55.

Table 7-6: Comparisons of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After the Toddler Dose - Evaluable Toddler Immunogenicity Population (Study 008)

	Vaccine Group (Sequence as Randomized)		Summary Statistics							
			Group 1			Group 2				
Serotype	Group 1	Group 2	N_1[a]	n_1[b]	%	N_2[a]	n_2[b]	%	Difference[c]	(95% CI[d])

Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/008/Reports, Tables, and Figures/Immunogenicity/ 6096-008 imm_pnc_elisa_comp_resp_pt35_eval_t.htm (modified).

Table 7-7: Pneumococcal IgG GMCs (µg/mL) and Geometric Mean Fold Rises for the Toddler Dose - Evaluable Toddler Immunogenicity Population (Study 008)

		Sampling Time								
		Before Toddler Dose			After Toddler Dose			Fold Rise (After/Before)		
Serotype	Vaccine Group (Sequence as Randomized)	n[a]	GMC[b]	(95% CI[c])	n	GMC	(95% CI)	n	GMFR[d]	(95% CI)
7vPnC										
4	13vPnC/13vPnC	239	0.3	(0.3, 0.3)	233	4.2	(3.8, 4.7)	231	13.1	(11.7, 14.7)
	7vPnC/7vPnC	131	0.5	(0.4, 0.5)	126	4.8	(4.2, 5.6)	125	10.5	(9.2, 12.0)
	7vPnC/13vPnC	118	0.5	(0.4, 0.5)	111	4.0	(3.4, 4.8)	109	8.9	(7.5, 10.7)
6B	13vPnC/13vPnC	235	1.0	(0.9, 1.1)	233	9.0	(8.0, 10.1)	227	9.1	(8.1, 10.2)
	7vPnC/7vPnC	131	1.1	(0.9, 1.3)	126	9.6	(8.3, 11.2)	125	8.7	(7.5, 10.2)
	7vPnC/13vPnC	115	0.9	(0.8, 1.1)	108	10.3	(8.2, 13.0)	105	11.1	(9.2, 13.5)
9V	13vPnC/13vPnC	239	0.4	(0.4, 0.5)	232	2.6	(2.3, 2.8)	230	6.2	(5.6, 6.8)
	7vPnC/7vPnC	131	0.5	(0.5, 0.6)	124	3.2	(2.8, 3.7)	123	6.2	(5.5, 7.1)
	7vPnC/13vPnC	118	0.4	(0.4, 0.5)	109	2.3	(2.0, 2.6)	107	5.5	(4.7, 6.4)
14	13vPnC/13vPnC	238	2.0	(1.8, 2.3)	233	9.5	(8.5, 10.6)	230	4.8	(4.3, 5.4)
	7vPnC/7vPnC	131	2.4	(2.1, 2.9)	125	10.8	(9.4, 12.5)	124	4.4	(3.8, 5.2)
	7vPnC/13vPnC	118	2.4	(2.0, 3.0)	111	7.8	(6.6, 9.3)	109	3.2	(2.7, 3.8)
18C	13vPnC/13vPnC	239	0.3	(0.3, 0.3)	230	2.3	(2.1, 2.5)	228	8.2	(7.5, 8.9)
	7vPnC/7vPnC	131	0.3	(0.3, 0.4)	125	2.8	(2.5, 3.2)	124	8.3	(7.4, 9.3)
	7vPnC/13vPnC	118	0.3	(0.3, 0.4)	113	2.4	(2.0, 2.9)	111	7.2	(6.2, 8.4)
19F	13vPnC/13vPnC	239	0.7	(0.6, 0.7)	233	5.2	(4.5, 6.0)	231	7.8	(6.7, 9.2)
	7vPnC/7vPnC	130	0.7	(0.6, 0.9)	126	4.1	(3.4, 5.0)	124	5.9	(4.7, 7.3)
	7vPnC/13vPnC	118	0.6	(0.5, 0.7)	112	3.7	(3.0, 4.6)	110	6.4	(5.1, 7.8)
23F	13vPnC/13vPnC	237	0.3	(0.2, 0.3)	232	3.0	(2.7, 3.4)	228	12.1	(10.8, 13.5)
	7vPnC/7vPnC	130	0.3	(0.3, 0.4)	123	3.7	(3.1, 4.3)	121	11.5	(9.9, 13.4)
	7vPnC/13vPnC	118	0.3	(0.2, 0.4)	111	3.1	(2.6, 3.7)	109	10.7	(9.2, 12.5)
Additional										

Table 7-7: Pneumococcal IgG GMCs (µg/mL) and Geometric Mean Fold Rises for the Toddler Dose - Evaluable Toddler Immunogenicity Population (Study 008)

		Sampling Time								
	Vaccine Group	Before Toddler Dose			After Toddler Dose			Fold Rise (After/Before)		
Serotype	(Sequence as Randomized)	n[a]	GMC[b]	(95% CI[c])	n	GMC	(95% CI)	n	GMFR[d]	(95% CI)
1	13vPnC/13vPnC	239	0.4	(0.4, 0.5)	233	4.1	(3.7, 4.5)	231	9.6	(8.6, 10.8)
	7vPnC/7vPnC	128	0.0	(0.0, 0.0)	119	0.0	(0.0, 0.0)	116	1.0	(0.9, 1.1)
	7vPnC/13vPnC	116	0.0	(0.0, 0.0)	112	1.8	(1.5, 2.2)	108	52.4	(41.6, 66.0)
3	13vPnC/13vPnC	232	0.2	(0.2, 0.2)	233	1.0	(0.9, 1.1)	225	5.0	(4.4, 5.7)
	7vPnC/7vPnC	128	0.1	(0.1, 0.1)	124	0.1	(0.1, 0.1)	121	1.1	(0.9, 1.3)
	7vPnC/13vPnC	115	0.1	(0.1, 0.1)	113	1.3	(1.1, 1.5)	108	17.8	(14.1, 22.6)
5	13vPnC/13vPnC	236	0.8	(0.7, 0.9)	236	3.3	(3.0, 3.7)	231	4.3	(3.8, 4.8)
	7vPnC/7vPnC	118	0.4	(0.4, 0.5)	111	0.5	(0.4, 0.6)	104	1.1	(1.0, 1.2)
	7vPnC/13vPnC	112	0.4	(0.4, 0.5)	111	1.1	(1.0, 1.3)	105	2.7	(2.3, 3.2)
6A	13vPnC/13vPnC	238	0.9	(0.8, 1.0)	235	6.1	(5.5, 6.8)	232	7.0	(6.2, 7.9)
	7vPnC/7vPnC	122	0.4	(0.3, 0.5)	124	1.5	(1.3, 1.9)	115	3.9	(3.3, 4.7)
	7vPnC/13vPnC	116	0.4	(0.3, 0.4)	109	2.6	(2.0, 3.4)	105	7.3	(5.8, 9.2)
7F	13vPnC/13vPnC	239	0.8	(0.7, 0.9)	234	4.5	(4.1, 5.0)	232	5.6	(5.0, 6.2)
	7vPnC/7vPnC	131	0.1	(0.0, 0.1)	124	0.1	(0.0, 0.1)	123	0.9	(0.7, 1.0)
	7vPnC/13vPnC	117	0.1	(0.1, 0.1)	110	3.7	(3.2, 4.3)	108	56.5	(43.4, 73.7)
19A	13vPnC/13vPnC	237	1.5	(1.3, 1.7)	233	9.5	(8.5, 10.6)	230	6.4	(5.5, 7.3)
	7vPnC/7vPnC	131	1.1	(0.9, 1.3)	127	4.0	(3.5, 4.5)	126	3.9	(3.4, 4.5)
	7vPnC/13vPnC	117	0.9	(0.7, 1.1)	112	5.3	(4.6, 6.2)	109	6.2	(5.1, 7.5)

a. n = 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 (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the concentrations or fold rises.
d. Geometric mean fold rises (GMFRs) were calculated using all subjects with available data from both the pretoddler and 1 month after toddler dose draws.

Program ID: Study 6096A1-008/CB IMM-PNEUM_ELISA_GMFR_T.SAS. Runtime ID: 17OCT2008 14:09.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/008/Reports, Tables, and Figures/Immunogenicity/6096-008 imm_pnc_elisa_gmfr_eval_t.htm.

Table 7-8: Pneumococcal IgG GMCs (µg/mL) for the 13vPnC Group After Dose 3 of the Infant Series – Evaluable Infant Immunogenicity Population (Study 008)

		Vaccine Group (as Randomized) 13vPnC	
Serotype	**n[a]**	**GMC[b]**	**(95% CI[c])**
7vPnC			
4	244	1.29	(1.14, 1.46)
6B	241	0.74	(0.62, 0.89)
9V	238	1.15	(1.03, 1.28)
14	236	2.74	(2.38, 3.16)
18C	242	1.42	(1.26, 1.60)
19F	241	1.55	(1.42, 1.70)
23F	244	0.92	(0.80, 1.06)
Additional			
1	240	1.21	(1.07, 1.38)
3	242	1.25	(1.13, 1.37)
5	243	0.93	(0.82, 1.06)
6A	243	0.94	(0.82, 1.06)
7F	238	1.93	(1.73, 2.15)
19A	244	2.10	(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.
Program ID: Study 6096A1-008/CB IMM-PNEUM_ELISA_GMC_I.SAS. Runtime ID: 17APR2008 14:43
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/008/Reports, Tables, and Figures/Immunogenicity/6096-008 imm_pnc_elisa_gmc_13_eval_i.htm

Table 7-9: Subjects Achieving an OPA Antibody Titer ≥1:8 for the Additional Serotypes After the Toddler Dose – Evaluable Toddler Immunogenicity Population (Study 008)

	Vaccine Group (as Randomized)							
	13vPnC/13vPnC				7vPnC/13vPnC			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
1	88	88	100.0	(95.9, 100.0)	90	89	98.9	(94.0, 100.0)
3	88	88	100.0	(95.9, 100.0)	90	88	97.8	(92.2, 99.7)
5	88	88	100.0	(95.9, 100.0)	90	88	97.8	(92.2, 99.7)
6A	86	86	100.0	(95.8, 100.0)	90	89	98.9	(94.0, 100.0)
7F	86	86	100.0	(95.8, 100.0)	89	89	100.0	(95.9, 100.0)
19A	86	85	98.8	(93.7, 100.0)	90	88	97.8	(92.2, 99.7)

a. N = number of subjects with a determinate 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.
Program ID: Study 6096A1-ISE/CP IMM_PNEUM_RESP_POP.SAS. Runtime ID: 08MAY2009 11:52

Table 7-10: Pneumococcal OPA GMTs for the Additional Serotypes After the Toddler Dose – Evaluable Toddler Immunogenicity Population (Study 008)

	Vaccine Group (as Randomized)					
	13vPnC/13vPnC			7vPnC/13vPnC		
Serotype	n[a]	GMT[b]	(95% CI[c])	n[a]	GMT[b]	(95% CI[c])
1	88	126.00	(99.87, 158.97)	90	61.58	(47.72, 79.47)
3	88	345.33	(296.06, 402.80)	90	428.88	(346.69, 530.56)
5	88	244.18	(200.14, 297.92)	90	130.99	(103.68, 165.50)
6A	86	1346.83	(1143.98, 1585.65)	90	891.44	(694.76, 1143.81)
7F	86	8126.24	(6657.36, 9919.21)	89	17034.59	(14316.59, 20268.60)
19A	86	804.06	(615.90, 1049.71)	90	1072.43	(799.06, 1439.32)

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 concentrations.
Program ID: Study 6096A1-ISE/CP IMM_PNEUM.SAS. Runtime ID: 08MAY2009 12:29

Table 7-11: IgG ELISA GMCs in 13vPnC Recipients for Studies 6096A1-004, 008 and 3002

Serotype	13vPnC Post Infant (Study 004) N=249-252	13vPnC Post Toddler (Study 004) N=232-236	13vPnC/13vPnC Post Toddler (Study 008) N=233-236	7vPnC/13vPnC Post-toddler Study 008 N=108-113	13vPnC X 2 12-24 mos. Old Study 3002 N=112	13v X 1 >24 mos. old Study 3002 N=152
1	2.03	5.06	4.08	1.83	2.74	1.78
3	0.49	0.94	0.99	1.32	1.86	1.42
4	1.31	3.73	4.20	4.04	4.28	3.37
5	1.33	3.72	3.30	1.14	2.16	2.33
6A	2.19	8.20	6.14	2.60	2.62	2.96
6B	2.10	11.53	8.99	10.33	3.38	3.41
7F	2.57	5.67	4.52	3.71	5.99	4.92
9V	0.98	2.62	2.59	2.29	3.08	2.67
14	4.74	9.11	9.52	7.81	6.45	2.24
18C	1.37	3.20	2.30	2.43	3.71	2.56
19A	2.07	8.55	9.50	5.33	4.94	6.03
19F	1.85	6.60	5.18	3.73	3.07	2.53
23F	1.33	5.07	3.01	3.12	1.98	1.55

8.0 IMMUNOGENICITY OF CONCOMITANTLY ADMINISTERED PEDIATRIC VACCINES

The immunogenicity of concomitantly administered pediatric vaccines that are routinely used in the United States, Canada, and Europe was evaluated in the 13vPnC clinical plan (Table 8-1, Table 8-2, Table 8-3, Table 8-4 and Table 8-5). Potential interference in the immune response to the pediatric vaccines administered concomitantly with 13vPnC was assessed by demonstrating non-inferiority to the immune responses, elicited by each pediatric vaccine, in subjects receiving these vaccines concomitantly with 7vPnC. Primary endpoints were the proportions achieving, for each vaccine antigen, predefined antibody concentrations or titers 1 month after the infant series. The following table 8-1 provides a general overview of all non-inferiority serologic

results of antigens administered concomitantly with 13vPnC compared to results after concomitant administration with 7vPnC in the U.S. and Canada (infant series).

Studies 004 and 3005 provide the pivotal concomitant immunogenicity data for the purposes of U.S. licensure. Study 3008 may also be of interest due to the use of the U.S. schedule and a U.S. licensed concomitant acellular pertussis containing vaccine.

Table 8-1: Non-inferiority Assessment of the Immunogenicity of Concomitantly Administered Infant Vaccines After the Infant Series

Concomitant Vaccine	Study (6096A1-)	Diphtheria Antitoxin[a]	Tetanus Antitoxin[b]	Antibody to Pertussis				Neutralizing Antibody - Polio Virus			Hepatitis B [h]	*H influenzae* type b[i]	*N meningitidis* C SBA[j]
				PT[c]	FHA[d]	PRN[e]	FIM[f]	Type 1[g]	Type 2[g]	Type 3[g]			
United States/Canada													
Pediarix	004	Pass		Pass	Pass	Pass							
Pediarix	3005		Pass					Pass	Pass	Pass	Pass		
Pentacel	3008			Pass	Pass	Pass	Pass					Pass	
ActHIB	004											Pass	
NeisVac-C	3008												Pass

Fail = fail primary endpoints for non-inferiority; Pass = pass primary endpoints for non-inferiority.

a. *Predetermined diphtheria antitoxin level* ≥0.1 IU/mL.
b. *Predetermined tetanus antitoxin level* ≥0.1 IU/mL.
c. *Comparisons were made at pertussis PT antibody level* ≥5 EU/mL and at the antibody level achieved by 95% of the 7vPnC recipients.
d. *Comparisons were made at pertussis FHA antibody level* ≥5 EU/mL and at the antibody level achieved by 95% of the 7vPnC recipients.
e. *Comparisons were made at pertussis PRN antibody level* ≥5 EU/mL and at the antibody level achieved by 95% of the 7vPnC recipients.
f. *Comparisons were made at pertussis FIM antibody level* ≥2.2 EU/mL and at the antibody level achieved by 95% of the 7vPnC recipients.
g. *Predetermined polio neutralizing antibody titer* ≥1:8.
h. *Predetermined anti-HBs level* ≥10 mIU/mL.
i. *Predetermined PRP antibody level* ≥0.15 µg/mL.
j. *Predetermined N meningitidis* C SBA antibody level ≥1:8.

In study 004, there were additional non-inferiority comparisons following the toddler dose, specifically for the *Haemophilus influenzae* type b vaccine (Hib) , measles, mumps, rubella, and varicella vaccine (MMR-V). All comparisons met predefined non-inferiority criteria.

The vaccines evaluated are listed in Table 5-1. It was not always possible to assess each vaccine antigen included in a given pediatric combination vaccine in a single study because of the limited amount of serum that can be obtained from infants. However, the selection of tested vaccine antigens across studies allows assessment of the antibody responses to each of the possible component vaccines that are commonly used in infant immunization programs. Details of responses are provided in Tables 8-2 through 8-5 at the end of this section.

The antibody response to all pediatric vaccine antigens generally exhibited non-inferior immune responses compared to concomitant administration with 7vPnC as shown for the infant vaccines. The non-inferiority criteria for immune responses to concomitantly administered pediatric vaccine antigens in the Phase 3 U.S. and Canadian studies were achieved without exception.

In addition, the antibody responses to each virus contained in MMR-V administered at 12 to 15 months of age simultaneously with the 13vPnC toddler dose were non-inferior to those observed in the 7vPnC group (study 004). Although the proportion of responders for varicella was low in both groups, the responses were nearly identical in the 2 groups and formal criteria for non-inferiority were met. At the time that study 004 was conducted, Wyeth did not have access to the glycoprotein enzyme-linked immunoabsorbent assay (gpELISA) used for licensing of the varicella vaccine. The gpELISA was not commercially available as it was proprietary to Merck & Co., Inc. Samples in study 004 assayed for varicella responses used the Trinity Biotech Captia™ Varicella-Zoster Virus (VZV) IgG enzyme-linked immunosorbent assay (ELISA). This kit uses a whole cell ELISA for the detection and quantitative determination of IgG antibody to VZV in human sera. This is a diagnostic test intended for use in immune status from natural exposure based on the obtained ISR (Immune Status Ratio). This assay was chosen because it was FDA approved and was being performed to rigorous standards; however this assay is not designed to determine immune response to the varicella vaccine.

Recently, Merck transferred their vaccine immunology testing group to PPD Inc.; the gpELISA is now commercially available and we were able to assay posttoddler sera from study 3005 (US

clinical consistency) from both the 7vPnC and pooled 13vPnC arms for varicella responses. Of note, in this study subjects received Varivax and not ProQuad due to an ongoing shortage of the latter vaccine. Responses were evaluated at two defined cutoffs associated with seroconversion (≥1.25 gpELISA units/mL) and long term protection (≥ 5.00 gpELISA units/mL). All (100%) Varivax recipients in both the 13vPnC and 7vPnC groups achieved levels ≥ 1.25 gpELISA units/mL, and 98.8% and 97.7% of the 13vPnC and 7vPnC groups achieved levels ≥ 5.00 gpELISA units/mL, respectively. GM values were 15.38 gp ELISA units/mL and 16.04 gp ELISA units/mL. Differences in responses were minimal. Responder rates and GMs are shown in Table 8-4 and Table 8-5 below. Findings indicate that coadministration of 13vPnC does not interfere with responses to Varivax, in comparison to results following coadminstration of 7vPnC.

At the time that study 004 was conducted, Wyeth also did not have access to the proprietary assay used for licensing of the mumps component in ProQuad® (Merck and Co., Inc.). Therefore, samples in study 004 were assayed for mumps responses using the Trinity Biotech Captia™ Mumps IgG enzyme-linked immunosorbent assay (ELISA). The assay is a diagnostic test intended for use in determining immune status from natural exposure. Although the proportion of responders for mumps in study 004 was low in both the 7vPnC and 13vPnC groups, the responses were nearly identical in the 2 groups and the formal criteria for non-inferiority was met.

As noted above, Merck has recently transferred their vaccine immunology testing group to PPD Inc. including Merck's proprietary varicella gpELISA and MMR assays. Mumps immunogenicity assays were performed on any remaining sera obtained 1 month after the toddler dose for all subjects in the 7vPnC group and for a randomly selected subset of equal number of subjects from the 13vPnC groups (combined 13v lots).

Results of this analysis indicate that coadministration of 13vPnC does not interfere with the response to mumps antigen, in comparison to results following coadminstration of 7vPnC.
In the 6096A1-3005 study, the proportion of subjects in the evaluable concomitant vaccine toddler immunogenicity population achieving a mumps serum antibody titer ≥10.0 Ab units/mL was 95.7% in the 13vPnC group (combined 13v lots) and 97.6% in the 7vPnC group (Table 8-6). The geometric mean (GM) for mumps antibodies after the toddler dose were 58.55 Ab units/mL

for the 13vPnC group (combined 13v lots) and 66.91 Ab units/mL for the 7vPnC group in the evaluable concomitant vaccine toddler immunogenicity population (Table 8-7).

Although the immunogenicity of hepatitis A vaccines was not evaluated, the safety profiles for each arm of the study were acceptable and comparable when the hepatitis A vaccine was administered concomitantly with 13vPnC or 7vPnC at the toddler dose in US study 004.

Finally, the immunogenicity of rotavirus vaccines administered simultaneously with 13vPnC was not formally evaluated because recommendations for rotavirus vaccines were issued after the initiation of the phase 3 clinical program. In the studies in which rotavirus vaccine was administered concomitantly with 13vPnC or 7vPnC, the safety profiles for each arm of the study were acceptable and comparable.

Table 8-2: Response to Concomitant Vaccine Antigens After the Infant Series in the United States and Canada –Evaluable Infant Immunogenicity Population

Antigen (Primary Level)	Vaccine	Study (Time Point)	13vPnC % Responders (n[a]/N[b])	7vPnC % Responders (n[a]/N[b])	Difference[c] (95% CI)	13vPnC GM (95% CI)	7vPnC GM (95% CI)	GMR[d] (95% CI)
Dip (≥0.1 IU/mL)	Pediarix	6096A1-004	95.7 (223/233)	96.1 (221/230)	-0.4 (-4.3, 3.5)	0.60 (0.53, 0.68)	0.65 (0.57, 0.75)	0.92 (0.77, 1.10)
Tet (≥0.1 IU/mL)	Pediarix	6096A1-3005	98.4 (181/184)	98.5 (193/196)	-0.1 (-3.3, 3.0)	0.73 (0.65, 0.83)	0.77 (0.68 0.86)	0.96 (0.80, 1.14)
Hib (≥0.15 µg/mL)	ActHIB	6096A1-004	97.9 (232/237)	97.8 (225/230)	0.1 (-2.9, 3.1)	3.50 (2.92, 4.20)	2.89 (2.40, 3.47)	1.21 (0.94, 1.57)
	Pentacel	6096A1-3008	97.8 (266/272)	99.6 (265/266)	-1.8 (-4.4, 0.1)	2.87 (2.48, 3.32)	3.14 (2.74, 3.60)	0.91 (0.75, 1.12)
MnC (titer ≥1:8)	NeisVac-C	6096A1-3008	96.8 (275/284)	99.3 (276/278)	-2.4 (-5.3, -0.1)	361.16 (305.46, 427.00)	302.55 (263.89, 346.86)	1.19 (0.96, 1.48)
Poliovirus Type 1 (titer ≥1:8)	Pediarix	6096A1-3005	100.0 (183/183)	100.0 (187/187)	0.0 (-2.1, 2.0)	302.43 (256.66, 356.35)	330.61 (278.14, 392.98)	0.91 (0.72, 1.16)
Poliovirus Type 2 (titer ≥1:8)	Pediarix	6096A1-3005	98.9 (181/183)	99.5 (186/187)	-0.6 (-3.4, 2.0)	244.62 (202.10, 296.09)	261.76 (219.06, 312.78)	0.93 (0.72, 1.21)
Poliovirus Type 3 (titer ≥1:8)	Pediarix	6096A1-3005	100.0 (182/182)	99.5 (186/187)	0.5 (-1.5, 3.0)	724.08 (606.25, 864.80)	545.30 (452.62, 656.96)	1.33 (1.03, 1.72)
PT ≥16.5 EU/mL[e]	Pediarix	6096A1-004	94.1 (225/239)	95.0 (228/240)	-0.9 (-5.2, 3.4)	51.35 (47.02, 56.08)	54.61 (49.33, 60.45)	0.94 (0.82, 1.08)
≥5 EU/mL	Pentacel	6096A1-3008	99.6 (281/282)	99.6 (276/277)	0.0 (-1.6, 1.7)	46.06 (42.83, 49.53)	40.37 (37.24, 43.75)	1.14 (1.02, 1.27)

Table 8-2: Response to Concomitant Vaccine Antigens After the Infant Series in the United States and Canada –Evaluable Infant Immunogenicity Population

Antigen (Primary Level)	Vaccine	Study (Time Point)	13vPnC % Responders (n[a]/N[b])	7vPnC % Responders (n[a]/N[b])	Difference[c] (95% CI)	13vPnC GM (95% CI)	7vPnC GM (95% CI)	GMR[d] (95% CI)
≥12.00 EU/mL[e]	Pentacel	6096A1-3008	98.6 (278/282)	96.0 (266/277)	2.6 (-0.2, 5.7)	46.06 (42.83, 49.53)	40.37 (37.24, 43.75)	1.14 (1.02, 1.27)
FHA								
≥40.5 EU/mL[e]	Pediarix	6096A1-004	96.7 (231/239)	95.0 (228/240)	1.7 (-2.1, 5.6)	131.96 (121.25, 143.62)	136.66 (124.61, 149.88)	0.97 (0.85, 1.09)
≥5 EU/mL	Pentacel	6096A1-3008	100.0 (283/283)	100.0 (278/278)	0.0 (-1.3, 1.3)	78.08 (72.47, 84.13)	69.52 (64.39, 75.05)	1.12 (1.01, 1.25)
≥ 7.82 EU/mL	Pentacel	6096A1-3008	100.0 (283/283)	100.0 (278/278)	0.0 (-1.3, 1.3)	78.08 (72.47, 84.13)	69.52 (64.39, 75.05)	1.12 (1.01, 1.25)
≥20.00 EU/mL[e]	Pentacel	6096A1-3008	99.3 (281/283)	95.7 (266/278)	3.6 (1.1, 6.8)	78.08 (72.47, 84.13)	69.52 (64.39, 75.05)	1.12 (1.01, 1.25)
PRN								
≥26 EU/mL[e]	Pediarix	6096A1-004	93.7 (224/239)	95.8 (230/240)	-2.1 (-6.4, 2.0)	116.15 (104.47, 129.14)	112.47 (100.70, 125.61)	1.03 (0.89, 1.20)
≥5 EU/mL	Pentacel	6096A1-3008	97.9 (277/283)	96.8 (268/277)	1.1 (-1.7, 4.2)	42.90 (38.17, 48.22)	40.69 (36.16, 45.79)	1.05 (0.89, 1.24)
≥7.00 EU/mL[e]	Pentacel	6096A1-3008	96.8 (274/283)	96.0 (266/277)	0.8 (-2.5, 4.2)	42.90 (38.17, 48.22)	40.69 (36.16, 45.79)	1.05 (0.89, 1.24)
FIM ≥2.2 EU/mL	Pentacel	6096A1-3008	95.4 (269/282)	97.5 (268/275)	-2.1 (-5.5, 1.2)	11.54 (10.48, 12.71)	12.98 (11.81, 14.27)	0.89 (0.78, 1.02)
≥4.00 EU/mL[e]	Pentacel	6096A1-3008	93.6 (264/282)	95.3 (262/275)	-1.7 (-5.7, 2.3)	11.54 (10.48, 12.71)	12.98 (11.81, 14.27)	0.89 (0.78, 1.02)

Table 8-2: Response to Concomitant Vaccine Antigens After the Infant Series in the United States and Canada –Evaluable Infant Immunogenicity Population

Antigen (Primary Level)	Vaccine	Study (Time Point)	13vPnC % Responders (n[a]/N[b])	7vPnC % Responders (n[a]/N[b])	Difference[c] (95% CI)	13vPnC GM (95% CI)	7vPnC GM (95% CI)	GMR[d] (95% CI)
HBV ≥10.0 mIU/mL	Pediarix	6096A1-3005	100.0 (153/153)	100.0 (173/173)	0.0 (-2.4, 2.2)	922.54 (768.51,1107.44)	980.25 (832.87, 1153.72)	0.94 (0.74, 1.20)

Note: Results for studies 501 and 3007 are identified as postdose 2 or postdose 3, as responses to concomitant vaccine antigens were assessed in blood samples obtained at these 2 time points during the infant series. In other studies, results for concomitant vaccine antigens were obtained at single time points as specified in the protocol.

Abbreviations: CI = confidence interval; Dip = diphtheria; EU = ELISA units; FIM = fimbrial agglutinogens; GM = geometric mean; GMR = geometric mean ratio; IU = international units; MnC = meningococcal C vaccine; Tet = tetanus.

Components of vaccines by trade name: ActHIB = Hib; Infanrix hexa = DTaP, Hib, HBV, and IPV; NeisVac-C = meningococcal C vaccine; Pediacel = DTaP, Hib, and IPV; Pediarix = DTaP, HBV, and IPV.

a. n = Number of subjects achieving antibody levels greater than or equal to the specified level.
b. N = number of subjects with a determinate assay result for the specified antigen and the denominator for percentages.
c. Difference in proportion of responders, 13vPnC – 7vPnC, and exact 2-sided CIs for the difference are expressed as percentages.
d. Ratio of GMCs: 13vPnC to 7vPnC. 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 – 7vPnC).
e. The comparison level cited is the antibody level that 95% of subjects in the 7vPnC group achieved.

ID: 19 Jan 2009

Table 8-3: Response to Concomitant Vaccine Antigens After the Toddler Dose in the United States – Evaluable Toddler Immunogenicity Population

Antigen (Primary Level)	Vaccine	Study	13vPnC % Responders (n^a/N^b)	7vPnC % Responders (n^a/N^b)	Difference 95% CI[c]	13vPnC GM	7vPnC GM	GMR 95% CI[d]
Hib (≥ 0.15 µg/mL)	PedvaxHIB	6096A1-004	100.0 (230/230)	100.0 (214/214)	0.0 (-1.6, 1.7)	6.57 (5.59, 7.72)	7.21 (6.11, 8.50)	0.91 (0.72, 1.15)
Measles (≥1.10 I.V.)	ProQuad	6096A1-004	96.4 (213/221)	97.1 (204/210)	-0.8 (-4.5, 2.9)	1.98 (1.81, 2.16)	2.02 (1.86, 2.20)	0.98 (0.86, 1.11)
Mumps (≥1.10 I.V.)	ProQuad	6096A1-004	76.5 (169/221)	72.9 (153/210)	3.6 (-4.7, 11.9)	1.33 (1.20, 1.47)	1.28 (1.16, 1.42)	1.03 (0.90, 1.19)
Rubella (≥15 IU/mL)	ProQuad	6096A1-004	91.9 (192/209)	90.7 (185/204)	1.2 (-4.4, 6.9)	75.24 (63.12, 89.68)	90.59 (75.71, 108.41)	0.83 (0.65, 1.07)
Varicella (≥1.09 I.V.)	ProQuad	6096A1-004	26.7 (59/221)	21.9 (46/210)	4.8 (-3.4, 13.0)	0.74 (0.69, 0.80)	0.73 (0.69, 0.78)	1.01 (0.92, 1.11)

Abbreviations: CI = confidence interval; GM = geometric mean; GMR = geometric mean ratio; IU = international units; I.V. = index value.
Components of vaccines by trade name: PedvaxHIB = Hib; ProQuad = MMR and varicella vaccine.

a. n = Number of subjects achieving antibody levels ≥ specified level.
b. N = number of subjects with determinate assay result for specified antigen and denominator for percentages.
c. Difference in proportion of responders, 13vPnC – 7vPnC, and exact 2-sided CIs for the difference are expressed as percentages.
d. Ratio of GMCs: 13vPnC to 7vPnC. 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 – 7vPnC).

ID: 19 Jan 2009

Table 8-4: Comparison of Subjects Achieving a Prespecified Level for Concomitant Vaccine Antigens Using Combined 13v Lots After the Toddler Dose – Evaluable Concomitant Toddler Immunogenicity Population

		Vaccine Group (as Randomized)									
		13vPnC				7vPnC					
Concomitant Vaccine Antigen	Comparison Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
Varicella	≥1.25 gpELISA units/mL	163	163	100.0	(97.8, 100.0)	173	173	100.0	(97.9, 100.0)	0.0	(-2.3, 2.2)
	≥5.00 gpELISA units/mL	163	161	98.8	(95.6, 99.9)	173	169	97.7	(94.2, 99.4)	1.1	(-2.3, 4.7)

a. N = number of subjects with a determinate IgG antibody concentration to the given concomitant vaccine component.
b. n = Number with an antibody concentration ≥ specified level for the given concomitant vaccine.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC – 7vPnC, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, (13vPnC – 7vPnC), expressed as a percentage.

Program ID: Study 6096A1-3005/CP IMM_CONC_COMPARE_RESP_VAR.SAS. Runtime ID: 07MAY2009 16:53
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/Immuno_6MAY09.zip/imm_conc_comp_respn_var_eval_t.htm

Table 8-5: Comparison of Concomitant Vaccine Antigen GMs Using Combined 13v Lots After the Toddler Dose – Evaluable Concomitant Toddler Immunogenicity Population

		Vaccine Group (as Randomized)							
		13vPnC			7vPnC				
Concomitant Vaccine Antigen	Unit of Measurement	n[a]	GM[b]	(95% CI[c])	n[a]	GM[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
Varicella	gpELISA units/mL	163	15.38	(14.22, 16.64)	173	16.04	(14.61, 17.61)	0.96	(0.85, 1.08)

a. n = Number of subjects with a determinate antibody concentration 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 transforms of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMs; 13vPnC to 7vPnC.
e. CIs for the ratio are back transforms of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – 7vPnC).
Program ID: Study 6096A1-3005/CP IMM_CONC_COMPARE_GMC_VAR.SAS. Runtime ID: 06MAY2009 18:21
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/Immuno_6MAY09.zip/imm_conc_comp_var_gmc_eval_t.htm

Table 8-6: Comparison of Subjects Achieving a Prespecified Level of Mumps Antibody Using Combined 13v Lots After the Toddler Dose in Study 6096A1-3005 – Evaluable Concomitant Vaccine Toddler Immunogenicity Population

		Vaccine Group (as Randomized)									
		13vPnC				7vPnC					
Concomitant Vaccine Antigen	Comparision Level	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(95% CI[e])
Mumps	≥10.0 Ab units/mL	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 posttoddler dose antibody concentration to the given concomitant vaccine component.
b. n = Number with an antibody concentration ≥ prespecified level for the given concomitant vaccine antigen.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, 13vPnC – 7vPnC, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, (13vPnC – 7vPnC), expressed as a percentage.

Program ID: Study 6096A1-3005/CP IMM_CONC_COMPARE_RESP_MUMP.SAS. Runtime ID: 06OCT2009 14:53
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/Mumps_headline.zip (modified)

Table 8-7: Comparison of Mumps Vaccine Antibody GMs Using Combined 13v Lots After the Toddler Dose in Study 6096A1-3005 – Evaluable Concomitant Vaccine Toddler Immunogenicity Population

	Vaccine Group (as Randomized)							
	13vPnC			7vPnC				
Concomitant Vaccine Antigen	n[a]	GM[b]	(95% CI[c])	n[a]	GM[b]	(95% CI[c])	Ratio[d]	(95% CI[e])
Mumps	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 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 transforms of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMs; 13vPnC to 7vPnC.
e. CIs for the ratio are back transforms of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (13vPnC – 7vPnC).

Program ID: Study 6096A1-3005/CP IMM_CONC_COMPARE_GMC_MUMP.SAS. Runtime ID: 06OCT2009 14:53
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/Mumps_headline.zip (modified)

9.0 IMMUNOGENICITY CONCLUSIONS

9.1 Pneumococcal Serotypes Common to 13vPnC and Prevnar

The overall comparative analysis of immune responses to 13vPnC, measured by both polysaccharide-binding IgG ELISA concentrations and functional OPA titers, shows that 13vPnC elicits responses that are similar to Prevnar for the 7 pneumococcal serotypes common to both vaccines and that are within the set of pre-established criteria for non-inferiority.

13vPnC elicits GMCs for the 7 common serotypes that are slightly lower than those for Prevnar.

The non-inferiority primary criterion was missed for serotype 6B in study 004; however, the GMC ratio criterion and additional criteria were all achieved. The responses after 3 doses, at 2, 4, and 6 months of age of 13vPnC (final formulation), whether produced at pilot or manufacturing scale, fell into the immune response ranges that are within historic values for Prevnar and non-inferior in study 3005 when 13vPnC vaccine was compared to 7vPnC, a vaccine that has been effective against IPD caused by serotype 6B.

Following administration of the toddler dose, both IgG antibody and OPA titers are boosted for all 7 serotypes. The antibody levels seen after the toddler dose are greater than those obtained following the infant series, which is consistent with the presence of specific immunologic memory.

Based on the prelicensure clinical trial experience and on the postlicensure surveillance experience, the immune response to Prevnar vaccination has consistently been associated with protection against IPD, as well as protection against otitis media. To reiterate, for IPD there is a close correlation between clinical efficacy and immunogenicity, exemplified by the benchmark threshold of 0.35 μg/mL.

9.2 Additional Pneumococcal Serotypes in 13vPnC

The immune responses elicited by 13vPnC against the 6 additional serotypes, measured by both polysaccharide-binding IgG concentrations and functional OPA, are substantially greater than those elicited by 7vPnC against these serotypes.

Immunogenicity results are summarized in Table 9-1 presented as the proportion of infants achieving an IgG ELISA concentration ≥ 0.35 µg/mL 1 month after 3 doses of 13vPnC, according to the primary endpoint recommended by the WHO TRS 927, for the 6 additional serotypes. [42]

Table 9-1: Proportion of Infants Achieving Pneumococcal IgG Antibody Concentrations ≥0.35 µg/mL 1 Month After the 3-Dose Infant Series With 13vPnC (Additional Serotypes)

Schedule Study, Country	Vaccine Formulation	Serotype 1	3	5	6A	7F	19A
Schedule 2, 4, 6 months							
6096A1-003, United States	-P80	97.9	98.9	100.0	96.8	98.9	100.0
6096A1-004, United States	-P80	95.6	63.5	89.7	96.0	98.4	98.4
6096A1-501, Spain	-P80	99.3	90.3	97.3	97.4	100.0	99.6
6096A1-3007, Spain	-P80	98.5	86.2	96.0	99.0	100.0	99.5
6096A1-3005, United States	Pilot lot 1 +P80	97.8	68.5	94.2	98.1	99.8	98.1
	Pilot lot 2 +P80	97.0	72.4	90.3	95.5	99.0	99.0
	Man lot +P80	98.5	79.1	94.4	98.2	99.7	98.7
6096A1-3008, Canada	+P80	95.7	79.6	87.0	96.4	98.6	97.8
Schedule 2, 3, 4 months							
6096A1-006, Germany	-P80	96.1	98.2	93.0	91.9	98.6	99.3
6096A1-008, France	-P80	90.8	96.3	84.0	85.6	97.5	97.5
6096A1-009, Poland	+P80	95.8	97.9	94.1	86.6	98.7	98.7
	-P80	92.4	99.2	92.4	86.1	99.6	100.0
6096A1-3000, Poland	Pilot lot +P80	90.8	95.4	88.5	86.3	100.0	99.2
	Man lot +P80	93.0	93.7	90.6	85.2	100.0	99.2
Schedule 6, 10, 14 weeks							
6096A1-011, India	-P80	96.1	79.4	87.6	88.5	96.0	99.0

Abbreviations: +P80 = 13vPnC formulated with polysorbate 80; -P80 = 13vPnC formulated without polysorbate 80; Man = manufacturing.

Serotypes 1 and 7F: In contrast to 7vPnC, 13vPnC induces substantially higher immunologic response to serotypes 1 and 7F, measurable by polysaccharide-binding IgG antibodies and OPA.

Serotype 3: The serotype 3 responses after the infant series with 13vPnC were variable, depending on the study. Nonetheless, in all cases, the IgG and OPA responses were notably greater than those elicited against this serotype by 7vPnC. Following the 13vPnC toddler dose, the serotype 3 IgG responses typically achieved levels equal or greater than those after the infant series, as did the OPA responses, which were often proportionately greater.

Serotypes 5 and 19A: Although 7vPnC induces some polysaccharide-binding IgG antibodies against serotypes 5 and 19A, these responses lack opsonophagocytic activity. By contrast, 13vPnC elicits polysaccharide-binding IgG antibodies and highly functional antibody responses against serotypes 5 and 19A.

Serotype 6A: As has been previously observed, 7vPnC gives rise to a certain degree of polysaccharide-binding IgG antibodies and of measurable OPA titers against serotype 6A, but these responses are notably superior for 13vPnC.

To summarize, there is no correlation between ELISA-binding antibodies and functional-activity titers for 5 of the 6 additional serotypes after Prevnar vaccination. (The exception is serotype 6A for which Prevnar gives rise to some functional antibody). Among recipients of 13vPnC, by contrast, there is a strong association for each additional serotype between IgG ELISA antibody concentrations and OPA titers, allowing the conclusion that IgG capsular polysaccharide-binding antibody elicited by 13vPnC is biologically relevant.

Furthermore, both IgG-antibody and functional-activity responses were boosted following administration of the toddler dose of 13vPnC, for 5 of the 6 serotypes. The antibody levels seen after the toddler dose were greater than those obtained following the infant series, consistent with the presence of specific immunologic memory, and this anamnestic response ought to contribute to the persistence of 13vPnC effectiveness.

Taken together, these observations support the conclusion that 13vPnC is likely to provide added protection, compared with 7vPnC, against pneumococcal disease caused by the additional 6 serotypes.

9.3 Protection against Otitis Media

In addition to protection against invasive disease, the data discussed in this document also support the perspective that 13vPnC will be effective for prevention of otitis media caused by serotypes included in the vaccine. Several lines of evidence support this view:

Prevnar (7vPnC) is efficacious against acute otitis media caused by vaccine serotypes.
The results of pre-licensure trials in Finnish and US infants demonstrated that Prevnar (7vPnC) was associated, respectively, with a 6% and an 8.9% overall reduction in clinical acute otitis media (AOM) incidence.[43, 99] Long-term follow-up of these cohorts revealed that there was approximately 10% to 50% vaccine efficacy against recurrent otitis media or for the prevention of tympanostomy tube placement.[66, 67]

Similar to the experience with IPD, reductions in otitis media have been observed in the United States since the introduction of Prevnar as a routine infant vaccine.[68, 69, 70]
In surveillance reports from the United States that followed infants with complicated otitis media, generalized Prevnar vaccination led to a substantial decrease in the incidence of pneumococcal otitis media, particularly for cases that would have been frequent or would have been refractory to antibiotic treatment. In addition, the rate of pneumococcal middle-ear fluid isolates fell by 39% for severe otitis media.[71] Rates of ambulatory visits and antibiotic prescriptions attributable to AOM were significantly reduced, 42.7% and 41.9% respectively, in the United States after wide use of Prevnar.[70] Hence, the impact of Prevnar on otitis media after licensure has exceeded the predicted effectiveness based on the pre-licensure Finnish otitis media trial (FinOM) and the NCKP efficacy trial. The priming series and the toddler dose have been shown to reduce nasal carriage of 7vPnC serotypes; the eradication of vaccine type carriage in the US is equivalent to a 100% reduction in 7vPnC vaccine type otitis through this herd immunity effect. This amplification effect is plausibly related to the 20% overall reduction in otitis media derived from analysis of national surveys.[68]

Serologic data from the 13vPnC clinical studies indicate that 13vPnC should provide protection comparable to 7vPnC for the 7 serotypes in common.
For noninvasive pneumococcal disease, serologic correlates of protection have not yet been defined. However, protection against otitis media is clearly based on the ability to induce functional anti-capsular antibody responses and therefore the magnitude of the antibody response is the criteria by which comparisons should be made.

Recent studies confirm that anti-polysaccharide IgG binding antibody responses after 7vPnC administration result in reductions in nasal acquisition of vaccine type pneumococci and reductions in otitis media. The link between nasal acquisition of pneumococci and subsequent otitis media is well established: New pneumococcal acquisition is associated with increased otitis risk, while absence of pneumococci in the nasopharynx is associated with lower likelihood of recovery from the middle ear in AOM. Failure to eradicate nasopharyngeal pneumococci after antibiotic therapy for AOM predisposes to recurrence.[72, 73, 74, 75] Comparison of antibody responses for serotypes in common to 7vPnC in otitis media effectiveness studies and nasal

colonization studies predict that 13vPnC will also be effective against otitis media (Table 9-2, Figure 9-1, and Table 9-3). Description of these studies follows:

Despite a reduced number of doses compared to the U.S. regimen of 2, 4, 6 and 12 months, two 7vPnC studies, using a 2-dose infant vaccination series, have demonstrated effectiveness against otitis media, in spite of the lower anti-pneumococcal antibody responses observed following such a reduced infant series compared with the U.S. regimen. In the Liguria region of Italy, a 2-dose series at 3 and 5 months of age, followed by a toddler dose at 11-15 months of age, reduced all cause acute otitis media by 34.6%.[76] Serotype specific IgG binding antibody responses obtained after the toddler dose from a subset of children in this region are shown in Table 9-2.

Similarly, in Quebec, a 2-dose infant primary series at 2 and 4 months of age followed by a toddler dose at 12 months of age prevented 100,000 visits in children <5 years of age, and reduced OM claims by 13.2% by the end of the study period.[77] While antibody responses were not evaluated in the children from Quebec, serologic responses to the same 2, 4, 12 month 7vPnC dosing regimen from UK children in the 007 study are likely to be similar and are shown in Table 9-2.

Serologic responses from the 13vPnC study 3005, after administration of the final manufactured 13vPnC formulation, are also compared in Table 9-2. Responses seen following the 13vPnC toddler dose are comparable to those after 7vPnC for serotypes in common; all are within 2-fold of values associated with effectiveness against otitis media in Italy and Quebec. These comparisons support the conclusion that 13vPnC is likely to provide protection against otitis media comparable to that of 7vPnC.

Comparisons of 13vPnC responses to those of 7vPnC recipients for whom reduction in nasal acquisition of pneumococcal serotypes has been demonstrated provide further support that 13vPnC will protect against otitis media. Dr. Ron Dagan and colleagues recently evaluated antibody responses in Israeli children after a three dose (2, 4, 6 month) infant series of 7vPnC followed by a single toddler dose, or a three dose (2, 4, 6 month) series alone.[78] These results were matched with evaluation of nasal acquisition of vaccine type pneumococci in this population (Table 9-3). Reductions were seen in nasal acquisition of vaccine type pneumococci prior to the toddler dose in comparison to a control group vaccinated at 12 and 18 months of age.

Importantly, equivalent reductions in nasal acquisition of pneumococcal vaccine types were observed after 1 year of age, in both groups compared to controls (Figure 9-1).

In 13vPnC study 3005, IgG polysaccharide binding antibody responses to the common serotypes after the 13vPnC infant series are comparable to levels seen after the 3 dose 7vPnC infant series in Israeli children (Table 9-3). Notably, antibody responses in the 13vPnC recipients after the toddler dose exceed those after the 7vPnC infant series and are comparable to toddler responses in Israeli children. Therefore, 13vPnC-elicited immune responses fall within the range of those observed in Israeli children who were protected against nasal acquisition of the serotypes in common. Accordingly, 13vPnC should provide comparable protection against nasal acquisition of the common serotypes to that observed among Israeli children after 7vPnC vaccination, and should protect against otitis due to these serotypes.

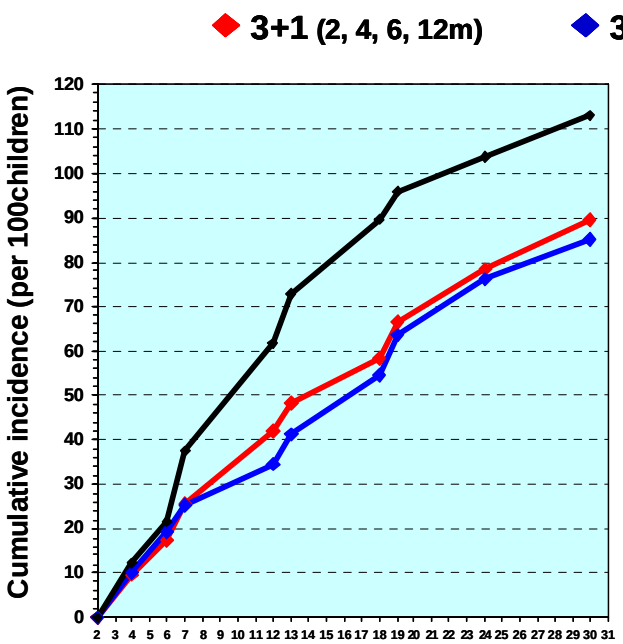
Table 9-2: IgG ELISA Serotype Specific Antibody GMCs:
7vPnC regimens associated with effectiveness against otitis media vs. 13vPnC Final Formulation
µg/mL

	Durando, Italy 7vPnC[76] 3, 5, 11-12 mo	007 Study, UK 7vPnC 2, 4, 12 mo[a]	3005 Study 13vPnC 2,4,6, 12 mo[b]
	Toddler dose	Toddler dose	Toddler dose
4	4.70	3.52	2.50
6B	6.73	7.67	10.12
9V	3.84	2.46	1.95
14	12.29	11.32	6.85
18C	2.50	2.14	2.20
19F	10.21	7.25	5.16
23F	4.41	3.13	3.30

[a] This dosing regimen was associated with 100,000 fewer otitis visits in Quebec and 13.2% reduction in otitis media claims in study period [77]

[b] Extracted from Table 5-16.

Figure 9-1: Cumulative Nasal Acquisition of 7vPnC Vaccine-type Pneumococci



Period	P value 3+1 *vs* 3+0
7-12 months (1st yr)	(-)
13-23 months (2nd yr)	*.698*
24-30 months (3rd yr)	*.257*
7-30 months	*.197*

P value corrected for ethnic group

Courtesy of Dr. Ron Dagan. Presented at 49th ICAAC, San Francisco, September, 2009.[78]

Table 9-3: IgG ELISA Serotype Specific Antibody GMCs: Clinical Study of Nasal Acquisition after 7vPnC[78] vs. 13vPnC Final Formulation µg/mL				
Serotype	Dagan, Israel 7vPnC 2, 4, 6 mo	Dagan, Israel 7vPnC 2,4,6, 12 mo	3005 Study(pooled data) 13vPnC 2,4,6, 12 mo	
	Infant series	Toddler dose	Infant series	Toddler dose
4	1.93	3.98	1.46	2.50
6B	1.87	11.01	2.52	10.12
9V	1.41	3.47	1.09	1.95
14	5.02	12.93	5.10	6.85
18C	1.70	3.68	1.37	2.20
19F	2.06	4.07	2.15	5.16
23F	1.04	5.60	1.18	3.30

[78]Courtesy of Dr. Ron Dagan. Presented at 49th ICAAC, San Francisco, September, 2009.

Functional OPA responses after 13vPnC overlap those after 7vPnC for the serotypes in common.

As for IPD, functional antibody responses to serotypes in common are an important measure of the likelihood that 13vPnC will provide comparable protection against otitis media to that provided by 7vPnC. Table 9-4 compares OPA GMTs and percent responders after the 13vPnC toddler dose in study 004 to those after 7vPnC for the seven common serotypes. (OPA titers are not available from study 3005.) 13vPnC recipients demonstrate high OPA functional antibody titers and closely approximate those after 7vPnC with most 95% CIs of GMT ratios crossing a ratio value of 1.0. Hence, the level of functional antibody after 13vPnC predicts a high likelihood of comparable protection against otitis for the common serotypes.

Table 9-4: OPA Responses after the Toddler Dose Study 6096A1-004

Serotype	13vPnC GMT	7vPnC GMT	Ratio (95% CI)
4	1180	1492	0.8 (0.51-1.22)
6B	3100	4066	0.8 (0.53- 1.09)
9V	11856	18032	0.7 (0.45-0.96)
14	2002	2366	0.9 (0.57-1.25)
18C	993	1722	0.6 (0.40-0.84)
19F	200	167	1.2 (0.76-1.88)
23F	2723	4982	0.6 (0.36-0.82)

Extracted from Table 5-5.

13vPnC should provide additional benefit compared to 7vPnC by protecting against otitis media due to the 6 additional serotypes. Results of several recent studies suggest that nonvaccine serotypes are also emerging as important causes of AOM or its complications in children, particularly serotype 19A, and that these are likely to be resistant to commonly used antimicrobial agents.[79] Another series of pneumococcal isolates from tympanocentesis samples collected from 5 centers across the United States identified serotype 3 most commonly, with a smaller percentage accounted for by serotypes 1 and 7.[80] It has become clear from this shift in the distribution of serotypes causing disease that direct protection by inclusion of these serotypes

in a candidate vaccine will be necessary to prevent otitis media caused by emerging serotypes. In study 004, GMTs after the toddler dose of 13vPnC exceed 7vPnC responses by 4.2 to 64.1-fold, for the additional serotypes (Table 9-5). The lowest ratio of 4.2 is seen for 6A for which 6B in 7vPnC may provide a limited degree of protection against nasal colonization and otitis. This suggests a high likelihood of 13vPnC induced protection against otitis due to these serotypes, superior to that of 7vPnC . In addition, if experience parallels that observed after the introduction of 7vPnC,[68] initial further reductions in otitis media after introduction of 13vPnC may be amplified by elimination of carriage of the 6 additional serotypes over time from the pediatric population.

Table 9-5: OPA Responses after the Toddler Dose Study 6096A1-004

Serotype	13vPnC GMT	7vPnC GMT	GMT Ratio
1	164	5	32.8 (22.0-48.8)
3	380	12	32.2 (21.8-47.5)
5	300	5	64.1 (47.1-87.2)
6A	2242	539	4.2 (2.7-6.6)
7F	11629	268	43.4 (25.2-75.0)
19A	1024	29	35.7 (21.3-59.9)

Extracted from Table 5-6

Consequently, for 13vPnC, effectiveness against otitis media similar to that established for Prevnar can be expected for pneumococcal serotypes in common, and added protection is expected for the additional serotypes. The applicant is committed to confirming this expectation. Ongoing studies in Alaskan children (6096A1-3011) and Israeli children (6096A1-3006) will examine the impact of 13vPnC on nasal acquisition and carriage of vaccine type pneumococcal strains. In addition, the applicant will conduct a tympanocentesis study to evaluate serotypes associated with AOM during and after introduction of 13vPnC into the community (see section 11).

9.4 Catch-up Vaccination in Older Infants and Young Children Aged Less Than 5 Years

Three (3) vaccination regimens were evaluated in study 3002, adjusted to the age at which a child is first vaccinated (7 to 11 months, 12 to 23 months, or 24 to 71 months). Each of the 3 regimens was shown to elicit good immune response levels against all 13 serotypes that were either comparable with or greater than the antibody concentrations achieved in infants after a 3-dose infant series. Therefore, 13vPnC can be used in older infants and young children who have not previously received a pneumococcal conjugate vaccine.

9.5 Switching From Prevnar to 13vPnC in Infants Previously Vaccinated With Prevnar

Given that the 7 common serotype conjugates are identical between the 2 vaccines, and given that the immunogenicity profile of 13vPnC has been shown to be similar to Prevnar for these serotypes, it can be recommended that switching to 13vPnC can occur at any time in the schedule for infants who have not completed the Prevnar series (infant series and toddler dose).

Data from study 008 in France in which children received 3 doses of Prevnar followed by a dose of 13vPnC in the second year of life showed that a toddler dose of 13vPnC yielded immune responses to the 7 common serotypes that are comparable to those seen in subjects boosted with 7vPnC. The 13vPnC toddler dose after an infant series with 7vPnC also elicited robust responses to the 6 additional serotypes that were comparable to the immune responses observed after a 3-dose infant series with 13vPnC, although somewhat less than the toddler response seen in children who had completed the infant series with 13vPnC. (The posttoddler responses to serotype 3 were comparable irrespective of whether the subjects had received 7vPnC or 13vPnC in the infant series.) These data indicate that only a single dose of 13vPnC is necessary when given after an infant series with 7vPnC to elicit appropriate levels of anti-polysaccharide antibodies against the 6 additional serotypes.

9.6 Catch-up in Children Who Have Been Fully Vaccinated With Prevnar

It is vitally important to provide physicians with information regarding what to do with children who have previously received 4 doses of 7vPnC, as soon as 13vPnC is available. As described above, the study in France (008) provides immunogenicity data indicating that only a single dose of 13vPnC is needed in children 12 to 15 months of age, who have received 3 doses of Prevnar,

to elicit appropriate anti-polysaccharide antibody levels against the 6 additional serotypes. Study 3002 in Poland demonstrated that children 24 months or older only need 1 dose of 13vPnC to be protected against the additional serotypes in 13vPnC as well. Thus, children who are between 12 months and 5 years of age require only a single dose of 13vPnC. However, for children who have completed the entire 4-dose Prevnar series, an additional dose of 13vPnC would result in the administration of a total of 5 doses of conjugate vaccine. A theoretical concern exists with regard to safety; the most likely reason for a potential safety issue would be the total amount of CRM_{197} that a child would receive. However, 4 doses of 13vPnC contain approximately 135 µg of CRM_{197}, which is considerably more carrier protein than 4 doses of 7vPnC plus 1 dose of 13vPnC (4+1), which represents approximately 100 µg of CRM_{197}. Hence, the total amount of carrier protein in such a scenario should not be of concern. There are no additional bases for concern.

9.7 Concomitant Vaccinations

Data from the 13vPnC clinical program have shown that concomitant administration of 13vPnC does not affect the safety profile and the immunogenicity of routinely recommended pediatric vaccines. Compared with Prevnar, non-inferiority of antibody response to each of the vaccine antigens was demonstrated with 13vPnC. The only exceptions were related to the antibody response to diphtheria and poliovirus type 2 antigens in Pentavac, although the antibody response to the same antigens in other vaccine formulations was not altered. Non-inferiority was demonstrated for all concomitantly administered infant vaccine antigens used in the United States and Canada. Immunogenicity of concomitantly administered hepatitis A vaccine was not evaluated; however, acceptable and comparable safety was demonstrated in study 004 when the vaccine was given with either 13vPnC or 7vPnC at the toddler dose.

The immunogenicity of rotavirus vaccines simultaneously given with 13vPnC has not been formally evaluated because recommendations for rotavirus vaccines were issued after the initiation of the phase 3 clinical program. Clinical experience with coadministration of Prevnar and rotavirus vaccines, demonstrated that the immunogenicity of the 2 vaccines was not altered and this information is included in the label for Rotarix and Rotateq. [81, 82, 83,] It is reasonable to expect similar findings for 13vPnC. In the studies in which the rotavirus vaccine was concomitantly administered with the 13vPnC, no change in the safety profiles of either vaccine was observed.

10.0 OVERVIEW OF SAFETY

10.1 Safety Profile of Prevnar and 13vPnC

10.1.1 Safety Profile of Prevnar (7vPnC)

The safety evaluation 13vPnC builds upon the favorable safety profile of 7vPnC that has been well studied and extensively documented. The carrier protein and adjuvant are also the same as those used in the HbOC (HibTITER) vaccine (indicated for immunization against Haemophilus influenzae type b invasive disease) that was approved for marketing in the EU and US in the early 1990's and meningococcal C conjugate (Meningitec, MnCC) vaccine, both of which have a favorable safety profile. The safety of 7vPnC has been evaluated in several randomized, controlled clinical trials in the EU and the US. The large pivotal efficacy trial in the US, with 18,927 infants vaccinated with 7vPnC found systemic reactions following 7vPnC were generally mild and local tolerance was good, and all clinical trials confirmed this.97 In an extension to the pivotal efficacy trial, 18,925 infants vaccinated with 7vPnC were followed for at least 5 years after the end of the trial to compare the incidence of developmental delay, autistic spectrum disorders, diabetes mellitus, Kawasaki disease, neutropenia, and reactive airways disease to the controls that received MnCC vaccine. No statistically significant differences were found between 7vPnC recipients and the control subjects. In addition, 7vPnC was found to be safe and efficacious in 4340 pre-term and 1756 low birth weight infants in the pivotal efficacy trial conducted at Northern California Kaiser Permanente.[84,85]

The safety of 7vPnC was evaluated in a large (N=162,305) post-licensure observational study of the safety of 7vPnC with up to 1 year of follow-up when used concomitantly with other routine infant immunizations in the general population. The study was conducted at Northern California Kaiser Permanente, a large health maintenance organization in the US.[86] The investigators concluded that the results from this intensive, large-scale surveillance support the safety and use of 7vPnC as a routine childhood vaccine. Scientists at the FDA reviewed the Vaccine Adverse Event Reporting System (VAERS) database for AE reports associated with 7vPnC and concluded that the majority of reports in the first 2 years after licensure of 7vPnC in the US described generally minor adverse events previously identified in clinical trials. [87] To date, global surveillance of spontaneously reported adverse events to Wyeth after 195 million doses distributed has confirmed the generally safe and well-tolerated profile of 7vPnC for use in the routine childhood immunization schedule.

10.1.2 Safety Profile of 13vPnC

Safety data obtained from more than 4700 infants who received at least 1 dose of 13vPnC and from 354 older infants and young children are presented in this overview.

As is the case with Prevnar, 13vPnC is composed of pneumococcal polysaccharides covalently conjugated to the diphtheria CRM_{197} protein. The antigenic content for each of the 6 additional serotypes is identical to 6 of the 7 Prevnar serotypes, i.e., 2.2 µg per 0.5-mL dose. The nature and content of the aluminum phosphate excipient are identical. Unlike Prevnar, 13vPnC to be marketed contains a succinate buffer and 0.02% P80; however, both are commonly used excipients in approved vaccines with no known safety issues.

Given the similarity of 13vPnC to Prevnar, the clinical development of 13vPnC builds on the record of safety and efficacy that has been established for Prevnar. Hence, most of the clinical trials of 13vPnC have included 7vPnC, thereby permitting a direct safety comparison between the 2 vaccines.

10.2 Safety Database

The total safety database includes data from 13 infant studies in which the safety and immunogenicity of 13vPnC, coadministered with other pediatric vaccines, were evaluated. Ten (10) of these studies included 7vPnC as a single active comparator. In the 3 remaining studies, different formulations or lots of 13vPnC were assessed.

Each of the 13 studies was conducted in a single country, and vaccination schedules varied across the studies, according to national recommendations for the pediatric immunization program in each country. Various countries were selected to allow a thorough evaluation of different schedules.

10.2.1 Safety Data Collection Methods

10.2.1.1 Solicited Adverse Events

After each dose of study vaccine, the parent/legal guardian was to monitor local reactions and systemic events daily. Local reactions at the injection site were monitored for the study vaccine

(13vPnC or 7vPnC) only, and not for the concomitant vaccines. The local reactions monitored included tenderness, induration, and erythema. The systemic events monitored included decreased appetite, irritability, increased sleep, and decreased sleep, as well as fever (temperature of 38.0°C [100.4°F] or higher) and the use of antipyretic medications to treat or prevent symptoms. In addition, information on hives (urticaria) was collected as a systemic event in studies 004 and 3005 only.

In the early phase 1-2 trial, study 003, the information was recorded in a paper diary for 8 to 15 days after each dose, depending on the symptom monitored and the stage of the study. Details are available in the study report

In all other infant studies, the information was entered into an electronic diary (e-diary) in response to the e-diary prompts. The e-diary prompts were designed to ensure not only that the presence of symptoms was documented, but also that the absence of symptoms was confirmed. In most studies, the e-diary information was recorded for 4 days after each dose (day 1 to day 4). In studies 004 and 3005 (both conducted in the United States), e-diary information was collected for 7 days after each dose. For symptoms that resolved before the last scheduled day of data recording, the last day on which the presence of the symptom was documented was captured as the end date. If any local reactions or systemic events were ongoing on the last scheduled diary day, then on each day thereafter, the e-diary prompted the parent/guardian to enter information regarding whether the symptom was still ongoing (yes or no) and, when no longer ongoing, the parent was prompted to enter the date on which the symptom had resolved. If an end date was not entered in the e-diary, it was captured at the next visit by the investigator on a symptom resolution case report form (CRF).

10.2.1.1.1 Local Reactions

The local reactions that were monitored included tenderness, induration (swelling), and erythema (redness). Tenderness was recorded as "none," "present," or "interfered with limb movement."

If induration was not present, the parent/legal guardian was to record "none"; if induration was present, the parent/legal guardian was to measure the maximum diameter of the area with a caliper provided by the sponsor (1 to 14 caliper units) and record the measurement in the e-diary, rounding up to the nearest whole number. If the diameter was greater than 14 caliper units,

14+ was recorded. Information regarding erythema was recorded in the same manner as for induration. If the measurement of either erythema or induration was greater than 14 caliper units, the subject was to be seen by study personnel. Each caliper unit corresponded to 0.5 cm. For data summarization and analysis, the measurements for erythema and induration were categorized as absent, mild (0.5 to 2.0 cm), moderate (2.5 to 7.0 cm), or severe (greater than 7.0 cm).

10.2.1.1.2 Systemic Events

After each vaccination, on each diary day, the parent/legal guardian was to record in the e-diary whether the infant had experienced decreased appetite (yes or no); irritability (yes or no); or any changes in sleep (increased sleep, decreased sleep, or no change) on that day. Similarly, information on the occurrence of hives was collected in the daily diary in studies 004 and 3005 only.

On each diary day, the parent/legal guardian was to take the infant's temperature at bedtime and also at any time during the day when a fever was suspected. At the end of the day (up to 11:59 PM), the highest temperature for each day was to be recorded to 1 decimal place in the e-diary. Fever was defined as core temperature of greater than or equal to 38.0°C (100.4°F). If a fever was present on the last scheduled diary day, then on each day thereafter, the e-diary prompted the parent/guardian to enter information regarding whether the infant still had a temperature of 38.0°C (100.4°F) or higher (yes or no); and when no longer ongoing, the parent/guardian was prompted to enter the date on which the fever had resolved (last date of temperature 38.0°C [100.4°F] or higher). For data summarization, temperature was categorized according to the following terms and scale:

Absent	<38.0°C (100.4°F)
Mild	≥38.0°C (100.4°F) to ≤39.0°C (102.2°F)
Moderate	>39.0°C (102.2°F) to ≤40.0°C (104.0°F)
Severe	>40.0°C (104.0°F)

On each diary day, the parents/legal guardians were to record whether or not they had given the infant any "fever medication" to prevent symptoms (yes or no) and whether they had given the infant any "fever medication" to treat symptoms (yes or no). If antipyretic use to treat symptoms was ongoing on the last scheduled diary day, then on each day thereafter, the e-diary prompted the parent/guardian to enter information regarding whether antipyretic medication had been

administered on that day to treat symptoms (yes or no); and when antipyretic use was no longer ongoing, the parents/guardians were prompted to enter the date on which they had stopped giving fever medication to treat symptoms. An analogous sequence was followed if the use of antipyretic medications to prevent symptoms was ongoing on the last scheduled diary day.

10.2.1.2 Unsolicited Adverse Events

An adverse event (AE) was defined as any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations, including any clinically significant worsening of a preexisting condition. The event did not need to be causally related to the test article or the clinical study.

A serious adverse event (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, or cancer. Additionally, important medical events that may not have resulted in death, were not life threatening, or did not require hospitalization could have been considered SAEs when, based on appropriate medical judgment, they jeopardized the subject and required medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias or convulsions that did not result in hospitalization.

Requirements for AE reporting were uniform across all infant studies. A subject's AEs were to be recorded from the signing of the informed consent form (ICF) to the postinfant series blood draw, and from the toddler dose to the posttoddler dose blood draw. At the toddler dose visit any newly diagnosed chronic medical conditions and SAEs since the last visit were to be recorded. At 6 months after the final study vaccination, any newly diagnosed chronic medical conditions, hospitalizations, and SAEs that had occurred since the last study visit were to be recorded. All SAEs were to be recorded from the signing of the ICF to 6 months after the final study vaccination.

Information regarding AEs was to be recorded both on source documents (the subject's medical file) and on CRFs. After each vaccination, clinic personnel observed the subject for at least 15 minutes for any significant, acute reactions. In addition, at the appropriate study visits, AEs

were identified based on clinical evaluation, review of any ancillary information reported in the e-diary, and information obtained by asking the parent/legal guardian a nonspecific question such as, "How has your child been doing since your last visit?" During the clinical trial, the investigator was to follow up on all AEs until the events had subsided, returned to baseline, or in case of permanent impairment, until the condition stabilized, even if it extended beyond the study closeout visit.

On the CRF, the investigator was to record signs and symptoms using standard medical terminology, rate the severity of the event (mild, moderate, severe, or life threatening), and note what actions were taken: in particular, indicating whether the AE resulted in withdrawal of the subject from the study or resulted in the permanent discontinuation of test article. In addition, the investigator was to assess the potential for a causal relationship between the study vaccine and the AE. In all studies except study 003, investigators were to respond to the question, "Is there a reasonable possibility of a causal relationship between the product and the AE?" (yes or no). AEs for which the investigator responded "yes" are designated as being "related to study vaccine" and are included in summaries of "related" AEs. In study 003, investigators assessed the AE as definitely, probably, possibly, definitely not, or probably not related to test article. Those that the investigator indicated were definitely, probably, or possibly related are designated as being "related to study vaccine" and are included in summaries of "related" AEs.

AEs continuing at a given visit were to be re-reported at the next visit with any changes in status documented, or with an indication that the event was continuing. If an event severity changed, then a stop date was to be entered and a new event reported with a new severity. The start date of the new event was to be the same as the stop date for the previous event.

10.2.2 Clinical and Statistical Analysis Methods for Individual Studies

Although some safety data are presented and discussed on a study-by-study basis (i.e., data for local reactions and systemic events), the primary purpose of this summary of clinical safety (SCS) is to present and discuss the results of the integrated safety analyses, which evaluate all safety data pooled across the 13 infant studies. Thus, the statistical methods used in the evaluation of individual study data are described only briefly here. Complete details of the by-study analyses can be found in the statistical analysis plans, which are included in the individual study reports.

For all studies, the database snapshots supporting the development of the clinical study reports (CSRs) were used for the integrated data analyses. For the integrated analyses, data from the 13 infant studies have been pooled across all 13vPnC groups, regardless of formulation or lot. The pooling is justified on the basis of data from the individual studies that demonstrate the similarity of reactogenicity of 13vPnC across lots and formulations. Pooling of the safety data provides the advantage of a larger database for examination, but differences between the studies (e.g., the lot of vaccine used, vaccination schedule, concomitant vaccines) should be kept in mind when evaluating pooled results.

Study 008 required special handling of subject data for pooling. One objective of this study was to evaluate the safety of 13vPnC administered at the toddler dose to subjects who had been vaccinated with 7vPnC during the 3-dose infant series. Subjects were randomly assigned to 1 of 3 vaccine groups, to receive 13vPnC during the infant series and at the toddler dose (13vPnC/13vPnC), 7vPnC during the infant series and at the toddler dose (7vPnC/7vPnC), or 7vPnC during the infant series and 13vPnC at the toddler dose (7vPnC/13vPnC). Data for the 7vPnC/13vPnC group were handled as follows. In summaries of local reactions, systemic events, and AEs that occurred during the infant series or between the infant series and toddler dose, data for subjects in this treatment group were pooled with data for subjects in the 7vPnC groups; and in summaries of events that occurred after the toddler dose, data for these subjects were pooled with data for the 13vPnC groups.

The following descriptions of data analyses apply both to the analyses of individual study data (as reported in the CSRs) and to the integrated data analyses, unless otherwise specified.

10.2.2.1 Solicited Adverse Events

Data regarding local reactions and systemic events are summarized separately for each dose in the infant series (dose 1, dose 2, and dose 3) and for the toddler dose. Separate safety populations are defined for each dose and include all subjects who were vaccinated at that dose and had e-diary data during the protocol-specified period (usually 4 days or 7 days) after the respective dose. Subjects who had no e-diary data for a particular dose period are excluded from that analysis. Details regarding the interpretation of diary data for inclusion in the analyses and the rules for exclusion of missing data are detailed in the individual study reports. Data for local

reactions and systemic events are analyzed according to the vaccine actually administered (13vPnC or 7vPnC) at the specified dose, rather than according to the randomly assigned vaccine group.

Statistical differences in incidence between the 13vPnC group and the 7vPnC group were evaluated in each study using the Fisher exact test. However, because of the large number of comparisons, significant findings must be interpreted with caution, and should be viewed primarily as identifying reactions and events that require additional evaluation.

10.2.2.2 Unsolicited Adverse Events

Adverse events are summarized separately for each dose (dose 1, dose 2, dose 3, and the toddler dose) and for any time during the infant series. These summaries include all AEs reported during the protocol-specified time frames as follows:

Dose 1: from dose 1 to the next scheduled visit
(generally between 4 and 10 weeks, depending on the study)
Dose 2: from dose 2 to the next scheduled visit
(generally between 4 and 10 weeks, depending on the study)
Dose 3: from dose 3 to the visit for the postinfant series blood draw
(generally between 4 and 6 weeks, depending on the study)
Infant series: from dose 1 through the visit for the postinfant series blood draw
Toddler dose: from the toddler dose to the visit for the posttoddler dose blood draw
(generally between 4 and 6 weeks, depending on the study)

In addition, AEs are summarized for the period between the infant series and the toddler dose (from the visit for the postinfant series blood draw to the visit for the toddler dose), and for the 6-month follow-up phone contact (from the visit for the posttoddler dose blood draw through the 6-month follow-up phone contact).

Separate safety populations are defined for each dose and include all subjects who were vaccinated at that dose and had AE data for the time period corresponding to the dose (i.e., either had an AE reported or had a CRF confirming "no AE"). Subjects who had no data for a particular dose period are excluded from that analysis. For summaries of AEs during the entire infant series, the safety population includes any subject who is included in the dose 1, dose 2, or dose 3 safety populations.

For the period between the infant series and the toddler dose, and for the 6-month follow-up, the AE summaries exclude subjects who did not have any AE data for the period summarized. Note that subjects could have been included in the summarization of AEs for the period between the infant series and the toddler dose even if they had not completed the infant series. This is because subjects could continue in the study even if they had technically failed to complete the infant series because of missing a dose or a blood draw.

In the individual study reports, data for subjects who received a vaccine other than the one to which they were randomly assigned were excluded from the summaries of AEs from the time of administration of the incorrect vaccine. AEs for these subjects are listed separately in the individual study reports. Similarly, in the summaries of integrated data for this SCS, data for subjects who were assigned to 13vPnC but received 7vPnC in error, and data for subjects who were assigned to 7vPnC but received 13vPnC in error, are excluded from the summaries of AEs from the time of administration of the incorrect vaccine. However, because the summaries of AEs in the SCS pool all data for subjects vaccinated with 13vPnC, regardless of formulation or lot, data for subjects in studies 009, 3000, and 3005 who were randomly assigned to 13vPnC but received the wrong lot or formulation of 13vPnC are not excluded from the integrated summaries of AEs for the SCS. This results in some small differences between the SCS and the CSRs in the total numbers of AEs summarized.

Pooled data from all 13 infant studies are used for the analyses of AEs that occurred during the infant series. Data for AEs collected after the infant series (i.e., after the visit for the postinfant series blood draw) are available for the 9 studies with toddler dose data included in this submission (003, 004, 006, 007, 008, 009, 500, 501, and 3000). Pooled data from these 9 studies are used for the summaries of AEs for the toddler dose and for the summaries of AEs reported during the period between the infant series and the toddler dose. The summaries of AEs reported at the 6-month follow-up include data for the 6 infant studies that are fully reported in this submission (studies 003, 004, 006, 009, 500, and 501).

In the data summaries, AEs are categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and are summarized by system organ class (SOC) and preferred term. Summaries show, for each SOC and preferred term, the number and percentage of subjects in each vaccine group who experienced at least 1 event corresponding to the SOC or preferred term and the number of occurrences of the events. For each subject, AEs with the same verbatim term

and same severity from a given visit to subsequent consecutive visits are combined into a single record based on unique start/stop dates. Then, each unique occurrence is summarized only for the period corresponding to the start of the event. It should be noted that because of some minor differences between the CSRs and the SCS in the methods used for summarization of AEs, the total number of AEs reported in the SCS does not precisely match the combined totals from the CSRs. Most of the discrepancies are differences in the number of occurrences counted for a given MedDRA preferred term, rather than differences in the AE incidence (number and percentage of subjects reporting the AE). The resulting differences in AE reports are small and do not affect the overall assessment of the safety of 13vPnC.

Statistical differences in incidence between the 13vPnC group and the 7vPnC group were evaluated in each study using the Fisher exact test. However, because of the large number of comparisons, significant findings must be interpreted with caution, and should be viewed primarily as identifying reactions and events that require additional evaluation.

10.3 Safety Comparison of a 13vPnC P80 containing formulation to 13vPnC without P80- 6096A1-009

Prevnar does not contain P80, and the original formulation of 13vPnC also did not include P80. However, during development, it was found that the addition of 0.02% P80 to the formulation ensured a more robust manufacturing process. Because most studies of 13vPnC had been conducted with the original clinical trial formulation (without P80), a bridging study was necessary to determine whether the addition of P80 affected the safety or immunogenicity of the vaccine. Study 009 was conducted to compare 13vPnC formulated with P80 (13vPnC+P80) with the original clinical trial formulation without P80 (13vPnC-P80), using an accelerated infant series schedule. Results of the final infant series analyses confirmed that the immunogenicity and safety profiles of the 2 formulations were similar (Tables 10-1 to 10-8).

Table 10-1: Subjects Reporting Local Reactions - Dose 1 Infant Series

	Vaccine Group (as Administered)						
	13vPnC+P80			13vPnC-P80			
Local Reaction	**N**[a]	**n**[b]	**%**	**N**[a]	**n**[b]	**%**	**p-Value**[c]
Tenderness							
Any	238	66	27.7	237	78	32.9	0.232
Significant[d]	235	5	2.1	233	10	4.3	0.201
Induration							
Any	236	54	22.9	239	73	30.5	0.063
Mild[e]	236	43	18.2	236	57	24.2	0.143
Moderate[e]	236	28	11.9	236	34	14.4	0.496
Severe[e]	235	0	0.0	233	0	0.0	N/A
Erythema							
Any	238	71	29.8	238	94	39.5	0.034
Mild[e]	238	67	28.2	235	84	35.7	0.093
Moderate[e]	235	5	2.1	232	10	4.3	0.200
Severe[e]	235	0	0.0	231	0	0.0	N/A
Any of the above	240	119	49.6	241	146	60.6	0.017

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = number of subjects reporting the specific characteristic.
c. Fisher exact test, 2-sided.
d. Significant = present and interfered with limb movement.
e. Mild, 0.5 - 2.0 cm; moderate, 2.5 - 7.0 cm; and severe, >7.0 cm.

Program ID: Study 6096A1-009/CP int_saf_loc_sum.sas. Runtime ID: 29NOV2007 13:45
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/009/Reports, Tables, and Figures/Safety_Locals/6096-009 int_saf_L_sum_dose1.htm.

Table 10-2: Subjects Reporting Local Reactions - Dose 2 Infant Series

	Vaccine Group (as Administered)						
	13vPnC+P80			13vPnC-P80			
Local Reaction	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**	**p-Value[c]**
Tenderness							
Any	228	61	26.8	229	75	32.8	0.184
Significant[d]	220	2	0.9	221	1	0.5	0.623
Induration							
Any	228	57	25.0	228	83	36.4	0.011
Mild[e]	227	46	20.3	226	72	31.9	0.005
Moderate[e]	224	25	11.2	224	32	14.3	0.395
Severe[e]	220	0	0.0	221	0	0.0	N/A
Erythema							
Any	232	90	38.8	231	112	48.5	0.039
Mild[e]	232	89	38.4	230	108	47.0	0.074
Moderate[e]	220	3	1.4	222	7	3.2	0.338
Severe[e]	220	0	0.0	221	0	0.0	N/A
Any of the above	237	133	56.1	235	156	66.4	0.024

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = number of subjects reporting the specific characteristic.
c. Fisher exact test, 2-sided.
d. Significant = present and interfered with limb movement.
e. Mild, 0.5 - 2.0 cm; moderate, 2.5 - 7.0 cm; and severe, >7.0 cm.

Program ID: Study 6096A1-009/CP int_saf_loc_sum.sas. Runtime ID: 29NOV2007 13:45
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/009/Reports, Tables, and Figures/Safety_Locals/6096-009 int_saf_L_sum_dose2.htm.

Table 10-3: Subjects Reporting Local Reactions - Dose 3 Infant Series

	Vaccine Group (as Administered)						
	13vPnC+P80			13vPnC-P80			
Local Reaction	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**	**p-Value[c]**
Tenderness							
Any	210	52	24.8	216	50	23.1	0.734
Significant[d]	203	3	1.5	211	4	1.9	>.99
Induration							
Any	210	77	36.7	225	86	38.2	0.767
Mild[e]	209	68	32.5	221	74	33.5	0.838
Moderate[e]	208	29	13.9	217	38	17.5	0.352
Severe[e]	203	0	0.0	211	0	0.0	N/A
Erythema							
Any	216	101	46.8	226	113	50.0	0.507
Mild[e]	215	100	46.5	226	106	46.9	>.99
Moderate[e]	206	8	3.9	211	19	9.0	0.045
Severe[e]	203	0	0.0	211	0	0.0	N/A
Any of the above	219	132	60.3	230	142	61.7	0.772

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = number of subjects reporting the specific characteristic.
c. Fisher exact test, 2-sided.
d. Significant = present and interfered with limb movement.
e. Mild, 0.5 - 2.0 cm; moderate, 2.5 - 7.0 cm; and severe, >7.0 cm.

Program ID: Study 6096A1-009/CP int_saf_loc_sum.sas. Runtime ID: 29NOV2007 13:45
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/009/Reports, Tables, and Figures/Safety_Locals/6096-009 int_saf_L_sum_dose3.htm.

Table 10-4: Subjects Reporting Systemic Events and Medication Use - Dose 1 Infant Series

	Vaccine Group (as Administered)						
	13vPnC+P80			13vPnC-P80			
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%	p-Value[c]
Fever ≥38°C but ≤39°C	236	33	14.0	235	38	16.2	0.522
Fever >39°C but ≤40°C	235	1	0.4	233	1	0.4	>.99
Fever >40°C	235	0	0.0	233	0	0.0	N/A
Decreased appetite	237	51	21.5	237	53	22.4	0.912
Irritability	240	132	55.0	239	132	55.2	>.99
Increased sleep	242	112	46.3	242	127	52.5	0.203
Decreased sleep	238	85	35.7	236	70	29.7	0.171
Use of medication to treat symptoms	236	33	14.0	235	39	16.6	0.445
Use of medication to prevent symptoms	235	34	14.5	234	37	15.8	0.701
Any systemic event[d]	244	194	79.5	245	203	82.9	0.357

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = number of subjects experiencing the event.
c. Fisher exact test, 2-sided.
d. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, and decreased sleep.

Program ID: Study 6096A1-009/CP int_saf_sys_sum.sas. Runtime ID: 27NOV2007 8:20
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/009/Reports, Tables, and Figures/Safety_Systemic/6096-009 int_saf_S_sum_dose1.htm.

Table 10-5: Subjects Reporting Systemic Events and Medication Use - Dose 2 Infant Series

	Vaccine Group (as Administered)						
	13vPnC+P80			13vPnC-P80			
Systemic Event	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**	**p-Value[c]**
Fever ≥38°C but ≤39°C	224	41	18.3	229	39	17.0	0.805
Fever >39°C but ≤40°C	221	2	0.9	221	1	0.5	>.99
Fever >40°C	221	0	0.0	221	0	0.0	N/A
Decreased appetite	221	36	16.3	224	54	24.1	0.045
Irritability	232	120	51.7	232	125	53.9	0.710
Increased sleep	231	83	35.9	229	90	39.3	0.501
Decreased sleep	227	56	24.7	227	60	26.4	0.747
Use of medication to treat symptoms	222	34	15.3	226	38	16.8	0.701
Use of medication to prevent symptoms	220	36	16.4	223	34	15.2	0.795
Any systemic event[d]	239	179	74.9	242	194	80.2	0.190

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = number of subjects experiencing the event.
c. Fisher exact test, 2-sided.
d. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, and decreased sleep

Program ID: Study 6096A1-009/CP int_saf_sys_sum.sas. Runtime ID: 27NOV2007 8:20
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/009/Reports, Tables, and Figures/Safety_Systemic/6096-009 int_saf_S_sum_dose2.htm.

Table 10-6: Subjects Reporting Systemic Events and Medication Use - Dose 3 Infant Series

	Vaccine Group (as Administered)						
	13vPnC+P80			13vPnC-P80			
Systemic Event	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**	**p-Value[c]**
Fever ≥38°C but ≤39°C	208	41	19.7	218	45	20.6	0.904
Fever >39°C but ≤40°C	203	2	1.0	211	2	0.9	>.99
Fever >40°C	203	0	0.0	211	0	0.0	N/A
Decreased appetite	210	45	21.4	222	46	20.7	0.906
Irritability	215	98	45.6	226	113	50.0	0.391
Increased sleep	209	54	25.8	221	61	27.6	0.744
Decreased sleep	209	53	25.4	217	53	24.4	0.911
Use of medication to treat symptoms	205	31	15.1	218	32	14.7	>.99
Use of medication to prevent symptoms	205	31	15.1	217	23	10.6	0.190
Any systemic event[d]	222	150	67.6	234	156	66.7	0.843

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = number of subjects experiencing the event.
c. Fisher exact test, 2-sided.
d. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, and decreased sleep.

Program ID: Study 6096A1-009/CP int_saf_sys_sum.sas. Runtime ID: 27NOV2007 8:20
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/009/Reports, Tables, and Figures/Safety_Systemic/6096-009 int_saf_S_sum_dose3.htm.

Table 10-7: Subjects Reporting Local Reactions - Toddler Dose

	Vaccine Group (as Administered)						
	13vPnC+P80			13vPnC-P80			
Local Reaction	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**	**p-Value[c]**
Tenderness							
Any	178	75	42.1	188	81	43.1	0.916
Significant[d]	160	4	2.5	165	2	1.2	0.442
Induration							
Any	174	52	29.9	181	63	34.8	0.364
Mild[e]	169	45	26.6	178	53	29.8	0.552
Moderate[e]	164	20	12.2	171	34	19.9	0.074
Severe[e]	159	0	0.0	164	0	0.0	N/A
Erythema							
Any	178	75	42.1	200	104	52.0	0.063
Mild[e]	176	63	35.8	194	90	46.4	0.045
Moderate[e]	164	21	12.8	173	34	19.7	0.105
Severe[e]	159	0	0.0	164	1	0.6	>.99
Any of the above	190	110	57.9	210	135	64.3	0.218

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the specific characteristic.
c. Fisher exact test, 2-sided.
d. Significant = present and interfered with limb movement.
e. Mild, 0.5 - 2.0 cm; moderate, 2.5 - 7.0 cm; and severe, >7.0 cm.

Program ID: Study 6096A1-009/CP tod_saf_loc_sum.sas. Runtime ID: 02JUL2008 16:30.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/009/ Reports, Tables, and Figures/Safety_Locals/6096-009 saf_lr_sum_tod.htm.

Table 10-8: Subjects Reporting Systemic Events and Antipyretic Medication Use - Toddler Dose

	Vaccine Group (as Administered)						
	13vPnC+P80			13vPnC-P80			
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%	p-Value[c]
Fever ≥38°C but ≤39°C	170	39	22.9	172	31	18.0	0.285
Fever >39°C but ≤40°C	162	4	2.5	164	3	1.8	0.722
Fever >40°C	160	0	0.0	164	0	0.0	N/A
Decreased appetite	172	45	26.2	183	53	29.0	0.635
Irritability	184	91	49.5	198	111	56.1	0.219
Increased sleep	174	33	19.0	182	56	30.8	0.010
Decreased sleep	170	33	19.4	180	46	25.6	0.201
Use of medication to treat symptoms	172	37	21.5	168	26	15.5	0.165
Use of medication to prevent symptoms	171	32	18.7	171	26	15.2	0.471
Any systemic event[d]	201	138	68.7	216	159	73.6	0.280

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Fisher exact test, 2-sided.
d. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, and decreased sleep.

Program ID: Study 6096A1-009/CP tod_saf_sys_sum.sas. Runtime ID: 02JUL2008 16:29.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/009/ Reports, Tables, and Figures/Safety_Systemic/6096-009 saf_se_sum_tod.htm.

In addition, in study 3000 and study 3005 in which 13vPnC in the final P80-containing formulation was used, the incidence rates of local reactions and systemic events were similar to those seen in study 009 (data not shown). Therefore, because the addition of P80 did not alter the safety and reactogenicity of 13vPnC (as expected), it was possible to pool the safety data from all 13 infant studies into an integrated database.

10.4 Integrated 13vPnC Safety Database

This integrated safety database includes data for 7532 subjects randomly assigned to treatment in the 13 infant studies: 4758 were assigned to 13vPnC and 2774 to 7vPnC. Of these, 4729 subjects in the 13vPnC group and 2760 subjects in the 7vPnC group were vaccinated at dose 1. Overall, 99.4% of randomly assigned subjects were vaccinated at dose 1, 95.1% were vaccinated at dose 2, and 81.7% received a third dose of study vaccine. The proportion of all randomly assigned subjects vaccinated at dose 3 (81.7%) describes the extent of exposure in all infant studies, but cannot be viewed as a measure of compliance because a total of 892 subjects (444 in the 13vPnC group and 448 in the 7vPnC group) were randomly assigned to vaccine in studies

that used a 2-dose infant series. Therefore, a true "compliance" rate for dose 3 would be calculated as 3990/4314 = 92.5% for 13vPnC, and 2160/2326 = 92.9% for 7vPnC. Among subjects randomly assigned to vaccine, 92.0% completed the infant series (i.e., completed the visit for the postinfant series blood draw after either dose 2 or dose 3, depending on the study). Tables 10-9 and 10-10 describe the disposition and demography of subjects in the infant safety database.

Table 10-9: Disposition of Subjects – Infant Series (All 13 Infant Studies)

	Vaccine Group (as Randomized)					
	13vPnC		7vPnC		Total	
	n	%	n	%	n	%
Randomized[a]	4758	100.0	2774	100.0	7532	100.0
Vaccinated						
Dose 1	4729	99.4	2760	99.5	7489	99.4
Dose 2	4526	95.1	2634	95.0	7160	95.1
Dose 3	3990	83.9	2160	77.9	6150	81.7
Completed infant series[b]	4375	92.0	2554	92.1	6929	92.0
Withdrawn during infant series	382	8.0	220	7.9	602	8.0
Reason for withdrawal						
Parent/legal guardian request	136	2.9	70	2.5	206	2.7
Clinical hold – consent withdrawn	56	1.2	57	2.1	113	1.5
Protocol violation	50	1.1	26	0.9	76	1.0
Lost to follow-up	51	1.1	21	0.8	72	1.0
Failed to return	34	0.7	22	0.8	56	0.7
Other	21	0.4	10	0.4	31	0.4
Adverse event	15	0.3	8	0.3	23	0.3
Investigator request	17	0.4	5	0.2	22	0.3
Death	2	0.0	1	0.0	3	0.0

Note: completion status is unknown. for Subject 3005-032-003041 in the 13vPnC group.
Infant series = from dose 1 to postinfant series blood draw.

a. The values in this row are used as the denominators for percentages. In this table, subjects in study 008 who were randomly assigned to receive 7vPnC during the infant series and 13vPnC at the toddler dose are included in the 7vPnC group.
b. Completed the visit for the postinfant series blood draw. All studies had a 3-dose infant series, except studies 007 and 500, which had a 2-dose infant series.

Program ID: Study 6096A1-ISS_US/CP CS_DISP.SAS. Runtime ID: 08DEC2008 16:47
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/adhoc1.zip (cs_disp_inf.htm) (footnote modified)

Table 10-10: Demographic Characteristics: Infant Series Safety Population (All 13 Infant Studies)

	Vaccine Group (as Randomized)					
	13vPnC N = 4728[b]		7vPnC[a] N = 2760[b]		Total N = 7488[b]	
	n	%	n	%	n	%
Sex						
Male	2473	52.3	1451	52.6	3924	52.4
Female	2255	47.7	1309	47.4	3564	47.6
Race						
White	4006	84.7	2282	82.7	6288	84.0
Black or African American	302	6.4	148	5.4	450	6.0
Asian	228	4.8	208	7.5	436	5.8
Other	171	3.6	114	4.1	285	3.8
Hispanic	11	0.2	6	0.2	17	0.2
Native Hawaiian or Other Pacific Islander	7	0.1	1	0.0	8	0.1
American Indian or Alaska Native	3	0.1	1	0.0	4	0.1
Ethnicity						
Non-Hispanic and Non-Latino	4262	90.1	2464	89.3	6726	89.8
Hispanic or Latino	343	7.3	168	6.1	511	6.8
Unknown	123	2.6	128	4.6	251	3.4
Age at enrollment (months)						
n	4728		2760		7488	
Mean (SD)	2.2 (0.5)		2.2 (0.5)		2.2 (0.5)	
Median	2.1		2.1		2.1	
Min, Max	0.0, 4.0		0.1, 4.1		0.0, 4.1	
Weight at enrollment (kg)						
n	4603		2630		7233	
Mean (SD)	5.3 (0.8)		5.3 (0.8)		5.3 (0.8)	
Median	5.3		5.3		5.3	
Min, Max	1.7, 9.8		2.2, 9.2		1.7, 9.8	

a. In this table, subjects in study 008 who were randomly assigned to receive 7vPnC during the infant series and 13vPnC at the toddler dose are included in the 7vPnC group.

b. The infant series safety population includes subjects who received at least 1 infant series vaccination and had safety data reported during the infant series. The number of subjects in this population may differ from the total number of subjects vaccinated during the infant series.

Program ID: Study 6096A1-ISS_US/CP CS_DEMO.SAS. Runtime ID: 18NOV2008 14:18

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/ISSResultsv1.zip (cs_demo_saf_inf.htm) (footnote modified)

During the infant series, AEs resulted in the withdrawal of 15 subjects (0.3%) vaccinated with 13vPnC and 8 subjects (0.3%) vaccinated with 7vPnC. In addition, 3 subjects died during the infant series (2 vaccinated with 13vPnC and 1 vaccinated with 7vPnC). All 3 deaths were attributed to sudden infant death syndrome (SIDS) by the investigator and considered not related to study vaccine.

Toddler safety data (in addition to infant data) are available for 2512 subjects who received 13vPnC and 1492 who received 7vPnC (Table 10-11 and 10-12). The rates of study withdrawal were 3.4% among 13vPnC recipients and 4.3% among 7vPnC recipients during the interval between the infant series and toddler dose (Table 10-13), and 0.8% and 1.4%, respectively, during the toddler dose period (Table 10-11). During the period between the infant series and toddler dose, AEs resulted in withdrawals of 0.3% and 0.5%, respectively. One (1) subject in the 13vPnC group died during this period. The investigator considered this death to be the result of SIDS and not related to study vaccine.

Table 10-11: Disposition of Subjects – Toddler Dose
(9 Infant Studies With Toddler Dose Data)

	Vaccine Group (as Randomized)					
	13vPnC[a]		7vPnC		Total	
	n	%	n	%	n	%
Randomized to receive toddler dose[b]	2741	100.0	1672	100.0	4413	100.0
Vaccinated toddler dose	2515	91.8	1500	89.7	4015	91.0
Completed toddler dose[c]	2494	91.0	1476	88.3	3970	90.0
Withdrawn during toddler dose	21	0.8	24	1.4	45	1.0
Reason for withdrawal						
Lost to follow-up	10	0.4	14	0.8	24	0.5
Parent/legal guardian request	6	0.2	5	0.3	11	0.2
Protocol violation	3	0.1	2	0.1	5	0.1
Failed to return	2	0.1	3	0.2	5	0.1

Toddler dose data are available for 9 infant studies in this submission: 003, 004, 006, 007, 008, 009, 500, 501, 3000.
Toddler dose = from toddler dose to posttoddler dose blood draw.
a. Subjects in study 008 who were randomly assigned to receive 7vPnC in the infant series followed by 13vPnC at the toddler dose are summarized in the 13vPnC group.
b. The values in this row are used as the denominators for percentages.
c. Completed visit for posttoddler dose blood draw.
Program ID: Study 6096A1-ISS_US/CP CS_DISP.SAS. Runtime ID: 06JAN2009 13:53
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/adhoc4.htm

Table 10-12: Demographic Characteristics: Toddler Dose Safety Population (9 Studies With Toddler Dose Data)

	Vaccine Group (as Randomized)					
	13vPnC[a] N = 2512[b]		7vPnC N = 1492[b]		Total N = 4004[b]	
	n	%	n	%	n	%
Sex						
Male	1274	50.7	810	54.3	2084	52.0
Female	1238	49.3	682	45.7	1920	48.0
Race						
White	2351	93.6	1337	89.6	3688	92.1
Black or African American	96	3.8	80	5.4	176	4.4
Other	46	1.8	54	3.6	100	2.5
Asian	15	0.6	19	1.3	34	0.8
Hispanic	4	0.2	1	0.1	5	0.1
Native Hawaiian or Other Pacific Islander	0	0.0	1	0.1	1	0.0
Ethnicity						
Non-Hispanic and Non-Latino	2346	93.4	1309	87.7	3655	91.3
Unknown	89	3.5	104	7.0	193	4.8
Hispanic or Latino	77	3.1	79	5.3	156	3.9
Age at toddler dose (months)						
n	2512		1492		4004	
Mean (SD)	12.6 (1.1)		12.6 (1.3)		12.6 (1.2)	
Median	12.3		12.2		12.2	
Min, Max	10.5, 16.7		10.8, 16.4		10.5, 16.7	

Toddler dose data are available for 9 infant studies in this submission: 003, 004, 006, 007, 008, 009, 500, 501, and 3000.

a. In this table, subjects in study 008 who were randomly assigned to receive 7vPnC in the infant series and 13vPnC at the toddler dose are summarized in the 13vPnC group.

b. The toddler dose safety population included subjects who were vaccinated at the toddler dose and had safety data reported between the toddler dose and the visit for the posttoddler dose blood draw. The number of subjects in this population may differ from the total number of subjects vaccinated at the toddler dose.

Program ID: Study 6096A1-ISS_US/CP CS_DEMO.SAS. Runtime ID: 12DEC2008 16:49
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/adhoc2.zip (cs_demo_saf_tod) (footnote modified)

Table 10-13: Disposition of Subjects – Between Infant Series and Toddler Dose (9 Infant Studies With Toddler Dose Data)

	Vaccine Group (as Randomized)					
	13vPnC		7vPnC		Total	
	n	%	n	%	n	%
Randomized in infant series[a]	2590	100.0	1823	100.0	4413	100.0
Vaccinated in the infant series	2578	99.5	1812	99.4	4390	99.5
Completed infant series	2465	95.2	1715	94.1	4180	94.7
Withdrawn after infant series, before toddler dose	87	3.4	78	4.3	165	3.7
Reason for withdrawal						
Parent/legal guardian request	28	1.1	23	1.3	51	1.2
Failed to return	19	0.7	18	1.0	37	0.8
Lost to follow-up	9	0.3	11	0.6	20	0.5
Protocol violation	10	0.4	9	0.5	19	0.4
Adverse event	7	0.3	9	0.5	16	0.4
Other	10	0.4	4	0.2	14	0.3
Investigator request	3	0.1	4	0.2	7	0.2
Death	1	0.0	0	0.0	1	0.0

Toddler dose data are available for 9 infant studies in this submission: 003, 004, 006, 007, 008, 009, 500, 501, 3000.
Infant series = from dose 1 to postinfant series blood draw.

a. The values in this row are used as the denominators for percentages. In this table, subjects in study 008 who were randomly assigned to receive 7vPnC during the infant series and 13vPnC at the toddler dose are included in the 7vPnC group.

Program ID: Study 6096A1-ISS_US/CP CS_DISP.SAS. Runtime ID: 08DEC2008 16:47
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/adhoc1.zip (cs_disp_btw_inf_tod.htm) (footnote modified)

There were no differences in demographic characteristics (sex ratio, race, ethnicity, age, and weight at enrollment) between infants assigned to 13vPnc and 7vPnC at the time of the first dose, or at the time of the toddler dose.

Information collected during the 6-month follow-up period is available for 6 studies, including 1713 subjects who received 13vPnC and 1226 who received 7vPnC (Table 10-14). A follow-up telephone contact was attempted for all subjects 6 months after their last vaccination, including those subjects who had been withdrawn from the study before receiving all vaccine doses. In the 6 studies, the contact was successfully completed for 91.3% of subjects in the 13vPnC group and 89.6% of subjects in the 7vPnC group.

Safety data were provided in 1 study (study 3002) for 354 children older than 6 months, up to the age of 5 years (<72 months), who had not previously received a pneumococcal vaccine (Table 10-15). The group assignments are as follows:

- Group 1: enrolled at 7 to <12 months of age and received 3 doses of 13vPnC.
- Group 2: enrolled at 12 to <24 months of age and received 2 doses of 13vPnC.
- Group 3: enrolled at 24 to <72 months of age and received 1 dose of 13vPnC.

Table 10-14: Disposition of Subjects – 6-Month Follow-up Telephone Contact (6 Studies With Data for 6-Month Follow-up)

	Vaccine Group (as Randomized)					
	13vPnC		7vPnC		Total	
	n	%	n	%	n	%
Randomized[a]	1876	100.0	1369	100.0	3245	100.0
Vaccinated in infant series	1869	99.6	1364	99.6	3233	99.6
Completed infant series	1776	94.7	1284	93.8	3060	94.3
Completed toddler dose[b]	1698	90.5	1205	88.0	2903	89.5
Withdrawn after toddler dose but before 6-month follow-up	14	0.7	12	0.9	26	0.8
Reason for withdrawal						
Lost to follow-up	13	0.7	11	0.8	24	0.7
Protocol violation	0	0.0	1	0.1	1	0.0
Parent/legal guardian request	1	0.1	0	0.0	1	0.0
Completed study[c]	1684	89.8	1193	87.1	2877	88.7
Entered 6-month follow-up[d]	1741	92.8	1251	91.4	2992	92.2
Completed 6-month follow-up	1713	91.3	1226	89.6	2939	90.6

Infant series = from dose 1 to postinfant series blood draw. Toddler dose = from toddler dose to posttoddler dose blood draw.

6-month follow-up data are available for 6 infant studies in this submission: 003, 004, 006, 009, 500, 501.

a. The values in this row are used as the denominators for percentages.
b. Completed visit for posttoddler dose blood draw.
c. Subjects completing the study are defined as those who did not withdraw from the study and completed the infant series, toddler dose, and 6-month follow-up contact.
d. A telephone contact was to be attempted for all subjects 6 months after their last vaccination, including subjects who withdrew from the study before receiving all vaccine doses. At completion of the posttoddler dose visit or at early withdrawal, the investigator was to indicate on the disposition form whether the subject intended to enter the 6-month follow-up.

Program ID: Study 6096A1-ISS_US/CP CS_DISP.SAS. Runtime ID: 08DEC2008 16:47
Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/adhoc1.zip (cs_disp_fup.htm)

Table 10-15: Disposition of Subjects – Study 3002 in Older Infants and Young Children

	Vaccine Group (as Enrolled)							
	13vPnC Group 1		13vPnC Group 2		13vPnC Group 3		Total	
	n	%	n	%	n	%	n	%
Consented	90	100.0	112	100.0	153	100.0	355	100.0
Enrolled[a]	90	100.0	112	100.0	153	100.0	355	100.0
Vaccinated								
Dose 1	90	100.0	112	100.0	152	99.3	354	99.7
Dose 2	90	100.0	112	100.0	0	0.0	202	56.9
Dose 3	89	98.9	0	0.0	0	0.0	89	25.1
Completed	88	97.8	112	100.0	152	99.3	352	99.2
Withdrawn	2	2.2	0	0.0	1	0.7	3	0.8
Reason for withdrawal								
Protocol violation	0	0.0	0	0.0	1	0.7	1	0.3
Parent/legal guardian request	1	1.1	0	0.0	0	0.0	1	0.3
Lost to follow-up	1	1.1	0	0.0	0	0.0	1	0.3

Subject 3002-009-000831, in Group 3, was enrolled but never vaccinated.
a. The values in this row are used as the denominators for percentages.
Program ID: Study 6096A1-3002/CP CS_DISP.SAS. Runtime ID: 07JUL2008 19:48
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3002/Reports, Tables, and Figures/Conduct of Study/6096-3002 cs_disp.htm

10.4.1 Population

All infant studies included healthy infants aged between 6 weeks and 3 months at time of the first dose of 13vPnC. In addition, study 3002 included healthy older infants and young children up to the age of 5 years. In all studies, previous vaccination with a registered or an investigational pneumococcal vaccine was an exclusion criterion.

A written and dated informed consent was obtained from the parent(s)/legal guardian(s) for all study subjects.

10.4.2 Limitations of the Safety Database

The study population across all trials represented a homogenous group of healthy infants and young children who had not previously received a pneumococcal vaccine. The safety of 13vPnC has not been evaluated in children presenting with a recognized medical condition that places them at increased risk of pneumococcal disease. To this end, the safety and immunogenicity of

13vPnC will be assessed in postapproval studies conducted in children with human immunodeficiency virus (HIV) infection, in premature infants, and in children with sickle cell disease who were previously vaccinated with 23vPS.

The safety of a fifth or sixth dose of a CRM_{197} conjugated pneumococcal vaccine is currently being evaluated, as such information will be useful in planning strategies for 13vPnC immunization of children who have received a complete series of Prevnar (7vPnC). This issue will be addressed in 2 studies (6096A1-3010 and 6096A1-3011).

10.4.3 Analysis of Adverse Reactions

The safety of 13vPnC was evaluated on the basis of prompted AEs, including local reactions and systemic events, as well as spontaneously reported AEs. Data on prompted AEs were recorded daily by the parent(s)/legal guardian(s) for 4 days after each dose. In studies 004 and 3005, information was collected for 7 days after each dose.

Comparisons between the 13vPnC and 7vPnC groups were made using a meta-analysis statistical procedure that detected significant numeric differences between the 2 groups. This approach is a sensitive screening tool designed to identify any small differences that would not otherwise be detected in a single trial. Any such differences were then evaluated for potential clinical importance.

10.4.4 Statistical Approach to Integrated Data Analyses

For analyses of integrated data comparing the incidence of local reactions, systemic events, and AEs between the vaccine groups, a generalized linear mixed model was used to characterize the effect of vaccination with 13vPnC relative to 7vPnC, employing a random effect term for study and a fixed effect term for vaccine group (13vPnC, 7vPnC) by dose. The logit link function was used. Odds ratios, p-values for the common null hypothesis of odds ratio = 1, and 95% confidence intervals were derived for 13vPnC:7vPnC for each endpoint by dose. For any analysis for which the model would not produce a p-value (due to sparsity of data, for example), a listing of relevant data was produced, and the Fisher exact test was used to compare vaccine groups if the models did not converge.

Meta-analyses of the safety data (including the incidence of local reactions, systemic events, and AEs) followed the principles of meta-analysis of individual patient binary data as described in

Whitehead's *Meta-Analysis of Controlled Clinical Trials*.[88] A brief summary of the statistical method follows. A full description of the methods used in the integrated data analyses is available in the integrated statistical analysis plan (ISAP).

The method assumes, for each given event, that a true (and unknown) numeric difference in vaccine effect (i.e., difference in incidence) exists between subjects who received 13vPnC and subjects who received 7vPnC. No assumption around the magnitude of this numeric difference is made, and it can be greater than or less than or equal to zero for a difference in observed rates between regimens. For each event, it is assumed that the measured magnitude of the difference in a given study will vary above or below the true (and unknown) numeric value in a random manner.

To derive a precise estimate of the true and unknown numeric difference, a mixed effect, meta-analysis model is employed pooling individual data across studies, accounting for each study as its own control. In this manner, all data collected are utilized in assessing statistical inference between 13vPnC and 7vPnC. Estimates for the treatment difference are weighted according to the degree of precision arising from each study such that those with greater sample size are deemed to contribute a higher degree of information. These estimates are then used to derive a test statistic (odds ratio) and are expressed as a p-value to assess whether the true (and unknown) magnitude of the treatment difference is non-null. More details of the analysis plan may be found in the ISAP. For events for which too few events were observed to allow the model to converge, the Fisher exact test was used to test for a difference between 13vPnC and 7vPnC.

This is an extremely powerful statistical method, and if differences are not observed between vaccines, it is unlikely that they exist in a manner that can be practically detected in clinical trials. Given the sample sizes involved (e.g., N = 4723 for the 13vPnC group and N = 2754 for the 7vPnC group in the infant series), and the multiplicative nature of such statistical testing (for AEs, in particular, this test is conducted for each preferred MedDRA term), it is expected that many false-positive findings will be generated.

For example, note that as percentages get closer to zero, the statistical measure of spread (variance) becomes smaller, since the incidence rate is bounded by zero (i.e., a percentage cannot be less than 0). The differences in the denominators (N = 4723 for 13vPnC, N = 2754 for

7vPnC) give enough of a difference in these "forced" small variances to be detected statistically. For example, for acute sinusitis, the percentages are 0.064% and 0.145% for 13vPnC and 7vPnC, respectively, corresponding to an odds ratio of about 44% for 13vPnC:7vPnC. Although this may be significant statistically, it is highly unlikely to be of clinical relevance.

In the tables of this document, unadjusted event counts and the percentage of subjects with an event are presented along with the model-derived p-value to facilitate clinical review of events for which the statistics deem that a difference between 13vPnC and 7vPnC may exist. These findings should be viewed as a statistical screening tool, and should be used only to highlight the potential need for clinical assessment of significance.

10.4.5 Prompted Adverse Events

10.4.5.1 Local Reactions

The frequency and intensity of local reactions at the injection site of 13vPnC were found to be similar to those for 7vPnC (Table 10-16).

Tenderness was reported in 39.9% to 46.7% of infants after each 13vPnC dose of the infant series, and in 48.8% after the toddler dose. Significant tenderness (interfering with limb movement) was reported in no more than 8.0% of infants.

Induration was noted in 21.8% to 28.5% of infants after each 13vPnC dose of the infant series, and 35.3% after the toddler dose. Most induration was mild (0.5 to 2.0 cm); severe induration (more than 7.0 cm) was reported for 2 infants after dose 2 and for 1 subject after the toddler dose.

Erythema was reported in 25.3% to 36.4% of infants after each 13vPnC dose of the infant series, and in 46.6% after the toddler dose. There was a trend for a dose-related increase in erythema from dose 1 to dose 4. Most erythema was mild (less than 2.0 cm). There were 6 reports of severe erythema (more than 7.0 cm) in the 13vPnC group (2 after dose 2, 1 after dose 3, and 3 after the toddler dose), and 1 report in the 7vPnC group following the toddler dose.

The results of the meta-analysis demonstrate that 13vPnC has a similar local reactogenicity profile as 7vPnC. This conclusion is supported by the analysis of local reactions in each study.

Although some differences were sporadically found between 13vPnC and 7vPnC, there was no consistent trend in the observed differences across studies.

Older subjects (in study 3002) generally exhibited increased rates of local reactions compared with the infants. This suggests that a trend toward increased rate of tenderness with age at first dose was seen across the 3 age groups. Most of these local reactions were mild.

- Group 1: enrolled at 7 to <12 months of age and received 3 doses of 13vPnC.
- Group 2: enrolled at 12 to <24 months of age and received 2 doses of 13vPnC.
- Group 3: enrolled at 24 to <72 months of age and received 1 dose of 13vPnC.

(Tables 10-17 through 10-19)

Table 10-16: Subjects Reporting Local Reactions: Infant and Toddler Doses (All 13 Infant Studies)

	Dose 1[a]			Dose 2[a]			Dose 3[a]			Toddler[b]		
	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]
Tenderness												
N	4159	2431		3652	2090		3054	1621		1798	959	
Any	1941 (46.7)	1088 (44.8)	0.552	1612 (44.1)	888 (42.5)	0.638	1218 (39.9)	611 (37.7)	0.856	878 (48.8)	522 (54.4)	0.005[f]
Significant[d]	304 (8.0)	194 (8.7)	0.911	193 (6.1)	148 (8.0)	0.047	154 (5.8)	71 (5.1)	0.186	82 (5.5)	53 (7.3)	0.965
Induration												
N	3872	2301		3338	1952		2846	1495		1646	823	
Any	844 (21.8)	464 (20.2)	0.130[f]	892 (26.7)	520 (26.6)	0.974[f]	812 (28.5)	402 (26.9)	0.757	581 (35.3)	305 (37.1)	0.279
Mild[e]	725 (18.8)	418 (18.3)	0.588[f]	813 (24.5)	476 (24.5)	0.973[f]	740 (26.2)	368 (24.8)	0.887	529 (32.6)	267 (33.3)	0.653
Moderate[e]	242 (6.4)	98 (4.4)	0.034	205 (6.5)	98 (5.3)	0.573	196 (7.4)	86 (6.2)	0.496	186 (12.4)	83 (11.3)	0.705
Severe[e]	0	0		2 (0.1)	0	0.534[f]	0	0		1 (0.1)	0	>0.999[f]
Erythema												
N	3893	2324		3413	2019		2928	1545		1705	872	
Any	984 (25.3)	609 (26.2)	0.158	1161 (34.0)	666 (33.0)	0.600	1067 (36.4)	523 (33.9)	0.305	794 (46.6)	406 (46.6)	0.275
Mild[e]	922 (23.8)	586 (25.3)	0.064	1106 (32.6)	640 (31.9)	0.354	1014 (34.8)	495 (32.3)	0.299	703 (42.0)	365 (42.6)	0.334
Moderate[e]	93 (2.5)	37 (1.7)	0.009	93 (3.0)	51 (2.8)	0.793[f]	121 (4.6)	63 (4.5)	0.340	205 (13.6)	94 (12.8)	0.519
Severe[e]	0	0		2 (0.1)	0	0.534[f]	1 (0.0)	0	>0.999[f]	3 (0.2)	1 (0.1)	0.745

Follow-up time = 4 days following each dose for all studies except studies 003 (stage 1 = 15 days; stage 2 = 8 days), 004 (7 days), and 3005 (7 days).

a. Infant dose data are included for all 13 infant studies in this submission.

b. Toddler dose data are included for the 9 infant studies with toddler dose data in this submission: studies 003, 004, 006, 007, 008, 009, 500, 501, and 3000.

c. Mixed model used to calculate difference between vaccine groups in percentages of subjects reporting an event (random effect for protocol).

d. Significant = present and interfered with limb movement.

e. Intensity of induration and erythema are rated by the diameter of the affected area: 0.5-2.0 cm = mild; 2.5-7.0 cm = moderate; >7.0 cm = severe.

f. Fisher exact test, 2-sided, used to calculate difference between vaccine groups in percentages of subjects reporting an event.

Program ID: Study 6096A1-ISS_US/CP SAF_LR.SAS. Runtime ID: 16DEC2008 10:58

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/adhoc3.zip (saf_lr_inf_tod)

Table 10-17: Older Children 6096A1-3002 Subjects Reporting Local Reactions Within 4 Days - Dose 1

	Vaccine Group (as Administered)								
	13vPnC Group 1			13vPnC Group 2			13vPnC Group 3		
Local Reaction	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**	**N[a]**	**n[b]**	**%**
Tenderness									
Any	86	13	15.1	108	36	33.3	149	63	42.3
Significant[c]	86	1	1.2	108	0	0.0	147	6	4.1
Induration									
Any	86	31	36.0	110	49	44.5	149	55	36.9
Mild[d]	86	28	32.6	109	40	36.7	149	42	28.2
Moderate[d]	86	10	11.6	109	27	24.8	148	30	20.3
Severe[d]	86	0	0.0	108	0	0.0	147	0	0.0
Erythema									
Any	86	42	48.8	110	77	70.0	148	74	50.0
Mild[d]	86	36	41.9	110	61	55.5	147	55	37.4
Moderate[d]	86	14	16.3	110	42	38.2	148	38	25.7
Severe[d]	86	0	0.0	108	0	0.0	147	0	0.0
Any of the above	86	46	53.5	110	83	75.5	151	102	67.5

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the specific characteristic.
c. Significant = present and interfered with limb movement.
d. Mild, 0.5 – 2.0 cm; moderate, 2.5 – 7.0 cm; and severe, >7.0 cm.

Program ID: Study 6096A1-3002/CP SAF_LR_WITHIN_SUM.SAS. Runtime ID: 07JUL2008 19:55.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3002/
Reports, Tables, and Figures/Safety_Locals/6096-3002 saf_lr_sum_d1.htm.

Table 10-18: Older Children 6096A1-3002 Subjects Reporting Local Reactions Within 4 Days - Dose 2

	Vaccine Group (as Administered)					
	13vPnC Group 1			13vPnC Group 2		
Local Reaction	N[a]	n[b]	%	N[a]	n[b]	%
Tenderness						
Any	86	13	15.1	103	45	43.7
Significant[c]	86	3	3.5	98	4	4.1
Induration						
Any	87	28	32.2	105	43	41.0
Mild[d]	87	25	28.7	105	38	36.2
Moderate[d]	86	12	14.0	99	12	12.1
Severe[d]	86	0	0.0	98	0	0.0
Erythema						
Any	87	40	46.0	106	58	54.7
Mild[d]	87	35	40.2	103	46	44.7
Moderate[d]	86	8	9.3	102	26	25.5
Severe[d]	86	0	0.0	98	0	0.0
Any of the above	87	44	50.6	107	74	69.2

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the specific characteristic.
c. Significant = present and interfered with limb movement.
d. Mild, 0.5 – 2.0 cm; moderate, 2.5 – 7.0 cm; and severe, >7.0 cm.

Program ID: Study 6096A1-3002/CP SAF_LR_WITHIN_SUM.SAS. Runtime ID: 07JUL2008 19:55.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3002/
Reports, Tables, and Figures/Safety_Locals/6096-3002 saf_lr_sum_d2.htm.

Table 10-19: Older Children 6096A1-3002 Subjects Reporting Local Reactions Within 4 Days - Dose 3

		Vaccine Group (as Administered) 13vPnC Group 1	
Local Reaction	**N[a]**	**n[b]**	**%**
Tenderness			
Any	79	12	15.2
Significant[c]	78	5	6.4
Induration			
Any	80	20	25.0
Mild[d]	78	16	20.5
Moderate[d]	80	9	11.3
Severe[d]	78	0	0.0
Erythema			
Any	82	31	37.8
Mild[d]	80	25	31.3
Moderate[d]	80	10	12.5
Severe[d]	78	0	0.0
Any of the above	82	33	40.2

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the specific characteristic.
c. Significant = present and interfered with limb movement.
d. Mild, 0.5 – 2.0 cm; moderate, 2.5 – 7.0 cm; and severe, >7.0 cm.

Program ID: Study 6096A1-3002/CP SAF_LR_WITHIN_SUM.SAS. Runtime ID: 07JUL2008 19:55.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3002/ Reports, Tables, and Figures/Safety_Locals/6096-3002 saf_lr_sum_d3.htm.

10.4.5.2 Systemic Events

Systemic Events Other Than Fever

The results of the meta-analysis of prompted data on systemic events shows no differences in the frequency of the 4 systemic events (decreased appetite, irritability, increased sleep, and decreased sleep) between recipients of 13vPnC and recipients of 7vPnC (Tables 10-20 and 10-21). These findings are consistent with data from individual studies yielding similar incidence rates for these 4 systemic events for both vaccines.

Fever and Antipyretic Medication

Temperatures of 38ºC or higher (i.e., "any fever") were recorded for between 22.5% and 34.4% of subjects in each vaccine group after each dose in the infant series (Table 10-20). There was a numerically significant difference between the vaccine groups in the incidence of fever after dose 1. However, the actual difference was small (23.9% for 13vPnC and 22.5% for 7vPnC), supporting the conclusion that the statistical difference was not clinically meaningful. After both dose 2 and dose 3 the trend was in the opposite direction, with a higher incidence of fever for the 7vPnC group than for the 13vPnC group (not significant). After the toddler dose, the incidence of fever was 36.9% for 13vPnC and 46.7% for 7vPnC.

When the incidence of fever was analyzed according to severity, numerically significant differences between the 13vPnC and 7vPnC groups were noted after the first dose. Mild fever ($\geq$ 38ºC but $\leq$ 39ºC) was recorded for 23.0% of subjects vaccinated with 13vPnC and for 21.8% of subjects in the 7vPnC group.

For both vaccines, febrile reactions were more common following the toddler dose, with fever between 38°C and 39°C noted in 35.3% and 45.1% of 13vPnC and 7vPnC recipients, respectively, and fever between 39°C and 40°C in 5.0% and 7.3%, respectively.

Overall, the small differences and inconsistencies in the trends, both for the first dose and across doses, suggest that any numerically significant findings are not clinically relevant.

Data from the meta-analysis indicate that, for each dose, the proportion of infants and children receiving an antipyretic medication, given either to treat or to prevent symptoms, were not different between the 2 vaccine groups.

In the older subjects (study 3002), febrile reactions were less common than in infants. Fever between 38°C and 39°C was reported in no more than 8.1% of children across the 3 age groups, and fever between 39°C and 40°C in 2.3% or fewer subjects. Other reports of systemic events occurred at comparable rates across the three age groups.

- Group 1: enrolled at 7 to <12 months of age and received 3 doses of 13vPnC.
- Group 2: enrolled at 12 to <24 months of age and received 2 doses of 13vPnC.
- Group 3: enrolled at 24 to <72 months of age and received 1 dose of 13vPnC.

(Table 10-22 through 10-24)

Table 10-20: Subjects Reporting Systemic Events, Fever, and Antipyretic Medications: Infant and Toddler Doses (All 13 Infant Studies)

	Dose 1[a]			Dose 2[a]			Dose 3[a]			Toddler[b]		
	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]
Fever[e]												
N	3864	2271		3359	1974		2817	1497		1670	884	
Any	923 (23.9)	512 (22.5)	0.013	1023 (30.5)	679 (34.4)	0.424	738 (26.2)	420 (28.1)	0.617	616 (36.9)	413 (46.7)	0.904
≥38°C but ≤39°C	887 (23.0)	495 (21.8)	0.034	971 (29.0)	656 (33.4)	0.207	708 (25.2)	405 (27.1)	0.676	585 (35.3)	394 (45.1)	0.962
>39°C but ≤40°C	52 (1.4)	24 (1.1)	0.340[d]	86 (2.8)	47 (2.6)	0.163	71 (2.7)	32 (2.3)	0.495	74 (5.0)	53 (7.3)	0.971
>40°C	1 (0.0)	4 (0.2)	0.068[d]	3 (0.1)	2 (0.1)	>0.999[d]	4 (0.2)	2 (0.1)	0.949	4 (0.3)	1 (0.1)	0.553
Antipyretic Medications												
N	4272	2444		3857	2208		3252	1709		1801	1015	
Treat	1880 (45.7)	1096 (45.9)	0.505	1790 (49.1)	1135 (53.5)	0.405	1396 (45.3)	796 (48.6)	0.204	709 (41.1)	486 (51.3)	0.920
Prevent	1911 (45.9)	1087 (45.4)	0.284	1792 (48.2)	1054 (49.6)	0.237	1435 (46.1)	807 (49.1)	0.086	584 (34.2)	449 (48.0)	0.037
Decreased Appetite												
N	4046	2377		3515	2044		2959	1556		1710	912	
	1565 (38.7)	880 (37.0)	0.192[d]	1306 (37.2)	813 (39.8)	0.561	1075 (36.3)	576 (37.0)	0.784	641 (37.5)	438 (48.0)	0.193
Irritability												
N	4313	2503		3889	2250		3290	1750		1894	1053	
	3017 (70.0)	1654 (66.1)	0.194	2681 (68.9)	1538 (68.4)	0.523	2054 (62.4)	1075 (61.4)	0.388	1127 (59.5)	715 (67.9)	0.371
Increased Sleep												
N	4245	2480		3642	2127		2986	1581		1683	912	
	2514 (59.2)	1446 (58.3)	0.798	1862 (51.1)	1090 (51.2)	0.870	1216 (40.7)	642 (40.6)	0.382	606 (36.0)	442 (48.5)	0.397
Decreased Sleep												
N	3985	2344		3478	2015		2949	1536		1639	827	
	1433 (36.0)	771 (32.9)	0.481	1204 (34.6)	694 (34.4)	0.391	991 (33.6)	492 (32.0)	0.633	450 (27.5)	272 (32.9)	0.721

Table 10-20: Subjects Reporting Systemic Events, Fever, and Antipyretic Medications: Infant and Toddler Doses (All 13 Infant Studies)

	Dose 1[a]			Dose 2[a]			Dose 3[a]			Toddler[b]		
	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]	13vPnC n (%)	7vPnC n (%)	p-Value[c]

Follow-up time 4 days following each dose for all studies except studies 003 (stage 1 = 15 days; stage 2 = 8 days), 004 (7 days), and 3005 (7 days).

a. Infant dose data are included for all 13 infant studies in this submission.

b. Toddler dose data are included for the 9 infant studies with toddler dose data in this submission: studies 003, 004, 006, 007, 008, 009, 500, 501, and 3000.

c. Mixed model used to calculate difference between vaccine groups in percentages of subjects reporting an event (random effect for protocol).

d. Fisher exact test, 2-sided, used to calculate difference between vaccine groups in percentages of subjects reporting an event. (For analyses in which the mixed model would not produce a p-value, the Fisher exact test was used to compare vaccine groups if the models did not converge.)

e. "Any" fever = subjects with any temperature ≥38°C (100.4°F); for subcategories of fever by degree of temperature, subjects may be included in more than 1 row. For studies conducted in the United States, Fahrenheit equivalents of °C are as follows: 38°C = 100.4°F; 39.0°C = 102.2°F; 40.0°C = 104.0°F.

Program ID: Study 6096A1-ISS_US/CP SAF_SE.SAS. Runtime ID: 16DEC2008 11:01

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/adhoc3.zip (saf_se_inf_tod) (modified, footnote modified)

Table 10-21: Ranges for Incidence of Systemic Events Across Studies (All 13 Infant Studies)

		Infant Series		Toddler Dose[a]	
		13vPnC	7vPnC	13vPnC	7vPnC
Decreased appetite	Low	14.7%	21.1%	20.9%	21.8%
	High	58.8%	55.8%	53.4%	57.4%
Irritability	Low	37.4%	39.4%	38.8%	46.5%
	High	86.1%	85.1%	88.1%	85.2%
Increased sleep	Low	20.2%	22.7%	16.8%	23.9%
	High	71.9%	72.5%	58.6%	55.0%
Decreased sleep	Low	18.5%	17.7%	13.1%	14.9%
	High	55.1%	57.0%	43.3%	45.4%

Follow-up time = 4 days after each dose for all studies except study 003 (stage 1 = 15 days, stage 2 = 8 days).

a. Toddler dose data are available for 9 infant studies: 003, 004, 006, 007, 008, 009, 500, 501, and 3000.

Source: Data compiled from 5.3.5.3, ISS Table 8-6.

Table 10-22: 6096A1-3002 Subjects Reporting Systemic Events and Antipyretic Medication Use Within 4 Days - Dose 1

	Vaccine Group (as Administered)								
	13vPnC Group 1			13vPnC Group 2			13vPnC Group 3		
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%	N[a]	n[b]	%
Fever ≥38°C but ≤39°C	87	3	3.4	108	4	3.7	147	1	0.7
Fever >39°C but ≤40°C	86	1	1.2	108	1	0.9	147	1	0.7
Fever >40°C	86	0	0.0	108	0	0.0	147	0	0.0
Decreased appetite	87	17	19.5	108	24	22.2	147	24	16.3
Irritability	87	21	24.1	108	33	30.6	147	21	14.3
Increased sleep	87	8	9.2	108	14	13.0	147	17	11.6
Decreased sleep	87	21	24.1	108	21	19.4	148	10	6.8
Use of medication to treat symptoms	87	8	9.2	109	11	10.1	147	4	2.7
Use of medication to prevent symptoms	87	7	8.0	109	15	13.8	147	7	4.8
Any systemic event[c]	89	42	47.2	108	54	50.0	148	52	35.1

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, and decreased sleep.
Program ID: Study 6096A1-3002/CP SAF_SE_WITHIN_SUM.SAS. Runtime ID: 07JUL2008 19:56.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3002/ Reports, Tables, and Figures/Safety_Systemic/6096-3002 saf_se_sum_d1.htm.

Table 10-23: 6096A1-3002 Subjects Reporting Systemic Events and Antipyretic Medication Use Within 4 Days - Dose 2

	Vaccine Group (as Administered)					
	13vPnC Group 1			13vPnC Group 2		
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%
Fever ≥38°C but ≤39°C	86	7	8.1	98	5	5.1
Fever >39°C but ≤40°C	86	2	2.3	98	0	0.0
Fever >40°C	86	0	0.0	98	0	0.0
Decreased appetite	87	15	17.2	98	25	25.5
Irritability	87	30	34.5	100	34	34.0
Increased sleep	86	8	9.3	99	10	10.1
Decreased sleep	87	16	18.4	98	20	20.4
Use of medication to treat symptoms	86	8	9.3	98	13	13.3
Use of medication to prevent symptoms	86	4	4.7	98	14	14.3
Any systemic event[c]	88	44	50.0	100	56	56.0

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, and decreased sleep.
Program ID: Study 6096A1-3002/CP SAF_SE_WITHIN_SUM.SAS. Runtime ID: 07JUL2008 19:56.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3002/ Reports, Tables, and Figures/Safety_Systemic/6096-3002 saf_se_sum_d2.htm.

Table 10-24: 6096A1-3002 Subjects Reporting Systemic Events and Antipyretic Medication Use Within 4 Days - Dose 3

	Vaccine Group (as Administered) 13vPnC Group 1		
Systemic Event	**N[a]**	**n[b]**	**%**
Fever ≥38°C but ≤39°C	78	4	5.1
Fever >39°C but ≤40°C	79	1	1.3
Fever >40°C	78	0	0.0
Decreased appetite	80	14	17.5
Irritability	81	20	24.7
Increased sleep	78	2	2.6
Decreased sleep	80	12	15.0
Use of medication to treat symptoms	79	6	7.6
Use of medication to prevent symptoms	79	4	5.1
Any systemic event[c]	81	33	40.7

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Includes fever ≥38°C, decreased appetite, irritability, increased sleep, and decreased sleep.
Program ID: Study 6096A1-3002/CP SAF_SE_WITHIN_SUM.SAS. Runtime ID: 07JUL2008 19:56.
Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3002/ Reports, Tables, and Figures/Safety_Systemic/6096-3002 saf_se_sum_d3.htm.

10.4.5.3 Hives (Urticaria)

Information regarding hives (urticaria) was collected in e-diaries only in studies 004 and 3005. In both studies the diary was to be completed for 7 days after each dose of study vaccine. In both studies, there were no statistically significant differences between the 13vPnC and 7vPnC groups in the incidence of hives reported at any time during the studies (Tables 10-25 and 10-26).

In conclusion, consistent with the results in each study comparing 13vPnC and Prevnar, the results of the meta-analysis shows no increase, either in frequency or in severity, of the common prompted AEs following vaccination with 13vPnC compared with 7vPnC.

Table 10-25: Subjects Reporting Hives Within 7 Days – Study 004

	Vaccine Group (as Administered)						
	13vPnC			7vPnC			
Dose	N[a]	n[b]	%	N[a]	n[b]	%	p-Value[c]
Dose 1	178	3	1.7	188	2	1.1	0.678
Dose 2	118	3	2.5	120	0	0.0	0.120
Dose 3	89	4[d]	4.5	79	0[d]	0.0	0.123
Toddler dose	62	3	4.8	47	3	6.4	>0.99

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Fisher exact test, 2-sided.
d. One (1) 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 7vPnC group.

Source: Program ID: Study 6096A1-004/CP SAF_SE_WITHIN_7_4_SUM_1234.SAS. Runtime ID: 18JUN2008 15:18
Source: compiled from: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/004/Reports, Tables, and Figures/Safety_Systemic/6096-004 saf_se_sum_within7_[inf_d1, d2, d3; and tod].htm

Table 10-26: Subjects Reporting Hives Within 7 Days – Study 3005

	Vaccine Group (as Administered)						
	13vPnC[d]			7vPnC			
Dose	N[a]	n[b]	%	N[a]	n[b]	%	p-Value[c]
Dose 1	996	7	0.7	164	0	0.0	0.602
Dose 2	741	10	1.3	127	1	0.8	>0.99
Dose 3	686	10	1.5	112	2	1.8	0.680

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Fisher exact test, 2-sided, of 13vPnC (combined across lots) versus 7vPnC.
d. Data are pooled across the three 13vPnC lots.

Source: compiled from: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Reports, Tables, and Figures/Safety_Systemic/6096-3005 saf_se_sum_within7_inf_[d1, d2, d3].htm

10.4.6 Spontaneously Reported Adverse Events

10.4.6.1 All Adverse Events

Based on the integrated analysis, there were no differences in the overall AEs reported at any time during the infant series, during the period between the infant series and the toddler dose, and after the toddler dose. In general, reported AEs corresponded to symptoms associated with medical conditions occurring in subjects of the age included in these studies.

During the infant series, "any event" was reported at similar frequencies in the 13vPnC (65.6%) and 7vPnC (64.7%) groups. Most reported types of events (grouped by system organ class [SOC]) were as follows: infections and infestations in 51.4% of 13vPnC recipients and in 50.0% of 7vPnC recipients; gastrointestinal disorders in 16.3% and 15.9%, respectively; skin and subcutaneous tissue disorders in 15.3% and 14.9%, respectively; respiratory, thoracic and mediastinal disorders in 14.4% and 12.3%, respectively; and general disorders and administration site conditions in 10.5% and 11.6%, respectively.

The rate of events reported following the toddler dose was lower in both groups: 31.7% in 13vPnC recipients and 36.0% in 7vPnC recipients. The most frequently reported types of events were the same as those in the infant series.

Using the statistical meta-analysis, a number of AEs showed a statistically significant difference in incidence between the 13vPnC and 7vPnC groups The statistical method used for these analyses is a very sensitive model that will detect small numerical differences between the groups. Because of this sensitivity and the large number of comparisons, significant findings must be interpreted with caution, and should be viewed primarily as identifying AEs that require additional clinical evaluation. AEs (preferred terms) with statistically significant differences in incidence between groups were reviewed by the clinical team to determine whether these numerically significant differences were clinically important. Among these AEs (preferred terms), the higher frequency was seen more often in the 7vPnC group than in the 13vPnC group, suggesting no concerns regarding the safety of 13vPnC relative to 7vPnC. Also, for most of these events, the difference in incidence between vaccine groups was less than 1.0%, suggesting that the statistical findings are not due to clinically important differences. Finally, there are no clear mechanisms by which a true clinical difference might be explained. Therefore, it is likely

that most of the statistically significant differences found are the result of chance alone, given the large number of comparisons being made.

10.4.6.2 Adverse Events Considered Related to Study Vaccine

During the infant series, AEs considered related to study vaccine by the investigator were reported in 5.2% and 6.6% of subjects vaccinated with 13vPnC and 7vPnC, respectively After the toddler dose, the rate was 2.0% and 2.9%, respectively. Related AEs that were most frequently reported were grouped into the following SOCs: general disorders and administration site conditions, gastrointestinal disorders (mostly diarrhea and vomiting), infections and infestations (mostly respiratory tract infections of various descriptions) and psychiatric disorders (largely crying and restlessness). There were no medically relevant increases in any of these events among 13vPnC recipients.

10.4.6.3 Older Infants and Young Children

In older infants and young children (study 3002), AEs considered to be related to study vaccine were infrequent and included injection site reactions (3 subjects), diarrhea (1 subject), and rhinitis (1 subject).

10.4.6.4 Deaths

The integrated safety database includes data for 7532 subjects randomly assigned to treatment in the 13 infant studies: 4758 were assigned to 13vPnC and 2774 to 7vPnC (Table 10-9). Of these, 4729 subjects in the 13vPnC group and 2760 subjects in the 7vPnC group were vaccinated at dose 1. During the study period, death occurred in 4 infants (Table 10-27). All 4 cases were attributable to SIDS. Three (3) cases were among 13vPnC recipients (3 days after dose 2, 14 days after dose 1, and 76 days after dose 3) and 1 was in the 7vPnC group (13 days after dose 1). In the United States (studies 003, 004, and 3005), a total of 2609 subjects received at least 1 dose of pneumococcal conjugate vaccine (1908 subjects received 13vPnC and 701 subjects received 7vPnC). A total of 2 deaths occurred among 1908 13vPnC recipients in U.S studies and 3 deaths among 4758 13vPnC recipients in all studies. SIDS death rates after 13vPnC vaccine and 7vPnC were consistent with expected rates based on information from California and U.S. national databases, shown below.

In order to compare SIDS rate from the 13vPnC clinical trial to general infant population, national or population-based age-specific data on SIDS incidence is necessary. This is because

peak age of SIDS incidence among general infant population is between 2-4 months of age. Unfortunately, age-specific national data are not available at this time. Therefore we relied on SIDS data from the state of California for calendar year 2000[89] which provided age-specific SIDS rates in population. Among the 13vPnC group two of the three reported SIDS occurred in that peak age category and among 7vPnC group one occurred in the peak age category. Using California SIDS rates we were able to evaluate if the observed number of cases within a specific age category is consistent with population background rate. The results of this evaluation showed that the standardized mortality ratios (SMRs) were less than 1 and not statistically significant for 13vPnC group. Thus, the observed number of infant deaths in the 13vPnC trials is consistent with the expected background incidence rates of SIDS in the infant population of specific age group. One case in 7vPnC also falls into the peak age category and is consistent with expected background incidence rate.

Although recently published national SIDS rates [90] are not directly comparable to our study rates (incidence rates and 95% CI are calculated in different ways), we provided an estimate of both (point estimates and 95% CI of incidence rates). The incidence rates in the US 13vPnC study group was 10.48/10,000 (95% CI 1.18- 37.69) and in overall 13vPnC group was 6.31/10000 (95% CI 1.27-18.45). The incidence rates of SIDS in the general infant population, based on a recently published US national statistics varied from 5.54 (95% CI 5.24-5.70) cases/10,000 non-hispanic whites to 11.16 cases/10,000 (95% CI 8.24-14.70) for American Indian or Alaskan Natives.[90] The CI in 13vPnC study is very wide due to small numbers, the 95% CI of rates overlapped with the estimates from the national SIDS data. Therefore, the observed number of sudden infant deaths in 13vPnC recipients in our clinical program is consistent with the expected based on both California and national rates.

Experience with Prevnar also suggests that no causal relationship exists between administration of the vaccine and SIDS. The SIDS rates in the pivotal Prevnar licensure efficacy trial (conducted in California) were observed to be lower than in the control group, and point estimates were lower than expected rates in California.[92]

In a US Food and Drug Administration (FDA)-mandated postmarketing evaluation of Prevnar, analyses of mortality and SIDS rates were performed using the SMR including adjustments for age in months, sex, and calendar month. The mortality and SIDS rates observed for the

population cohort of 162,305 subjects receiving Prevnar were much lower than expected based on historical rates for children in the years before Prevnar introduction.

Mortality statistics in the time periods both before and after Prevnar introduction for the entire state of California (1996 through 2003) are available publicly through the California SIDS Program, under the direction of the California Department of Health Services' Maternal, Child, and Adolescent Health Branch. In 1996, the SIDS rate was 0.6 per 1000 live births, whereas in 2003, the rate was 0.3 per 1000 live births. The 50% decline in SIDS rate during this time period was similar to the SMR observed for the study's population cohort.

Table 10-27: Listing of Adverse Events Resulting in Death (All 13 Infant Studies)

Study	Site	Subject	Adverse Event MedDRA Term	Adverse Event Verbatim Term	Vaccine Administered	Last Dose	Days Since Last Dose	Related to Study Vaccine[a]
501	009	000452	Sudden infant death syndrome	Sudden unexpected death in infancy	13vPnC	Vaccination 3	76	No
3005	002	000107	Sudden infant death syndrome[b]	Infant death cause unknown[b]	7vPnC	Vaccination 1	13	Yes[b]
3005	004	000320	Sudden infant death syndrome	Sudden unexplained infant death	13vPnC	Vaccination 1	14	No
3005	079	007651	Sudden infant death syndrome	Asphyxia due to sids	13vPnC	Vaccination 2	3	No

Narratives for each subject are in the respective study reports in section 5.3.5.1, study 501-infant and toddler, and study 3005-infant.

a. Based on investigator assessment.

b. Before the cause of death was determined, the investigator wanted to take the most conservative approach in assessing the potential causality of the death. However, when the autopsy later revealed that the cause of death was sudden infant death syndrome (SIDS), the investigator changed his assessment of causality, determining that the death was not related to study vaccine.

Program ID: Study 6096A1-ISS_US/CP CDL_AE.SAS. Runtime ID: 18NOV2008 14:16

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/ISSResultsv1.zip (saf_ae_dth.htm) (footnote modified)

10.4.6.5 Serious Adverse Events

Overall, most reported serious adverse events (SAEs) were not statistically different at any time during the vaccination series and follow-up observation period. The incidence for each of the study periods was 4.6% or less for each vaccine group. By far, the most frequently reported SAEs were infections and infestations. Of the SAEs, the System Organ Class (SOC) "Respiratory, thoracic and mediastinal disorders" met the predefined conservative statistical cutoff for a possible difference in rates for the infant series using the mixed model approach; the observed incidence was 0.4% after 13vPnC compared to 0.1% after 7vPnC (0.049, 2-sided. mixed model.)No differences were observed between the infant series and toddler dose, at the toddler dose, or at the 6 month follow-up after the toddler dose, using the mixed model approach.No differences overall for this SOC were observed at dose 1, dose, 2, or dose 3. Taken as a whole, findings do not support an increased rate of serious adverse events in the SOC "Respiratory, thoracic and mediastinal disorders" after 13vPnC compared to 7vPnC.

Thirteen (13) of the SAEs were considered by the investigator to be related to the study vaccine, 7 in the 13vPnC group and 6 in the 7vPnC group (Table 10-28). Eight (8) of 13 related SAEs, fever (n=3), febrile seizures (n=3), crying (n=1), and allergic reaction (n=1) could be expected given the known reactogenicity profile of Prevnar.

Table 10-28: Listing of Serious Adverse Events Considered Related to Study Vaccine by the Investigator (All 13 Infant Studies)

Study	Site	Subject	Adverse Event MedDRA Preferred Term	Adverse Event Verbatim Term	Vaccine Administered	Last Dose	Days Since Last Dose	Duration (days)	Severity[a]	Related[b]
004	003	000160	Nephroblastoma	Bilateral wilms tumor	7vPnC	Vaccination 3	117	C	LT	Yes
004	025	002269	Febrile convulsion	Febrile seizure	13vPnC	Vaccination 2	4	1	MI	Yes
004	025	002269	Pyrexia	Fever	13vPnC	Vaccination 2	4	5	MO	Yes
006	007	000244	Febrile convulsion	Fever convulsion	7vPnC	Toddler Dose	1	3	MO	Yes
009	005	000420	Bronchitis	Bronchitis	13vPnC	Vaccination 3	2	6	MO	Yes
500	011	001824	Infantile spasms	Infantile spasms	7vPnC	Vaccination 2	38	C	SE	Yes
501	004	000205	Pyrexia	High fever	7vPnC	Vaccination 3	2	6	MO	Yes
501	019	001430	Febrile convulsion	Febrile seizures	7vPnC	Vaccination 3	2	2	SE	Yes
3000	009	000812	Crying	Unconsolable crying <3 hours, hospitalization	13vPnC	Vaccination 1	1	1	MI	Yes
3005	002	000107	Sudden infant death syndrome[c]	Infant death cause unknown[c]	7vPnC	Vaccination 1	13	1	LT	Yes[c]
3005	030	002857	Allergy to vaccine	Vaccine allergic reaction	13vPnC	Vaccination 2	1	8	MI	Yes
3005	044	004255	Bronchiolitis	Bronchiolitis	13vPnC	Vaccination 3	1	13	SE	Yes
3005	044	004275	Pyrexia	Fever	13vPnC	Vaccination 2	8	3	SE	Yes

Abbreviations: C = continuing; SIDS = sudden infant death syndrome.

a. Mild (MI), moderate (MO), severe (SE), or life threatening (LT).

b. Based on investigator assessment.

c. Before the cause of death was determined, the investigator wanted to take the most conservative approach in assessing the potential causality of the death. However, when the autopsy later revealed that the cause of death was SIDS, the investigator changed his assessment of causality, determining that the death was not related to study vaccine.

Program ID: Study 6096A1-ISS_US/CP CDL_AE.SAS. Runtime ID: 18NOV2008 14:16

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/ISSResultsv1.zip (saf_sae_rel_stdy_lst.htm)

10.4.6.6 Withdrawals and Vaccination Discontinuations

Overall, an AE resulted in the withdrawal from the study for 39 infants, of whom 22 (0.47%) were in the 13vPnC group and 17 (0.62%) were in the 7vPnC group (Table 10-29). In both groups, subjects were withdrawn because of AEs during the infant series and during the period between the infant series and the toddler dose, but not after the toddler dose or during the 6-month follow-up period. The most frequent AEs resulting in withdrawal from the study included nervous system disorders (8 subjects in the 13vPnC group and 9 subjects in the 7vPnC group) and infections (5 and 3 subjects in the 13vPnC and the 7vPnC groups, respectively).

In older infants and young children (study 3002), no subjects were withdrawn because of AEs.

Table 10-29: Number and Percentage of Subjects With Adverse Events Resulting in Withdrawal From Study Vaccination: Infant Series, Between Infant Series and Toddler Dose, Toddler Dose, and 6-Month Follow-up (All 13 Infant Studies)

System Organ Class\ Preferred Term	Infant Series		Between Infant Series and Toddler Dose[a,b]		Toddler Dose[b]		6-Month Follow-up[c]	
	13vPnC N = 4723	7vPnC N = 2754	13vPnC N = 2569	7vPnC N = 1800	13vPnC N = 2499	7vPnC N = 1482	13vPnC N = 1860	7vPnC N = 1356
Any event	15 (0.3)	8 (0.3)	7 (0.3)	9 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	1 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemolytic anaemia	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukocytosis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pelizaeus-Merzbacher disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrooesophageal reflux disease	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	2 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site erythema	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reaction	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site swelling	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergy to vaccine	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	4 (0.1)	1 (0.0)	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchitis	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kawasaki's disease	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningitis bacterial	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningitis meningococcal	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 10-29: Number and Percentage of Subjects With Adverse Events Resulting in Withdrawal From Study Vaccination: Infant Series, Between Infant Series and Toddler Dose, Toddler Dose, and 6-Month Follow-up (All 13 Infant Studies)

	Infant Series		Between Infant Series and Toddler Dose[a,b]		Toddler Dose[b]		6-Month Follow-up[c]	
System Organ Class\ Preferred Term	**13vPnC N = 4723**	**7vPnC N = 2754**	**13vPnC N = 2569**	**7vPnC N = 1800**	**13vPnC N = 2499**	**7vPnC N = 1482**	**13vPnC N = 1860**	**7vPnC N = 1356**
Meningitis pneumococcal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Meningococcal sepsis	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Varicella	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Near drowning	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscular weakness	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nephroblastoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	5 (0.1)	4 (0.1)	3 (0.1)	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Convulsion	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile convulsion	1 (0.0)	1 (0.0)	3 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemiplegia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
High-pitched crying	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hydrocephalus	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertonia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokinesia	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infantile spasms	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breath holding	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Crying	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 10-29: Number and Percentage of Subjects With Adverse Events Resulting in Withdrawal From Study Vaccination: Infant Series, Between Infant Series and Toddler Dose, Toddler Dose, and 6-Month Follow-up (All 13 Infant Studies)

	Infant Series		Between Infant Series and Toddler Dose[a,b]		Toddler Dose[b]		6-Month Follow-up[c]	
System Organ Class\ Preferred Term	**13vPnC N = 4723**	**7vPnC N = 2754**	**13vPnC N = 2569**	**7vPnC N = 1800**	**13vPnC N = 2499**	**7vPnC N = 1482**	**13vPnC N = 1860**	**7vPnC N = 1356**
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wheezing	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.0)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash erythematous	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria	2 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Infant series = from dose 1 through postinfant series blood draw. Between infant series and toddler dose = from the postinfant series blood draw through the toddler dose. Toddler dose = from the toddler dose through the posttoddler dose blood draw. 6-Month follow-up = from posttoddler dose blood draw to 6-month follow-up contact.

Mixed model used to calculate difference between vaccine groups in percentages of subjects reporting an event (random effect for protocol).

* Denotes statistically significant difference in model-adjusted incidence between 13vPnC and 7vPnC at the 0.05 (2-sided) level.

** Denotes AEs for which the model-adjusted incidence is significantly higher in the 13vPnC group than in the 7vPnC group at the 0.05 (2-sided) level.

a. Adverse events were collected differently for the period between the infant series and the toddler dose and for the 6-month follow-up than they were for the infant and toddler doses. At the toddler dose visit and at the 6-month follow-up contact, parents/guardians were to report any new chronic medical condition and any serious adverse events that had occurred since the previous visit. See the description of AE collection methods in section 12.1.1.

b. Postinfant series data are available for 9 studies: 003, 004, 006, 007, 008, 009, 500, 501, and 3000.

c. 6-Month follow-up data are available for 6 studies: 003, 004, 006, 009, 500, and 5001.

Program ID: Study 6096A1-ISS_US/CP SAF_AE_SIG.SAS. Runtime ID: 18NOV2008 14:29

Source: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/ISSResultsv1.zip (saf_ae_num_withd_series.htm)

10.4.6.7 Adverse Drug Reactions

A specific AE is identified as an adverse drug reaction (ADR) if a causal relationship between the vaccine and the AE is at least a reasonable possibility. Because 13vPnC includes the components of Prevnar, all ADRs previously identified for Prevnar using data from both clinical trials and from postmarketing experience have been included as ADRs for 13vPnC. Data for these events from the 13 infant studies of 13vPnC were reviewed to determine the frequency of ADRs. In addition, all AEs reported during these studies were reviewed to identify any additional ADRs. Criteria included the frequency of occurrence, the finding of a statistically significant difference in incidence between the 13vPnC and 7vPnC groups, and the theoretical existence of a biologic mechanism by which the AE could be causally related to 13vPnC. Details from the medical review of data for some of the ADRs are discussed in the following sections.

The ADRs for 13vPnC are listed below, categorized by SOC and by the frequency of all AEs in the 13vPnC group. Frequencies for each AE are determined based on the highest incidence of AEs reported after any dose of 13vPnC (dose 1, dose 2, dose 3, or toddler dose).

The frequency categories are as follows:

Very common: ≥ 10%
Common: ≥ 1% and <10%
Uncommon: ≥ 0.1% and <1%
Rare: ≥ 0.01% and <0.1%
Very rare: <0.01%

Administration site conditions

Very common: Injection site erythema, induration/swelling, pain/tenderness

Common during infant series, very common after toddler dose and in older children:
Injection site erythema or induration/swelling 2.5-7.0 cm

Common: Injection site pain/tenderness interfering with limb movement

Uncommon: Severe reactions – injection site erythema or induration/swelling greater than 7.0 cm

General disorders

Very common: Fever (temperature 38°C [100.4°F] or higher)

Common: Fever greater than 39°C (102.2°F)

Metabolism and nutrition disorders

Very common: Decreased appetite

Nervous system disorders

Very common: Drowsiness/increased sleep, restless sleep/decreased sleep

Psychiatric disorders

Very common: Irritability

10.4.6.7.1 Adverse Drug Reactions: Unsolicited Adverse Events

Gastrointestinal disorders

Common: Diarrhea, vomiting

Immune system disorders

Uncommon: Hypersensitivity reaction including face edema, dyspnea, bronchospasm

Nervous system disorders

Uncommon: Seizures (includes MedDRA preferred terms of convulsion, febrile convulsion, epilepsy, and partial seizures)

Psychiatric disorders

Uncommon: Crying

Skin and subcutaneous tissue disorders

Common: Rash (includes MedDRA preferred terms of rash, rash papular, rash erythematous, rash macular, rash maculopapular, rash generalized, rash morbilliform, rash pruritic, rash rubelliform, and rash vesicular)

Uncommon: Urticaria or urticaria-like rash

10.4.6.7.2 Prevnar Adverse Drug Reactions Not Observed in Trials of 13vPnC

Although the following ADRs were not observed in clinical trials of 13vPnC, they are considered ADRs for Prevnar and thus are considered ADRs for 13vPnC as well.

Clinical Trials of Prevnar

The following ADRs are listed according to the frequency observed in clinical trials of Prevnar.

Nervous system disorders

Rare: Hypotonic-hyporesponsive episode

Prevnar Postmarketing Experience

The following ADRs were identified from postmarketing experience with Prevnar. The frequencies are based on spontaneous reporting rates for Prevnar and have been calculated using the number of reports and the number of doses distributed.

Blood and lymphatic system disorders

Very rare: Lymphadenopathy localized to the region of the injection site (lymphadenopathy)

Immune system disorders

Very rare: Anaphylactic/anaphylactoid reaction including shock, angioneurotic edema (angioedema)

Skin and subcutaneous tissue disorders

Very rare: Erythema multiforme

Administration site conditions

Very rare: Injection site dermatitis, injection site urticaria, injection site pruritus

10.4.6.7.3 Seizures

To determine the overall incidence of any type of seizure event, the MedDRA preferred terms of febrile convulsions, convulsions, partial seizures, and epilepsy were pooled for analysis. Based on these analyses, seizures were reported at similar frequencies in the 13vPnC and 7vPnC groups, with no statistically significant differences in incidence between the 2 groups in any study period (Table 10-30) or after any dose (Table 10-31). A total of 29 subjects experienced 1 or more seizures during the studies. In the 13vPnC group, 18 subjects (0.38%) experienced seizures: 13 had febrile convulsions, 4 had convulsions, and 1 had epilepsy. One (1) of the subjects who experienced a febrile seizure also had an AE of partial seizures reported on the same day; and 1 of the subjects who experienced convulsions had the event reported both during the infant series and during the 6-month follow-up. In the 7vPnC group, 11 subjects (0.40%) experienced febrile seizures.

Table 10-30: Number (%) of Subjects With Seizures (Combined Terms): Infant Series, Between Infant Series and Toddler Dose, Toddler Dose, and 6-Month Follow-up Telephone Contact (All 13 Infant Studies)

	Infant Series		Between Infant Series and Toddler Dose		Toddler Dose		6-Month Follow-up	
Preferred Term	**13vPnC N = 4723**	**7vPnC N = 2754**	**13vPnC N = 2569**	**7vPnC N = 1800**	**13vPnC N = 2499**	**7vPnC N = 1482**	**13vPnC N = 1860**	**7vPnC N = 1356**
Seizures[a]	5 (0.1)	1 (0.0)	7 (0.3)	3 (0.2)	2 (0.1)	2 (0.1)	5 (0.3)	6 (0.4)

Mixed model used to calculate difference between vaccine groups in percentages of subjects reporting an event (random effect for protocol).

* Denotes statistically significant difference in model-adjusted incidence between 13vPnC and 7vPnC at the 0.05 (2-sided) level.

a. "Seizures" includes MedDRA preferred terms of partial seizures, convulsion, febrile convulsion, and epilepsy.

Program ID: Study 6096A1-ISS_US/CP SAF_AE_SIG.SAS. Runtime ID: 18NOV2008 14:29

Source: compiled from: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/ISSResultsv1.zip (saf_ae_seizures_series.htm) (modified)

Table 10-31: Number (%) of Subjects With Seizures: Dose 1, Dose 2, Dose 3, and Toddler Dose (All 13 Infant Studies)

	Dose 1		Dose 2		Dose 3		Toddler Dose[a]	
Preferred Term	**13vPnC N = 4723**	**7vPnC N = 2754**	**13vPnC N = 4510**	**7vPnC N = 2624**	**13vPnC N = 3976**	**7vPnC N = 2142**	**13vPnC N = 2499**	**7vPnC N = 1482**
Seizures[a]	2 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	2 (0.1)	2 (0.1)

Mixed model used to calculate difference between vaccine groups in percentages of subjects reporting an event (random effect for protocol).

* Denotes statistically significant difference in model-adjusted incidence between 13vPnC and 7vPnC at the 0.05 (2-sided) level.

a. "Seizures" includes MedDRA preferred terms of partial seizures, convulsion, febrile convulsion, and epilepsy.

Program ID: Study 6096A1-ISS_US/CP SAF_AE_SIG.SAS. Runtime ID: 18NOV2008 14:29

Source: compiled from: CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/USA ISA/ISS/ISSResultsv1.zip (saf_ae_seizures_dose.htm) (modified)

10.4.6.7.4 Rash

During the infant series, rash (MedDRA preferred term) was reported at a lower incidence among subjects vaccinated with 13vPnC (2.2%) than among subjects who received 7vPnC (2.7%), and the numeric difference between the groups, although small, was statistically significant (p=0.008). This was also true after the toddler dose (13vPnC = 0.5%, 7vPnC = 1.2%; p=0.038). In order to determine the overall incidence of rash, regardless of clinical type, the data were reviewed for all preferred terms corresponding to rashes of various clinical descriptions. These included the following MedDRA preferred terms: rash, rash papular, rash erythematous, rash macular, rash maculopapular, rash generalized, rash morbilliform, rash pruritic, rash rubelliform, and rash vesicular. Using the combined terms, the incidence of any type of rash during the infant series was 2.8% in the 13vPnC group and 3.3% in the 7vPnC group; and after the toddler dose the incidence was 0.5% and 1.3%, respectively. None of the occurrences of rash of any type were serious, and only 2 subjects discontinued study vaccine because of rash. In each case, the subject developed the rash immediately after vaccination with 7vPnC.

10.4.6.7.5 Hives/Urticaria

During the infant series, urticaria (MedDRA preferred term) was reported in approximately 0.4% of subjects vaccinated with 13vPnC and 0.5% of subjects vaccinated with 7vPnC. After the toddler dose, the incidence was 0.2% and 0.1%, respectively. Urticaria was considered related to study vaccine in 5 subjects (0.11%) vaccinated with 13vPnC and in 1 subject (0.04%) vaccinated with 7vPnC during the infant series as well as in 1 subject (0.04%) in the 13vPnC group after the toddler dose.

10.4.6.7.6 Lymphadenopathy

"Lymphadenopathy localized to the region of the injection site" was identified as an ADR associated with Prevnar, based on postmarketing experience. Although AEs corresponding to the MedDRA preferred terms of lymphadenopathy and lymphadenitis were reported in a few subjects in both the 13vPnC and 7vPnC groups during the infant studies of 13vPnC, a review of the cases shows that the verbatim terms describing these events do not indicate that any of the occurrences were localized to the region of the injection site. Therefore no event equivalent to the ADR identified during postmarketing experience with Prevnar has been observed in studies of 13vPnC in infants.

10.4.6.7.7 Hypersensitivity Reaction

"Hypersensitivity reaction including face edema, dyspnea, bronchospasm" was identified as an ADR for Prevnar based on postmarketing reports. The 13vPnC safety data were reviewed for the specific MedDRA preferred terms of hypersensitivity, face edema, dyspnea, and bronchospasm. There have been no reports of face edema in trials of 13vPnC, and all cases of hypersensitivity, dyspnea, and bronchospasm were determined to be not associated with study vaccine because they did not have a temporal association with the vaccine. Along with the cases of hypersensitivity, additional preferred terms within the immune disorders SOC were reviewed. One (1) occurrence of a vaccine allergic reaction (MedDRA preferred term, allergy to vaccine) was identified that occurred on the day of vaccination with 13vPnC, Pediarix®, and ActHib®.

10.4.7 Safety Following a Toddler Dose of 13vPnC in Recipients of 7vPnC During the Infant Series

When 13vPnC is first introduced, it is likely that some infants who have received 1 or more doses of Prevnar in the course of a standard pediatric vaccination program may be switched to 13vPnC to complete the vaccination series. Study 008 explored the outcomes in such a situation, evaluating the safety and immunogenicity of 13vPnC when administered at the toddler dose to subjects who had received 7vPnC during a 3-dose infant series. Subjects were randomly assigned to 1 of 3 vaccine groups to receive vaccines during the infant series/toddler dose as follows: 304 subjects to 13vPnC/13vPnC; 158 subjects to 7vPnC/7vPnC; and 151 subjects to 7vPnC/13vPnC. Results for local reactions, systemic events, and spontaneously reported AEs

after the toddler dose showed that there were no clinically important differences in outcomes between the 7vPnC/13vPnC group and either of the other vaccine groups. The safety profile of 7vPnC administered during the infant series followed by 13vPnC at the toddler dose is similar to the safety profiles of 7vPnC or 13vPnC administered at all doses.

10.4.8 Safety Conclusions

Based on the results of the 13vPnC clinical studies, the reactogenicity profile of 13vPnC has been shown to be similar to that of Prevnar, with no clinically significant difference in the frequency or severity of AEs reported among infants in the clinical studies.

11.0 PLANNED POST MARKETING EVALUATIONS

Planned post marketing evaluations build on the experience with Prevnar and the cumulative experience to date with 13vPnC. No important risks have been identified during the 13vPnC clinical program. However additional data will be useful in further defining potential benefits and risks with 13vPnC administration. These items include: post-authorization effectiveness, potential changes in the epidemiology of nonvaccine *Streptococcus pneumoniae* serotypes, safety and immunogenicity in high-risk children, effects of vaccine on AOM and nasal carriage, and other safety and effectiveness considerations that can best be addressed in large populations of vaccinated children. The following sections provide a brief summary of how such information will be obtained. (Table 11-1)

Table 11-1: Post Licensure Studies		
Study Type	**Study Site/ Population**	**Objective**
Safety Surveillance	NCKP N=43,000+	Expand understanding of 13vPnC safety profile in routine use
IPD Effectiveness	NCKP N~150,000 < 5 yr *(3.5MM total)*	Demonstrate overall effectiveness of 13vPnC after introduction
	US – CDC ABCs N~2.2MM <5 yrs *(18.5MM total)*	Demonstrate effectiveness in: ▸ Target population (direct effect) ▸ Unvaccinated populations (indirect effect) ▸ Per-serotype basis ▸ Per-dose basis (for vaccinated populations -case-control method)
AOM Effectiveness	Rochester, NY N~300	Demonstrate effectiveness of 13vPnC for culture-proven AOM and NP carriage ▸ Tympanocentesis study
	US national ambulatory and hospital ambulatory surveys (NAMCS, NHAMCS)	Demonstrate effectiveness of 13vPnC for AOM ▸ Assess change in office visits for AOM, URTI, ambulatory care visits and antibiotic Rx in children <5 yr[68]

NAMCS=National Ambulatory Medical Care Survey. NHAMCS=National Hospital Ambulatory Medical Care Survey

In addition to the studies shown in the above table the following study is in progress to assess the impact of 13vPnC on nasopharyngeal pneumococcal acquisition:

6096A1-3006, A Phase 3, Randomized, Active-Controlled, Double-Blind Trial Evaluating the Impact of a 13-Valent Pneumococcal Conjugate Vaccine on Nasopharyngeal Colonization With Vaccine Serotypes of *Streptococcus pneumoniae* in Healthy Infants in Israel. In this study approximately 1860 subjects are randomly assigned 1:1 to receive either 13vPnC or 7vPnC vaccine at 2, 4, 6 and 12 months of age. Children will be followed until 24 months of age. Differences in nasal acquisition of common serotypes and additional serotypes, with particular attention to frequent colonizers 6A and 19A, will be evaluated with respect to antibody responses after the infant series and toddler dose. This study is now fully enrolled. (See also study 6096A1-3010 Alaska study described below.)

More detailed descriptions of some of the ongoing or planned trials are included below.

11.1 Safety and Immunogenicity

11.1.1 Post licensure safety surveillance study

A favorable safety profile of 13vPnC was observed in clinical trials, consistent with the 7vPnC experience in clinical trials and post-licensure. However, as 13vPnC will be a new licensed product, a post-marketing observational safety study of 43,000 children receiving the 3-dose primary series will be performed in an HMO setting, Northern California Kaiser Permanente (NCKP). The goal of the study is to expand the understanding of the safety profile of 13vPnC in a post-marketing approval environment. The specific objectives of the observational safety study are:

1. To assess the incidence rates of all medically attended events occurring in the hospital and emergency room setting, and pre-specified medically attended events occurring in the outpatient clinic setting following vaccination with 13vPnC.
2. To assess the incidence rates of pre-specified medically attended events across all settings (hospital, emergency room, and outpatient clinic settings).
3. To compare postvaccination incidence rates with corresponding control period rates for each vaccination dose (individually for dose 1, 2, or 3), for the primary series combined (dose 1, 2 and 3 combined), and for all doses combined (3 primary series doses plus booster dose).

Study Population: The 13vPnC safety cohort will consist of 43,000 infants starting immunization with 13vPnC at 2 months of age who receive 3 doses of 13vPnC as part of the primary vaccination series at NCKP. Additionally, any infants who receive at least one dose of 13vPnC at NCKP and were 7vPnC naïve at the time of the 13vPnC dose during the course of accruing the 43,000 completed primary series vaccinations will be included.

Study Design: This is a post-authorization observational safety study using a cohort of subjects who receive 13vPnC beginning at 2 months of age as part of routine medical care. Vaccination with 13vPnC will be conducted in accordance with the product labeling and routine clinical practice.

The rates of medically attended events occurring within the 30 day risk window after vaccination will be compared to two self-control periods, the self-control period 31 to 60 days after vaccination and the self-control period -30 to -5 days before vaccination. This analysis will be conducted separately for each healthcare setting (hospital, ED, and outpatient clinic [pre-specified medically attended events only]) and for each dose (1st, 2nd, 3rd dose and infant primary series combined). Similar comparisons will also be performed after the 4th dose for those children who have received this dose by the end of the study observation period. Pre-specified events for the outpatient clinic setting include the following: anaphylaxis/hypersensitivity, apnea, asthma, bronchiolitis, bronchitis (obstructive airway diseases), fever, flushing, gastroenteritis, milk/food allergies/intolerance, pneumonia, upper respiratory tract infection (URI), and wheezing diagnoses.

This study design incorporates a five-phase approach to safety assessment. These phases occur sequentially, and include:

1) WINDOW ANALYSIS

Comparison of medically attended event incidence rates during the 30-day post vaccination risk window compared to two self-control window periods (days 31-60 and days -30 to -5).

2) HISTORICAL CONTROL ANALYSIS

If above analysis along with predefined criteria identify a possible signal, additional analysis will be performed to an historical control cohort who received only 7vPnC or a combination of 7vPnC and 13vPnC during product transition, as appropriate.

3) ADDITIONAL STATISTICAL ANALYSES

Additional statistical analyses may be performed to assess the temporal association between the medically attended event and time of vaccination or stratification by receipt of concomitant vaccines. These analyses may include scan statistic methodology.

4) MEDICAL CHART REVIEW

Medical chart review, which will be conducted based on feasibility and medical judgment to further evaluate events identified above.

5) COMPREHENSIVE ASSESSMENT

A comprehensive assessment of available data using medical, statistical and epidemiological judgment, including consistency of statistical associations across comparison groups/control groups, healthcare setting, and number of doses, and results of medical chart review. This step will be conducted in collaboration with Regulatory Authorities.

The study has over 80% power to detect a 2.5-fold increase over background rates of 1 per 10,000 vaccine doses of a medically attended event for each setting (ED, hospital, and outpatient clinic setting), assuming a two-sided alpha = 0.05.

11.1.2 Evaluation of Safety and Immunogenicity in Special Populations

Additionally, the safety of the vaccine in the following high risk pediatric groups will be assessed in postmarketing studies:

- HIV-infected children 6 years of age and older
- Children as young as 2 years of age undergoing human stem cell (HSCT) transplant
- Premature infants <37 weeks of gestational age
- Children with sickle cell disease previously immunized with 23vPS.

11.2 Catchup immunization in older children

To prepare for potential catch-up immunization, the safety of more than 4 doses of CRM197-based pneumococcal conjugate vaccine when 13vPnC is administered after a Prevnar series is currently being assessed in study 6096A1-3011 (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). This study is currently ongoing. The planned total enrollment is N ≈ 1200 (approx 300 subjects for each of four groups.)

This study is enrolling healthy children with prior 7vPnC vaccination(s) and aged >15 months to <10 years, or without prior vaccinations and aged ≥10 years to <18 years at study entry as follows:

- Group 1: >15 months to <2 years with prior 7vPnC immunization (must have received at least 3 Prevnar doses)
- Group 2: ≥ 2 years to <5 years with prior 7vPnC immunization
- Group 3: ≥ 5 years to <10 years with prior 7vPnC immunization
- Group 4: ≥ 10 years to <18 years without prior 7vPnC immunization

Group 1 will receive 2 doses of 13vPnC administered 2 months apart and Groups 2, 3, and 4 will receive a single dose of 13vPnC.

One purpose of this study is to evaluate the safety of more than 4 doses of CRM_{197}-based pneumococcal conjugate vaccine when 13vPnC is administered after a Prevnar series. Also, this study will evaluate pneumococcal immune responses 1 month after last dose of 13vPnC in each age group.

In addition, Study 6096A1-3010 (A Phase 3, Open-Label Trial Evaluating the Safety, Immunogenicity, and Impact of 13-valent Pneumococcal Conjugate Vaccine in Alaskan Native Children) is in progress. This study will also provide some important catch-up data. The planned enrollment is N = 2500.

The subjects will receive 13vPnC vaccinations as appropriate for their age and prior vaccination history in accordance with the following groups:

- Group 1: Subjects 6 weeks to <10 months of age with 0 prior dose of Prevnar.
- Group 2: Subjects <12 months of age with 1 prior dose of Prevnar.
- Group 3: Subjects <12 months of age with 2 prior doses of Prevnar.
- Group 4: Subjects ≥ 12 months to <2 years of age.
- Group 5: Subjects ≥ 2 years to <5 years of age.

The primary objective of the study is to assess the impact of 13vPnC on the incidence of IPD in the YK Delta region due to the 13 vaccine serotypes. In addition, the immune response is being measured one month after the infant series and one month after the toddler dose (Groups 1, 2, and 3) as well as 1 month after completion of the relevant catch-up doses (Groups 4 and 5). With regard to catch-up, Groups 4 and 5 will get 2 doses and 1 dose, respectively.
Nasopharngeal colonization of vaccine type strains and potential replacecement strains will also be assessed in this population during 13vPnC introduction. All subjects will be followed for 6 months after their last study vaccination for safety.

11.3 Effectiveness

Post-authorization effectiveness of 13vPnC will be monitored by by the national IPD surveillance in the US conducted by the Centers for Disease Control and Prevention and three national or provincial surveillance systems in Canada. They will be complemented by established population-based pneumococcal disease surveillance systems in 5 European countries (France, Germany, Netherlands, Norway, and the UK). These surveillance systems will evaluate the effectiveness of 13vPnC by comparing the incidence rates of pneumococcal disease in the period after 13vPnC introduction with the period before 13vPnC introduction and before Prevnar introduction. The pneumococcal disease surveillance systems will assess the effectiveness of 13vPnC against the additional 6 serotypes, against the common 7 serotypes, and the potential changes in the incidence rate of non-vaccine serotypes. Additionally, the serotype distribution in IPD will be specifically evaluated in high-risk populations, such as HIV-infected individuals, that are most susceptible to replacing serotypes. Over time, the surveillance systems will have accrued a large enough sample of pneumococcal disease cases to evaluate the effectiveness of 13vPnC against the individual serotypes included in 13vPnC that occur with higher background incidence, e.g., serotype 19A.

By combining individual national surveillance systems into one larger surveillance program, effectiveness evaluations will be conducted for both a "2+1" and "3+1" schedule against IPD, pneumonia, and AOM-related outcomes. Information on changes in the distribution of serotypes of *Streptococcus pneumoniae* after 13vPnC introduction as well as the impact of 13vPnC on nasopharyngeal carriage will be collected and reported to regulatory authorities.

In addition, a prospective evaluation of pneumococcal AOM will be performed.. The objectives of this study are to demonstrate the effectiveness of 13vPnC in reducing AOM and NP colonization caused by serotypes included in the vaccine, with specific attention to potential for serotype replacement. This is an observational study in which children presenting with AOM undergo diagnostic tympanocentesis. Following the expected licensure of 13vPnC and implementation into the routine infant immunization schedule, children will be recruited prospectively beginning at 2 months of age and followed until 30 months of age. 13vPnC will be given along with other recommended infant vaccines as part of routine care. Nasopharyngeal (NP) and oropharyngeal (OP) samples will be obtained using standard techniques at 6, 9, 12, 15, 18, 24, and 30 months of age, and middle ear fluid (MEF) samples will be obtained via tympanocentesis from:

1) every child presenting with a first and second episode of AOM, and
2) children who are identified as "otitis-prone" and experience either recurrent AOM (rAOM) or AOM with treatment failure (AOM-TF) throughout the course of the study.

Tympanocentesis will be performed using standard techniques. All samples will be tested by standard microbiologic techniques to identify the presence of *S. pneumoniae*. *S. pneumoniae* isolated from any sample will be serotyped using standard methods. Samples that are culture-negative will be evaluated by multi-locus PCR to evaluate the possible presence of *S. pneumoniae*. Vaccine effectiveness for pneumococcal AOM and NP colonization will be assessed by estimating the difference in the rate of each by serotype and overall to a pre-13vPnC baseline period.

12.0 BENEFITS AND RISKS CONCLUSIONS

12.1 Clinical Development

13vPnC has been developed to be the successor to Prevnar. The clinical plan for 13vPnC builds on the established safety and efficacy record of Prevnar. The 13vPnC clinical plan conforms to WHO recommendations issued for the evaluation of a new pneumococcal conjugate vaccine.

12.2 Efficacy (Immunogenicity)

Immunogenicity data indicate that 13vPnC elicits immune responses to the 7 common serotypes that are similar to those induced by Prevnar and are within the set of preestablished criteria for non-inferiority. Moreover, 13vPnC elicits immune responses against the 6 additional serotypes, measured by both polysaccharide-binding IgG concentrations and functional OPA antibody that are substantially higher than those evoked by Prevnar. 13vPnC is immunogenic from the age of 2 months. Data from several studies support the recommendations on schedules of vaccination for infants and for catch-up vaccination in older infants and children. Studies have also provided the clinical evidence that conjugates for each of the 6 additional serotypes can be consistently produced and that 13vPnC can be manufactured at the scale intended for marketing. It is therefore highly probable that 13vPnC will be as effective as Prevnar in preventing pneumococcal disease caused by the 7 common serotypes and is likely to offer added protection against disease caused by the 6 additional serotypes.

A Wyeth sponsored study has been performed to assess the potential public health and economic impact of 13vPnC, and has been accepted for presentation at 47th IDSA, Philadelphia, September 2009.[91] This investigation used a decision-analytic Markov model to assess the impact of infant vaccination with 13vPnC versus 7vPnC on pneumococcal disease incidence and mortality over 10 years. The incremental benefit of a catch up program to provide protection against pneumococcal disease due to 6 additional serotypes in children 15-59 months of age was also assessed. The model was estimated from CDC data and published sources. Effectiveness of 13vPnC was extrapolated from observed 7vPnC data, using assumptions regarding serotype prevalence and 13vPnC protection against the 6 additional serotypes. Infant vaccination coverage was assumed to be the same for both vaccines. Outcome measures were incidence of IPD, pneumonia, AOM, mortality; and total medical-care costs.

The model predicts that broadly applied infant vaccination with 13vPnC compared to 7vPnC could prevent the following additional pneumococcal disease morbidity and mortality over 10 years in the US (IPD includes direct and herd immunity effects; other outcomes include only direct effects):

- 110,00 cases of IPD
- 166,000 cases of inpatient pneumonia
- 545,000 cases of outpatient pneumonia
- 10.3 million cases of AOM
- 9,800 pneumococcal disease deaths

A one time catch-up program for children 15-59 months of age, previously immunized with Prevnar (7vPnC), could provide the following additional protection against pneumococcal disease (IPD includes direct and herd immunity effects; other outcomes include only direct effects):

- 13,000 cases of IPD
- 145,000 cases of pneumonia
- 1.8 million cases of AOM

Surveillance by the CDC "ABC" and European networks, case-control evaluations from national databases, and a tympanocentesis study evaluating AOM will be used to determine whether this significant health impact is realized and to evaluate for potential serotype replacement. Additional immunogenicity studies will be performed to determine the potential role of 13vPnC in high risk populations including premature infants, children with sickle cell disease or HIV infection, and children undergoing human stem cell transplant.

12.3 Safety

The safety evaluation 13vPnC builds upon the favorable safety profile of 7vPnC that has been well studied and extensively documented. The large pivotal 7vPnC efficacy trial in the US found that systemic reactions in 18,927 infants after vaccine administration were generally mild and local tolerance was good.[92] In an extension to this pivotal efficacy trial, 18,925 infants vaccinated with 7vPnC were followed for at least 5 years after the end of the trial to compare the incidence of target serious adverse events including developmental delay, autistic spectrum

disorders, diabetes mellitus, and reactive airways disease to the controls that received MnCC vaccine. No statistically significant differences were found between 7vPnC recipients and the control subjects.

Safety of 7vPnC and support for continued routine use was reported by investigators of a large (N=162,305) post-licensure observational study of the safety of 7vPnC.[86] FDA review of reports to the Vaccine Adverse Event Reporting System (VAERS) in the first 2 years after licensure of 7vPnC in the US described generally minor adverse events previously identified in clinical trials.[87] To date, global surveillance of spontaneously reported adverse events to Wyeth after 195 million doses distributed has confirmed the generally safe and well-tolerated profile of 7vPnC for use in the routine childhood immunization schedule.

The 13vPnC clinical program demonstrated similar rates of local reactions and systemic events among 13vPnC and 7vPnC recipients. The rates and nature of SAEs and other AEs associated with 13vPnC compared favorably with 7vPnC. The safety profile of 13vPnC supports a recommendation for licensure and routine use of this vaccine in infants and children. Based on 13vPnC safety evaluations to date and the extensive postmarketing safety evaluations for 7vPnC (Prevnar), it is expected that 13vPnC will maintain a favorable safety profile in post-marketing assessments equivalent to that of Prevnar (7vPnC). Wyeth has committed to a large (N=43,000 children, 4 dose series; 15,000 additional children) post-licensure observational US study to further evaluate the safety profile of 13vPnC.

An ongoing study in Alaska (3010) and Study 3011 will inform decisions about catch-up immunization by providing safety and immunogenicity information in older children, some of whom have been previously fully immunized with Prevnar.

12.4 Conclusions

13vPnC provides a real and substantial benefit given its demonstrated ability to elicit immune responses to each of the 13 pneumococcal serotypes in the vaccine, broadening coverage to the 6 additional serotypes.

Based on immunogenicity evidence presented in this submission, it can be expected that the transition from Prevnar to 13vPnC will continue to provide high levels of protection against

pneumococcal disease caused by the 7 common serotypes. Similar effectiveness can be anticipated for the 6 additional serotypes in 13vPnC.

Surveillance data from the United States and Canada indicate that 13vPnC will offer a significant increase in serotype coverage, which would provide a notable improvement compared with Prevnar.

Given that the clinical program provided convincing evidence that 13vPnC is as well tolerated and as safe as Prevnar, the benefit-to-risk ratio of 13vPnC appears to be highly favorable.

13.0 APPENDICES

13.1 Efficacy of conjugated pneumococcal vaccines in clinical trials

13.1.1 Efficacy of Prevnar (7vPnC) against IPD

The large Northern California Kaiser Permanente (NCKP) efficacy trial conducted between 1995 and 1998 has shown that 7vPnC, given to infants at 2, 4, 6, and 12 to 15 months of age significantly reduces IPD due to vaccine serotypes.[92] In this study 37,868 children were randomly assigned in a 1:1 ratio to receive either 7vPnC or meningococcal group C conjugate vaccine (MnCC). In the per-protocol population (fully vaccinated), 40 cases of IPD caused by vaccine serotypes were reported: 39 cases in the control group and 1 case in the 7vPnC group (i.e., a child with bacteremic pneumonia caused by serotype 19F). 7vPnC demonstrated 97.4% efficacy (95% CI: 84.8, 99.9, $p<0.001$) relative to control vaccine in this population.92

In the intent-to-treat population, which included all randomly assigned subjects whether or not they completed the primary series or booster dose, the number of IPD cases was 49 in the control group and 3 cases in 7vPnC recipients. Efficacy in this population was 93.9% (95% CI: 81.0, 98.8).[92] These 3 cases of IPD in 7vPnC recipients included the 1 child mentioned above, 1 child who developed acute myelogenous leukemia after vaccination and while on chemotherapy became bacteremic from serotype 19F, and a child who developed infection from type 6B 317 days after receiving a single dose.

Postmarketing surveillance data collected by NCKP from April 1999 through March 2002 support the above findings, showing that IPD due to vaccine serotypes in children less than 2 years old declined by over 50% within one year of introduction of 7vPnC.[93,94]

Another study of 7vPnC was conducted in Navajo and White Mountain Apache children, who have some of the highest rates of IPD worldwide.[95] By 2 months of age, 50% of infants in this population have pneumococcal colonization. Furthermore, IPD rates in Navajo adults are 3- to 5-fold higher than in the general US population.[96] The study enrolled 8292 children between 6 weeks and 24 months of age who received either 7vPnC or the control vaccine, MnCC. In the per-protocol primary efficacy group (i.e., children aged 6 weeks to less than 7 months old), 10 cases of vaccine type IPD were reported, 8 in the control group and 2 in 7vPnC recipients (serotypes 9V and 14). In the intent-to-treat population, 13 vaccine type cases were reported, 2 in 7vPnC recipients and 11 in MnCC recipients. Efficacy against vaccine type IPD was 76.8% (95% CI: -9.4, 95.1) in the per-protocol population and 82.6% (95% CI: 21.4, 96.1) in the intent-to-treat population. Rates of vaccine type IPD were similar in subjects less than 24 months of age; efficacy in this age group was 81.7% (95% CI: 16.3, 96.0) in the per-protocol subjects and 86.4% (95% CI: 40.3, 96.9) in the intent-to-treat population. Eighteen (18) episodes of nonvaccine type disease were reported; i.e., 11 in the 7vPnC group and 7 in the MnCC recipients (serotype 12F: 8 cases; serotype 7F: 2 cases; serotype 5: 2 cases; and 1 case each of serotypes 3, 6A, 18B, 19A, 23B, and 38).

13.1.2 Efficacy of Prevnar (7vPnC) against Pneumonia

Although not currently included in the U.S. as a labeled indication due to failure to meet a pre-defined primary endpoint, vaccination with Prevnar (7vPnC) has been reported to significantly reduce cases of pneumonia in children less than 2 years of age in a prospective controlled trial. Children enrolled in the large NCKP efficacy trial and with first episodes of clinically diagnosed pneumonia were identified through review of automated inpatient, emergency, and outpatient databases. The subset of those children who also had chest radiographs with a pneumonia diagnosis was identified, and rates of pneumonia were compared between subjects vaccinated with 7vPnC and those receiving the control vaccine (MnCC). Per-protocol follow-up demonstrated that episodes of clinically diagnosed pneumonia in subjects with radiographs were reduced by 9.8% ($p<0.05$, 95% CI: 0.1, 18.5), and episodes with positive radiographs were reduced by 20.5% ($p=0.02$, 95% CI: 4.4, 34.0). In the intent-to-treat analysis (included all episodes after randomization), episodes with a positive radiograph were reduced by 17.7% ($p=0.01$, 95% CI: 4.8, 28.9). The greatest impact was in the first year of life, with a 32.2% reduction in pneumonia ($p=0.03$, 95% CI: 3.3, 52.5), a 23.4% reduction in the first 2 years

(p=0.01, 95% CI: 5.2, 38.1), and a 9.1% reduction in children >2 years of age (p=0.61, 95% CI: 30.9, 36.8).[97] Subsequent reanalysis of an available subset of original radiographs using WHO standardized criteria revealed efficacy against first episode of radiograph confirmed pneumonia of 25.5% (95% CI = 6.5– 40.7%, *P* =0.011) for intent-to-treat and 30.3% (95% CI =10.7– 45.7%, *P* =0.0043) for per protocol.[98]

13.1.3 Efficacy of Prevnar (7vPnC) against Acute Otitis Media (AOM)

The ability of 7vPnC to prevent otitis media due to serotypes included in the vaccine was assessed in 2 clinical trials, both in children less than 2 years of age at the time of vaccination: a trial in infants conducted by the Finnish Otitis Media Study Group and a study conducted as part of the NCKP IPD efficacy trial. The primary endpoint in the Finnish trial was efficacy against AOM episodes caused by vaccine serotypes in the per protocol population. The efficacy of 7vPnC in the Finnish trial against vaccine-serotype AOM was 57% (95% CI: 44, 67) (primary analysis) and against all pneumococcal AOM was 34% (95% CI: 21, 45).[99]

In assessing the vaccine efficacy against AOM in the NCKP trial, data from 52,786 episodes of otitis media that occurred through 30 Apr 1998 were analyzed. The primary otitis media endpoint in the NCKP trial was efficacy against all otitis media episodes (regardless of etiology) in the per protocol population, which reached statistical significance, VE=7% (95% CI: 4, 10). (No routine tympanocentesis was performed.) In 23 children in the study population who had disease caused by the 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), confirmed by cultures of spontaneously ruptured tympanic membranes, point estimates of efficacy were 66.7% in fully vaccinated children (p=0.077), and 64.7% in the intent-to-treat population (p=0.035).[92]

A later analysis of AOM in the same trial demonstrated a 7.8% reduction in otitis media visits observed in children in the per-protocol analysis who received the 3-dose primary series (95% CI, 5.4, 10.2). A 24.2% (95% CI: 11.7, 35.0) reduction in tympanostomy tube placement was also observed in fully vaccinated 7vPnC recipients in the NCKP trial.[67]

13.1.4 9vPnC in Infants and Toddlers: IPD and Pneumonia

A phase 3 trial has been completed in Soweto, South Africa (D124-P502) to determine the protective efficacy of 9vPnC (Prevnar serotypes plus serotypes 1 and 5) against invasive disease due to vaccine serotypes and to determine the clinical efficacy of the vaccine in reducing

radiologically confirmed pneumonia requiring hospitalization in infants. In this trial, 37,146 subjects were enrolled and randomly assigned to receive either 9vPnC or placebo at 6, 10, and 14 weeks of age. In intent-to-treat analyses among children without human immunodeficiency virus (HIV) infection, 9vPnC reduced the incidence of first episodes of IPD due to vaccine serotypes by 83% (95% CI: 39, 97) and first episodes of radiologically confirmed alveolar consolidation by 20 percent (95% CI:2,35).[45] In addition, 9vPnC prevented pneumonia associated with viral infection, indicating that many episodes of viral pneumonia are actually secondary pneumococcal infections.[100]

In another double-blind, placebo-controlled trial conducted in children 6 to 51 weeks old in eastern Gambia, the efficacy of 3 doses of 9vPnC against first episodes of radiologic pneumonia was 37% (95% CI: 27, 45). The total numbers of enrolled subjects in the trial were 8718 in the 9vPnC group and 8719 in the placebo group. The absolute rate reduction in the per-protocol analysis was 15 cases per 1000 child years (95% CI: 10, 19). In the per-protocol population of the Gambia trial, efficacy against IPD caused by vaccine serotypes was 77% (95% CI: 51, 90) and against IPD caused by all serotypes was 50% (95% CI: 21, 69). Hospitalizations with potential IPD-related diagnoses were reduced by 19% (95% CI: 11, 27), and reduction in overall all-cause mortality was 16% (95% CI: 3, 28) in the per-protocol analysis. The vaccine provided significant protection against the most common vaccine serotypes 14, 5, and 23 F. In the placebo group, 65% of invasive disease episodes were due to vaccine serotypes, and the investigators indicated that a vaccine with additional serotypes could have a greater effect.[101]

The Gambia trial noted a lack of efficacy for IPD caused by serotype 1 (4 and 2 cases, among vaccine and control recipients, respectively).[57] In contrast, the trial in South Africa suggested a trend for effectiveness against serotype 1, with 4 cases among controls compared with 1 case in infants immunized with 9vPnC; during the long-term follow-up trial, efficacy was supported by observations of a total of 1 and 5 cases of serotype 1 IPD among vaccine and control recipients, respectively.[59]

13.2 Effectiveness of Prevnar (7vPnC) against pneumococcal disease based on postlicensure experience

To understand the impact of the introduction of Prevnar on public health, it is worthwhile to review the epidemiology of pneumococcal disease prior to its introduction and after its recommendation for routine use in children.

13.2.1 Epidemiology of Pneumococcal Infection Prior to the Introduction of Prevnar (7vPnC)

Prior to the introduction of Prevnar (7vPnC), the incidence of IPD among children less than 2 years of age was approximately 180 to 200 cases per 100,000 per year,[36, 38] with an overall estimated case-fatality rate of 1.4%.[102] The incidence of pneumococcal meningitis in this age group was estimated to be approximately 7 to 10 cases per 100,000 per year, with an associated mortality rate as high as 8% to 25%.[36, 103] Among survivors, a significant proportion had serious sequelae including developmental delay, seizure disorders, and deafness.[103] Additionally, while pneumonia is generally not considered to be an invasive disease *per se*, it may be accompanied by bacteremia or may be complicated by local invasion into a normally sterile space with empyema; both of these invasive manifestations of pneumonia are more severe and carry considerably higher morbidity and mortality rates than do noninvasive pneumonia, even among children. Prior to the licensure of Prevnar, the estimated incidence of pneumonia among children <2 years of age was 24 per 100,000.[102]

S. pneumoniae is also a major cause of noninvasive disease in children. AOM is the most common, estimated to occur in up to 90% of all US children by the age of 3 years.[104] While AOM is generally considered benign, it does carry the risk of complications which range from the development of chronic or recurrent otitis media necessitating surgical intervention (tympanostomy tube placement) and often accompanied by hearing losses with attendant developmental and language delays,[104] to invasive complications including mastoiditis and meningitis, both of which are clinically significant and carry their own risks. The same serotypes causing IPD in children are also prominent causes of AOM, though the number of serotypes commonly causing AOM is larger than that for IPD due to variations in the ability of each serotype to cause invasive versus mucosal disease.

13.2.2 Post-Marketing Effectiveness of Prevnar (7vPnC)

13.2.2.1 Post-Marketing Effectiveness of Prevnar against IPD

Since the vaccine's introduction, a 98% reduction in IPD caused by Prevnar serotypes has been observed among children younger than 5 years of age through 2005,[37] attesting to the high effectiveness of Prevnar in routine use. IPD incidence rates for all age groups have declined, since the introduction of Prevnar. By 2003, disease incidence had declined by 55% in those aged 50 years and older and by 53%, 62%, and 55% in adults aged 65 to 74 years, 75 to 84 years, and 85 years and older, respectively.[105] This noteworthy benefit is presumed to be due to reductions in carriage of vaccine type pneumococcal strains in children and consequent reduced transmission to susceptibles.

While the effect of routine use of Prevnar in infants and young children has been dramatic, the near-total elimination of the serotypes contained in this vaccine has resulted in a proportional increase in other serotypes causing IPD. This phenomenon of "replacement" was to some extent expected, although which serotypes might cause the highest frequency of replacement disease was not entirely predictable from previous knowledge of pneumococcal epidemiology. Specifically, while serotype 19A was the ninth most commonly isolated serotype causing IPD in the United States prior to the introduction of Prevnar, it was hoped that "cross-protection" from inclusion of serotype 19F in the vaccine might also reduce disease caused by serotype 19A. However, according to the Centers for Disease Control and Prevention (CDC) surveillance, serotype 19A has now become the predominant pneumococcal serotype causing IPD in US children, accounting for approximately 40% of the residual IPD in 2005 in children <5 years of age;[37] this finding has also been observed in various regions in the United States. Furthermore, approximately 52% of the serotyped IPD cases occurring in children <2 years of age in 2005 in the CDC's Active Bacterial Core surveillance (ABCs) were due to new serotypes (19A, 7F, 3, 6A, and 5) in 13vPnC. The predominance of emerging serotype 19A is compounded by the increasing likelihood of this serotype to be nonsusceptible to commonly used first-line antimicrobial agents.[106, 107, 108, 109, 110] It has become clear from this shift in the distribution of serotypes causing disease that direct protection by inclusion of these serotypes in a candidate vaccine will be necessary to prevent disease.

13.2.2.2 Post-Marketing Effectiveness of Prevnar (7vPnC) against Pneumonia

After the introduction of Prevnar in the United States, hospitalization admission rates for all-cause pneumonia declined by 39% for children younger than 2 years.[111] Nelson et al reported a significant reduction in risk of confirmed outpatient pneumonia in children less than one year of age in the period after 7vPnC introduction compared to the period during 7vPnC introduction (Incidence Rate Ratio, 0.74).[112] This was accompanied by the suggestion of a decrease in the rate of hospitalized pneumonia in same comparison periods (IRR, 0.60). Reductions in pneumonia were not observed for older children and adults. Microbiological diagnosis is not routinely performed in pneumonia cases, and for young children, in particular, no sputum diagnosis can be performed. Therefore, the diagnosis is performed in the more severe cases. In older children, the additional 13vPnC serotypes, 1, 3, 6A, and 19A, are associated with complicated pneumonia or parapneumonic empyema (PPE). In a multicenter, retrospective study of 8 children's hospitals in the United States, among isolates from complicated pneumonia, pneumococcal serogroups/types 1, 6, 14, and 19 were the most prevalent causes of disease, with serotype 1 causing 24.4% of the complicated cases versus 3.6% of the uncomplicated cases.[113] Other investigators found that PPE in the pre-Prevnar period was most often caused by serotype 1 (46%), but in the post-Prevnar period, in addition to serotype 1 (34%), serotypes 3 (20%) and 19A (14%) were also prevalent.[114]

13.2.2.3 Post-Marketing Effectiveness of Prevnar (7vPnC) against AOM

Please see section 9.3 for a description of post-marketing Prevnar effectiveness against otitis in the U.S.

13.2.3 Manifestations of Invasive Pneumococcal Disease Other Than Meningitis in the Post-Prevnar (7vPnC) Period

Serotypes 1, 3, and 7F have emerged as important causes of invasive disease in the post-Prevnar period in US children, especially as causes of complicated pneumonia with empyema or necrotizing pneumonia,[107, 114, 115, 116, 117] and serotype 19A has been specifically identified as the most prominent serotype causing acute mastoiditis.

Byington and colleagues have recently evaluated trends in pneumococcal parapneumonic empyema (PPE), an invasive complication of pneumonia, occurring in children at Primary Children's Medical Center (PCMC), a referral center in Salt Lake City, UT serving the Intermountain West.[116] Before licensure of Prevnar in 2000, the PPE rate among Utah children

was 5 per 100,000 children, and molecular characterization of isolates causing PPE during that time period revealed that the majority of PPE was due to serotype 1, multilocus sequence type (MLST) 227. By 2006, PPE in Utah increased to 24 per 100,000 children, and a more complete evaluation of archived PPE isolates from the last 6 years was conducted to describe trends in the serotypes causing disease in this population.

Sixty-six (66) isolates collected between January 2001 and February 2007 were identified, of which 51 (78%) were viable for serotyping and further characterization by MLST. Ninety-eight percent (98%) of PPE during this time period was due to non-Prevnar serotypes (1 case was caused by serotype 9V). Four (4) serotypes, all included in 13vPnC, caused 90% of PPE: serotypes 1 (33%), 3 (27%), 19A (26%), and 7F (4%). Serotype 3 emerged in 2001 and all isolates were MLST 180. Serotype 19A emerged in 2002; most isolates (70%) were MLST 199. One (1) 19A isolate was MLST 667, a MLST including both serotypes 14 and 19. Serotype 7F was first seen in 2004. These data suggest that the emergence of virulent clones of nonvaccine serotype pneumococci has been responsible for the increasing incidence of PPE among Utah children, and further, that a vaccine containing these additional serotypes might be effective in reducing the burden of this invasive disease.

The same group of investigators has also published their experience regarding necrotizing pneumonia, also an invasive complication of noninvasive bacterial pneumonia.[117] In this retrospective review of all children <18 years of age at PCMC, Bender et al evaluated the temporal trends in pneumococcal necrotizing pneumonia (PNP), including the causative pneumococcal serotypes.

All children included in this analysis had sterile-site isolates of *S. pneumoniae* as well as radiographic evidence of pneumonia; radiographic evidence of necrosis was determined by the presence of necrotic lung parenchyma, lung abscess, or pneumatocele on chest radiograph or computed tomography (CT). The study time was divided into 2 periods: (1) pre-7vPvC introduction, (01 January 1997 to 31 December 2000), and (2) post-7vPnC (01 January 2001 to March 2006). Over the observation period, 124 children with culture-confirmed pneumococcal pneumonia were identified, and 33 (27%) had radiographic evidence of necrotizing pneumonia. A total of 23 different pneumococcal serotypes were identified among children with pneumococcal pneumonia, the majority of which (77%) were non-7vPnC serotypes. Non-7vPnC serotypes comprised 49% of the isolates from 1997-2000 and 88% of isolates from 2001-2006

(odds ratio [OR], 7.89; 95% CI: 2.91 – 21.9). Pneumonia due to serotype 3 was most often associated with PNP, with 11 of 14 patients (79%) developing necrosis. Pneumococcal serotype 3 was 15 times more likely to be associated with radiographic evidence of lung necrosis (OR, 14.67; 95% CI: 3.39 – 86.25). Additionally, while not a statistically significant finding, children with PNP caused by serotype 3 were somewhat younger than those with PNP caused by other serotypes (mean age, 27.4 vs. 42.3 months). Finally, children with pneumonia due to serotype 3 showed a statistically significant increase in morbidity compared with children with pneumococcal pneumonia due to other serotypes ($p<0.005$), including the need for chest tube placement and other surgical procedures, as well as to have longer hospital stays (and attendant costs). These data are of interest as serotype 3 has, to date, not been much described as a cause of IPD, in the face of relatively more dramatic increases in serotype 19A in IPD and AOM, and in the pneumonia/empyema literature that has been more focused on increases in serotypes 1, 5, and 7F. However, serotype 3 has been known previously to be cause of necrotizing pneumonia in adults,[118] and this is the first substantial report demonstrating that this serotype can be problematic for children as well. While it is not clear that the experience in Utah, which differs demographically from the rest of the US population and from the populations of other countries in several important ways, will be observed elsewhere, certainly this report demonstrates that serotype 3 is capable of causing serious disease.

13.2.3.1 Pneumococcal Meningitis in the Post-Prevnar (7vPnC) period

Trends in pneumococcal meningitis from 1998-2005 in the United States were examined using data collected from 8 ABCs sites.[119] This evaluation included patients with pneumococcal meningitis with culture dates between 01 January 1998 and 31 December 2005. Pneumococcal serotypes were classified into 3 groups: 7vPnC serotypes, 7vPnC-related serotypes (excluding serotype 19A), and non-7vPnC serotypes (all other serotypes, including 19A).

Overall rates of meningitis declined by 30.1% between 1998-1999 (baseline period) and 2004/2005, from 1.13 cases to 0.79 cases per 100,000 persons ($p <0.001$). Among all age groups from baseline to 2004/2005, the rates of meningitis caused by 7vPnC and 7vPnC-related serotypes declined, while the rate of meningitis caused by non-7vPnC serotypes increased. Age- and serotype-specific pneumococcal meningitis incidence rates for children (0-17 years) are shown in Table 13-1. The authors estimated that 13vPnC would have covered 50.0% of cases of pneumococcal meningitis during 2004/2005.

Table 13-1: Mean Annual Incidence of Pneumococcal Meningitis, According to Age Group, Serotype Group, and Year

Age Group	1998/1999 Cases per 100,000 Persons	2004/2005 Cases per 100,000 Persons	2004/2005 vs. 1998/1999 p-Value	2004/2005 vs. 1998/1999 Relative Difference in Incidence (%)
All Serotypes				
All ages	1.13	0.79	<0.001	-30.1
<2 yrs	10.16	3.66	<0.001	-64.0
2-4 yrs	0.95	0.87	0.85	-8.4
5-17 yrs	0.27	0.29	0.87	9.5
7vPnC Serotypes				
All ages	0.66	0.18	<0.001	-73.3
<2 yrs	8.20	0.59	<0.001	-92.8
2-4 yrs	0.88	0.13	0.01	-84.7
5-17 yrs	0.10	0.09	1.00	-7.8
7vPnC-Related Serotypes				
All ages	0.14	0.10	0.08	-32.1
<2 yrs	1.20	0.20	0.01	-83.5
2-4 yrs	0.07	0.00	0.48	-100.0
5-17 yrs	0.00	0.03	0.50	—
Non-7vPnC Serotypes				
All ages	0.32	0.51	<0.001	60.5
<2 yrs	0.77	2.87	0.001	275.3
2-4 yrs	0.00	0.74	0.001	—
5-17 yrs	0.17	0.17	1.00	1.4

It is interesting that the authors chose to separate serotype 19A out of the "7vPnC-related" serotype category and include it instead in the "unrelated" serotypes – highlighting the fact that, despite the ability of 7vPnC to raise cross-reactive antibodies to this serotype, these antibodies are essentially entirely clinically nonfunctional. Of course, this characteristic was already well-

known simply in the observation of the emergence of serotype 19A as a major cause of pneumococcal disease; however, the fact that these authors have decided to treat this serotype as completely unrelated emphasizes the point that clinical cross-protection cannot be assumed, even when cross-reactivity is measurable – direct inclusion of this antigen in a vaccine will apparently be required to achieve predictable protection against disease caused by this serotype.

13.2.3.2 Manifestations of invasive pneumococcal disease by serotype for the six additional serotypes in 13vPnC in the post-Prevnar period

13.2.3.2.1 Serotypes 1 and 5

It is commonly accepted that serotypes 1 and 5 are encountered more frequently in the developing world than in the developed world.[120] The incidence of serotype 1 or 5 IPD can vary from year to year, reflecting the occurrence of an outbreak.[121, 122, 123] There have been reports of serotype 1 pneumonia cases that are complicated by empyema in Europe much like those described in the United States.[114, 124, 125, 126, 127] Recent published experience in Alberta, Canada demonstrates the sporadic but dramatic nature of serotype 5 epidemics. During surveillance for IPD in Alberta, Canada, serotype 5 was not isolated in 2000 but was the single most common isolate in 2006, accounting for 37.57% of all isolates.[128] The large increase of serotype 5 cases of IPD in 2005 and 2006 was judged an unusual epidemic event and was singularly responsible for a large scale outbreak of pneumococcal disease above the background rates in preceding years. Invasive infections by serotype 5 are unusual in Europe, but recent reports from Spain underscore the increasing importance of this serotype.[129] In line with national surveillance data, 5% of invasive isolates in children <5 years of age were caused by serotype 5 in 2007. An increase in the proportion of serotype 5 isolates, from 0.2% to 4.2% of IPD cases, has also been recently reported from England and Wales (2007/2008), predominately because of an outbreak.

13.2.3.2.2 Serotype 3

Invasive infections by serotype 3, which are more commonly seen in older children than in the very young, show an association with severe pneumonia. The results of a study of pediatric pneumococcal parapneumonic empyema (PPE) in the United States (specifically, the state of Utah) demonstrated that serotype 3 was present in 20% of cases in recent years, [114] and that serotype 3 was strongly associated with pulmonary necrosis.[130] The severity of serotype 3 invasive pneumonia had already been observed in the 1960s, underscoring the invasive potential of this particular serotype.

13.2.3.2.3 Serotype 6A

Serotype 6A accounts for a substantial portion of disease caused by pneumococcal serogroup 6. Within this serogroup, cross-reactivity due to the anti-serotype 6B response may allow Prevnar to provide some protection against serotype 6A-specific disease. Data from the United States indicate that Prevnar was able to significantly reduce the incidence of 6A IPD in vaccinated children,[38] and the incidence of infections by serotype 6A was significantly reduced from 4.8 cases per 100,000 children younger than 5 years of age in 1998/1999 to 0.9 cases per 100,000 in 2004.[131] The results of an efficacy study of acute otitis media (FinOM) demonstrated 57% efficacy of Prevnar against serotype 6A AOM. [99] However, in a study using a candidate 9-valent pneumococcal conjugate (CRM_{197}) vaccine (9vPnC), reduction in nasopharyngeal carriage of serotype 6A in vaccinated children was seen to a lesser extent than for the actual vaccine serotypes.[132] Initially, mass vaccination of children with Prevnar in the United States did not yield a reduction of serotype 6A-specific IPD cases in adults through a herd protection effect as was seen with each of the 7 serotypes in the vaccine. Incidence rates of 3.9 cases per 100,000 adults >65 years of age in 1998/1999 and 3.3 cases per 100,000 in 2004 were reported in the United States.[131] However, more recent reports indicate an overall reduction of 58% (95% CI, 43%–69%) in children and adults ≥ 5 years of age. [62] Of note, serotype 6A is among the most important serotypes responsible for IPD in Europe, with a mean proportion of 4.9% (Table 15-5) The highest proportion of cases is reported from Germany (9.8% of cases, peaking at 14% in 2006/2007). Moreover, serotype 6A has been shown to be associated with diminished antibiotic susceptibility.[133, 134]

The newly identified serotype 6C deserves mention at it is not easily distinguished from serotype 6A. Serotype 6C differs from 6A only by inclusion of a glucose residue in place of galactose in the polysaccharide repeat unit. The Neufeld Quellung reaction classically used for serotyping pneumococci[135] as well as a variety of other antibody-based techniques used for serotyping pneumococci, including latex bead agglutination[136, 137] and multiplex bead-based inhibition assays,[138,139,140] do not distinguish between serotype 6A and 6C isolates when using conventional serotyping reagents.[141,142] However, specific monoclonal antibodies,[142] PCR-based serotyping methods,[143,144] and multiplexed PCR-based serotyping methods[145,146,147,148] using serotype-specific primer sequences derived from the capsular operon of *S. pneumoniae* can be used to distinguish serotype 6C from 6A. Nahm et al[141] reported that the prevalence of 6C isolates in the

nasopharynx (carriage) of US children less than 7 years of age has gradually increased between 1994 (0.8 %) and 2007 (8.7%) whereas serotype 6C carriage was not or very rarely detected prior to 2000. Recent publications have also described in increasing incidence of IPD due to serotype 6C. [62, 149] However, the absolute rate increase of 0.52 and 0.35 /100.000 in less than 5 years and all ages, respectively has remained small.[149] These observations suggest that 6B in Prevnar does not confer protection against invasive disease caused by either serotype 6A or 6C.

13.2.3.2.4 Serotype 7F

Serotype 7F has accounted for 7-18% of pneumococcal isolates from a Massachusetts surveillance study performed in recent years and approximately 6% of cases in recent CDC ABC surveillance. It was one of the key serotypes responsible for PPE in the Utah report described above, and was the most commonly reported isolate from the UK in 2007-2008 in children ≤ 2 years of age.[116, 150]

13.2.3.2.5 Serotype 19A

Serotype 19A IPD increased in the United States after the introduction of Prevnar, from 0.8 to 2.5 cases per 100,000 population between 1998 and 2005,[151] demonstrating the absence of impact by Prevnar against serotype 19A IPD. Of concern, the prevalence of IPD due to penicillin-resistant and often multiply antibiotic-resistant 19A isolates increased from 6.7% to 35%.[151] In addition to the ineffectiveness of Prevnar against serotype 19A, antibiotic resistance, clonal expansion and emergence, and capsular switching may have each contributed to the genetic diversity of the serotype and to its emergence as the predominant invasive pneumococcal serotype in the United States. As noted above this serotype has been responsible for over 25% of cases of pneumonia with parapneumonic effusion (PPE) based on a Utah report, and is now the most common cause of meningitis, increasing 5-fold since Prevnar introduction. [116, 119] It has now also been reported as the most common cause of acute mastoiditis in children and seems to carry a higher risk of complications such as subperiosteal abscess and surgical intervention.[152]

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