Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed

Proprietary Product Name: Prevenar 13

Sponsor: Pfizer Australia Pty Ltd

**Date of first round report: 30 October 2012**
**Date of second round report: 8 May 2013**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

**Copyright**
© Commonwealth of Australia 2014
This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| 7vPnC | 7-valent pneumococcal conjugate vaccine |
| 9vPnC | 9-valent pneumococcal conjugate vaccine (experimental) |
| 13vPnC | 13-valent pneumococcal conjugate vaccine |
| 23vPPV | 23-valent pneumococcal polysaccharides vaccine |
| AE | Adverse Event |
| AOM | Acute Otitis Media |
| CDC | (US) Centers for Disease Control and Prevention |
| CI | Confidence Interval |
| CORE II | Clinical Operations Randomisation Environment II |
| CRF | Case Report Form |
| $CRM_{197}$ | cross-reacting material $_{197}$ (nontoxic mutant form of diphtheria toxin) |
| DoB | Date of Birth |
| ELISA | Enzyme-linked immunosorbent assay |
| GCP | Good Clinical Practice |

| Abbreviation | Meaning |
|---|---|
| GMC | Geometric mean concentration |
| GMFR | Geometric mean field rise |
| GMT | Geometric mean titres |
| IgG | immunoglobulin G |
| IM | intramuscular |
| IPD | Invasive Pneumococcal Disease |
| LLOQ | lower limit of quantitation |
| LOD | limit of detection |
| NI | Non-inferiority |
| NP | nasopharyngeal |
| OM | otitis media |
| OPA | opsonophagocytic activity |
| PD | Pneumococcal Disease |
| Prevenar | 7-valent pneumococcal conjugate vaccine |
| Prevenar13 | 13-valent pneumococcal conjugate vaccine |
| RCDC | reverse cumulative distribution curve |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| WHO | World Health Organisation |
| YK | Yukon Kuskokwim |

# 1. Clinical rationale

The sponsor submitted an extensive clinical summary with a reasoned argument for a change to the extension of age indication and change in Product Information (PI) wording for nasopharyngeal carriage. The following is a summarised extract from their clinical summary document.

## 1.1. Extension of age

Pfizer has developed the 13-valent pneumococcal vaccine (13vPnC, Prevenar13) as a successor of 7-valent pneumococcal vaccine (7vPnC, Prevenar) for use in infants and young children to prevent pneumococcal disease (invasive pneumococcal disease, IPD and acute otitis media, AOM) caused by the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) contained in the vaccine. To overcome the limited immunogenicity of pneumococcal polysaccharide vaccines, the protein conjugation technology was applied to the development of 7vPnC and 13vPnC. Each of the pneumococcal polysaccharides is covalently conjugated to the diphtheria cross-reactive material 197 ($CRM_{197}$), which acts as an immunologic carrier.

While there has been a significant reduction in IPD since the introduction of Prevenar in young children up to 5 years of age, there remains a significant burden of disease in children and adolescents 6 to 17 years of age. In the United States, the Centers for Disease Control (CDC) estimated that in 2007, 1,300 cases of IPD occurred annually in this age group (population 54 million) and between 52.4% and 61.3% were caused by 13vPnC serotypes.[1] A study from the United States found that approximately 10% of patients admitted to a paediatric hospital with IPD were aged between 5 to 10 years.

7vPnC has demonstrated a high degree of efficacy against IPD in infants and young children; published studies have reported efficacy and effectiveness again pneumonia. 13vPnC has been licensed subsequently for children up to 5 years of age, with an expectation of effectiveness for all serotypes. The introduction of 13vPnC in the USA began in March 2010. An analysis of the quarterly incidence of IPD (cases per 100,000) in 2010 compared to 2006-2008 (baseline) showed that among children <2 years, overall 13vPnC serotype rates were significantly lower ($p<0.0001$) in the fourth quarter of 2010 when compared to baseline (13vPnC serotypes 8.5 cases versus 24.1 cases respectively). The authors concluded that these preliminary findings are consistent with early effects of 13vPnC on IPD among young children. These observations are in line with those made in England and Wales after the introduction of 13vPnC in the National Immunisation Program. Evaluation of the immune response after 13vPnC in children and adolescents 6 to 17 years of age in Study 6096A1-3011 indicates that 13vPnC immunisation would likely confer similar benefits for this population.

Children with underlying conditions such as chronic heart or lung disease, diabetes and others have an increased risk of pneumococcal disease. The relative risk of children with a predisposing medical condition (diabetes, asthma) is often 2 to 4 fold, when compared to the healthy population of the respective age group. Vaccination with 23-valent pneumococcal polysaccharide vaccine (23vPPV) of at risk and high-risk children and young adults has been recommended. However, the degree of protection afforded by 23vPPV remains a critical issue. 13vPnC would provide a new alternative to protect children and adolescents 6 to 17 years of age who are at increased risk for pneumococcal disease. There is also a smaller group of children with complex immunocompromising conditions (HIV, sickle cell disease) who have an increased risk for pneumococcal infections.

The Australian Immunisation Handbook (9th Ed)[2] has not been updated to include information regarding 13vPnC. The current recommendation is for children[3] with specified underlying medical conditions to receive 2 doses of 7vPnC followed by a dose of 23vPPV.

Some of the highest rates of IPD ever reported in the world were in young central Australian Aboriginal children before the availability of conjugate vaccine. As well as higher rates of IPD, a

[1] Evaluator Comment: Based on Australian census data 2010, the number of children aged 6-17 years in Australia is approximately 4 million. Using the CDC calculations this would amount to an estimate of 96 IPD cases annually, of which 52-61% would be caused by 13vPnC serotypes.

[2] <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/78CDF41C283426A8CA2574E40020CCAB/$File/handbook-9.pdf>

[3] Sponsor comment: "This recommendation refers to children 6 to ≤9 years of age."

wider range of serotypes are responsible for disease in Aboriginal and Torres Strait Islander children, resulting in a lower percentage of cases (<60%) caused by serotypes included in the 7vPnC. A booster dose of 23vPPV at 18-24 months is currently recommended for Indigenous children living in areas of high incidence. There has been a rapid decline in invasive pneumococcal disease in Indigenous children since the introduction of the 7vPnC in 2001 (Australian Immunisation Handbook)[2]. An extension of age indication, if proven, would have a benefit for this subset of the Australian population.

### 1.2. Nasopharynx

Colonisation with *Streptococcus pneumoniae* in the nasopharynx is the necessary first step in the pathogenesis of all types of pneumococcal disease (PD), whether invasive IPD (such as sepsis, meningitis, arthritis) or mucosal (for example otitis media, pneumonia). Studies suggest that nasopharyngeal (NP) colonisation early in life may result in increased susceptibility to pneumococcal infections, specifically to acute otitis media, later in life. Data from randomised controlled trials and from observational studies of pneumococcal conjugate vaccines that is, 7vPnC, 13vPnC and the experimental 9-valent pneumococcal conjugate vaccine (9vPnC) have shown a reduction in NP colonisation by vaccine serotypes after vaccination. The result of this effect is a reduction of transmission of *S pneumoniae,* leading to an indirect effect (herd protection) and to the reduction in transmission of antibiotic resistant strains. Thus, the protection conferred by pneumococcal conjugate vaccines results from:

1. Direct protection against invasive disease caused by vaccine-type serotypes, which is mediated through functional antibodies
2. Reduction of NP colonisation in the individual and thus a reduction of transmission to unvaccinated subjects or "herd protection"

Prevention of pneumococcal NP colonisation has emerged as a relevant surrogate marker of vaccine efficacy of 7vPnC and 13vPnC against pneumococcal disease, including invasive disease, as well as the biological basis for the additional benefits listed above for pneumococcal vaccines.

Evaluator Comment: The critical factor here is differentiating between a reduction in nasopharyngeal acquisition (colonisation) by pneumococcal serotypes versus a reduction in the nasopharyngeal carriage of the bacteria. This difference also has implications in terms of showing herd immunity.

A quick PubMed literature search shows that there have been a number of theories postulated for the herd immunity effect that has been shown with 7vPnC. The conclusion of these studies was that it was not yet clear if NP carriage plays a pivotal role in 'herd protection'. In addition, several studies that undertook long-term follow-up of subjects and their families post 7vPnC and found that the drop in NP carriage rates initially seen following vaccination could not be reproduced >2 years post-vaccine.

There is currently no evidence to show that the effect results in a reduction in transmission of *S. pneumoniae* antibiotic-resistant strains.

# 2. Contents of the clinical dossier

### 2.1. Scope of the clinical dossier

The clinical dossier is confined to clinical information related to the extension of indications and application for an additional mode of action to be added to the PI.

The submission contained the following clinical information:

- 1 pivotal efficacy study for the extension of indications to include 6 to 17 year olds (6096A1-3011).
- 2 pivotal efficacy studies for the inclusion of nasopharyngeal carriage (6096A1-3006, 6096A1-3010).

### 2.2. Paediatric data

The submission deals exclusively with a paediatric population and includes data on infants and children aged 2 months to 17 years.

### 2.3. Good clinical practice

All three studies were conducted in accordance with the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the ethical principles that have their origins in the Declaration of Helsinki.

# 3. Pharmacokinetics

### 3.1. Studies providing pharmacokinetic data

There were no new pharmacokinetic data submitted with this application.

# 4. Pharmacodynamics

### 4.1. Studies providing pharmacodynamic data

There were no new pharmacodynamic data submitted with this application.

# 5. Dosage selection for the pivotal studies

The dose selected for the pivotal studies is in line with the current dosage indications; 0.5 mL of vaccine containing 2.2 μg/dose of each of the serotypes, except for serotype 6B which is present at 4.4 μg/dose. Up to four doses of Prevenar 13 are administered with a typical regimen being 3 infant doses at 2, 4 and 6 months and a toddler dose at 12 months of age.

# 6. Clinical efficacy

* Clinical efficacy for Prevenar 13 is based on a surrogate immunogenicity marker. This standard was established during the initial approval of the Prevenar 13 vaccine and is based on non-inferiority of immunogenicity profiles to Prevenar.

## 6.1. Extension of indication (Age inclusion 6 to 17 years)

### 6.1.1. Pivotal efficacy study (Immunogenicity)

#### *6.1.1.1. Study 6096A1-3011*

##### *6.1.1.1.1. Study design, objectives, locations and dates*

Study 6096A1-3011 was an open-label study designed to evaluate the safety, tolerability and immunogenicity of 13vPnC when administered to healthy children aged >15 months to < 2 years (Group 1) who had been previously vaccinated with at least 3 doses of Prevenar, children aged ≥2 years to <5 years (Group 2) who had been previously vaccinated with at least 3 doses of Prevenar, children ≥5 years to <10 years (Group 3) who had been previously vaccinated with at least 1 dose of Prevenar, and children ≥10 years to <18 years (Group 4) who had never been vaccinated with Prevenar or any other pneumococcal vaccine. There were no control groups.

The study was conducted at 37 sites in the United States over the period 18 November 2008 and 4 November 2011. Twenty-nine (29) of the 37 sites enrolled subjects in Group 3 and 4.

Informed consent and medical history including prior vaccinations were obtained and a physical examination was performed before receipt of the study vaccine. Demographic data, including sex, race, ethnicity and date of birth were collected. Blood samples were obtained before study vaccine administration at visit 1 (Day 1) and 1 month (28-42 days) after the vaccination. Safety parameters including local reactions and systemic events were recorded by subjects in an e-diary for 7 days after vaccination. All serious adverse events (SAEs) were recorded and reported from the signing of the initial informed consent form to the 6 month telephone follow-up (visit 3).

Evaluator Comment: Only Groups 3 and 4 (children aged ≥ 5 to < 18 years) were included in the analysis for the extension of indication. The remaining information regarding the trial will include information only related to these groups.

##### *6.1.1.1.2. Inclusion and exclusion criteria*

Eligible subjects for Groups 3 and 4 were healthy children aged ≥ 5 years and <18 years at the time of enrolment who were available for the entire study period and whose parent/legal guardian could be reached by telephone. Subjects in Group 3 had to have received at least 1 previous dose of Prevenar. In Group 4, female and male subjects who were biologically capable of having children agreed to abstinence or committed to the use of a reliable method of hormonal and/or non-hormonal contraception for 3 months after the vaccination.

Children were excluded if they had a major illness or condition that would have substantially increased the risk associated with study participation and completion or precluded the evaluation of the child's responses. Children were also excluded if previously vaccinated with 23vPPV or if they were direct descendants of site study personnel. Subjects in Group 4 were excluded if previously vaccinated with Prevenar or any other pneumococcal vaccine or were pregnant or breastfeeding.

Medical conditions precluding enrolment included previous anaphylactic reaction to any vaccine or vaccine-related component, contraindication to vaccination with a pneumococcal conjugate vaccine, bleeding diathesis or condition associated with prolonged bleeding time that would have contraindicated intramuscular injection, history of culture-proven invasive disease caused by *S. pneumoniae* and major known congenital malformation or serious chronic disorder, significant neurological disorder or history of seizure (excluding simple febrile convulsion), receipt of blood products or gamma-globulin, known or suspected immune deficiency or suppression.

Evaluator Comment: Inclusion and Exclusion criteria are appropriate

*6.1.1.1.3. Study treatments*

13vPnC (lot no. 7-5095-005A) was administered by a medically qualified member of the investigator's staff by injecting 0.5 mL intramuscularly into the subject's left arm or leg.

*6.1.1.1.4. Efficacy variables and outcomes*

Subjects in Groups 3 and 4 received a single dose of 13vPnC. Subjects were evaluated for immunogenicity at approximately 1 month after vaccination and for safety through the 6 month telephone follow-up. The main efficacy variables were:

- Serum concentrations of anti-capsular immunoglobulin G (IgG) for each of the 13 pneumococcal serotypes contained in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) expressed as micrograms per millilitre (μg/mL) collected at baseline and 1 month after vaccination
- Serum opsonophagocytic assays (OPA assays) to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) reported as antibody titers. (exploratory objective) collected at baseline and 1 month after vaccination
- Age at time of vaccination

The primary efficacy outcome was the proportion of subjects achieving a serotype-specific immunoglobulin G (IgG) antibody concentration ≥0.35 μg/mL induced by 13vPnC when measured 1 month after last scheduled dose of 13vPnC.

Evaluator Comment: The primary efficacy outcome as listed here is not correct – based on recommendations from the FDA the Group 3 was split into an exploratory and confirmatory cohort and data compared to IgG data from an historical cohort. Group 4 data was compared to OPA RCDC from Group 3.

*6.1.1.1.5. Randomisation and blinding methods*

Each subject was registered at visit 1 using the Clinical Operations Randomisation Environment II (CORE II) system. The CORE II system provided a randomisation number for each subject, although subject allocation to age groups was based on the subject's age at enrolment.

This was an open-label study. There was no blinding.

*6.1.1.1.6. Analysis populations*

The *evaluable immunogenicity population* included all subjects who were eligible for the study; met the age requirement (≥5 to <10 years of age for Group 3 and ≥10 to <18 years of age for Group 4): received the required study vaccination; had a least 1 valid and determinate assay result before and after the study vaccination; had blood drawn before and after the vaccination within the required time frame; and had no other major protocol violations.

The *all-available immunogenicity population included* subjects for each age group who had at least 1 valid and determinate assay result. The *safety population* included all subjects who received at least 1 dose of 13vPnC.

Evaluator Comment: Populations are appropriate.

*6.1.1.1.7. Sample size*

The initial sample size was calculated based on the proportion of responders for pneumococcal serotypes for Groups 3 and 4 based on data from Wyeth study D118-P18. The following assumptions were made in estimating the proportion of subjects assumed to achieve an antibody concentration ≥0.35 μg/mL for a 95% CI for Groups 3 and 4; (a) a sample size of 80 and 80 evaluable subjects from Groups 3 and 4 respectively; (b) a 2-sided, and type I error rate of 0.05. A dropout rate of 20% was assumed providing a sample size of at least 100 subjects per

group. The antibody concentration of ≥0.35 µg/mL was based on the WHO guidelines for the pneumococcal serotypes.

Following discussions with the FDA[4] the ≥0.35 µg/mL cut-off was changed. The FDA requested that the sample size be enlarged and Groups 3 and 4 be split into exploratory and confirmatory cohorts. The exploratory cohort (the first 100 subjects enrolled in each group) would be used to obtain reference IgG antibody concentrations for children aged 5-17 years. The confirmatory cohort (next 200 subjects enrolled in each group) would then be used to validate the exploratory cohort results. Based on these considerations the sample size was increased to 600 (that is, 300 subjects in Group 3; 300 in Group 4). The sample size was agreed upon by the sponsor and the FDA prior to study start.

Some 598 subjects consented to participate in the study and were randomised to treatment; 299 in Group 3 and 299 in Group 4. The majority of the enrolled subjects in Group 3 and Group 4 were vaccinated (Group 3, 98.3%; Group 4, 99.7%) and completed the study (Group 3, 92.6%; Group 4, 98.3%).

Evaluator Comment: FDA recommendations were implemented. These enlarged sample size increases the robustness of results, however, the analysis methodology seems to unnecessarily complicate the results.

*6.1.1.1.8. Statistical methods*

*6.1.1.1.9. Data handling*

For each sample assayed, the serotype-specific IgG concentrations of the 13 pneumococcal serotypes were determined using enzyme-linked immunosorbent assay (ELISA). This resulted in 7,800 assays for Group 3 (300 subjects x 13 serotypes x 2 visits) and 7,800 assays for Group 4 (300 subjects, 13 serotypes x 2 assays. In addition, OPA to the 13 pneumococcal serotypes were performed on each blood sample in a randomly selected subject of 200 subjects (100 from Group 3 and 100 from Group 4). This results in 5,200 assays using OPA (100 subjects x 13 serotypes x 2 visits x 2 groups).

Pneumococcal IgG concentration data were logarithmically transformed for analysis. Geometric means of the pneumococcal IgG antibody concentrations (GMCs) were calculated at each visit that blood was drawn. The geometric mean fold rises (GMFRs) in antibody concentration (post-vaccination/pre-vaccination) were also derived by geometric means.

The proportion of subjects achieving a serotype-specific OPA antibody titre ≥1:8[5] were derived. OPA antibody titres were logarithmically transformed for analysis. Geometric means of the OPA titres (GMTs) were calculated for each serotype at each visit blood was drawn. The GMFRs in OPA titres (post vaccination/pre vaccination) will be also derived for each of the 13 serotypes if post vaccination and pre vaccination assay data are 'non-missing'. Otherwise they will be recorded as missing values.

Wyeth's ELISA lower limit of quantitation (LLOQ) is conservatively defined as the 95% upper bound of the lowest mean titre values established during the validation proves. The LLOQ in µg/mL for each serotype was set as follows; serotype 1, 0.02; serotype 3, 0.03; serotype 4, 0.02; serotype 5, 0.03; serotype 6A, 0.03; serotype 6B, 0.03; serotype 7F, 0.04; serotype 9V, 0.02; serotype 14, 0.04; serotype 18C, 0.02; serotype 19A, 0.02; serotype 19F, 0.03; serotype 23F, 0.03. The limit of detection (LOD) was established as 50% of the LLOQ. Antibody concentrations

[4] Sponsor comment: "As per a request from the United States Food and Drug Administration, the protocol is being amended (Amendment 3) to increase the sample size to 1200 subjects (300 subjects in each group). The additional subjects will enhance the precision of the immunogenicity results and provide additional safety data for 13vPnC in older children. The subjects enrolled into Groups 1 and 2 prior to Amendment 3 will be classified as Cohort 1. The additional subjects enrolled into Groups 1 and 2 as part of Amendment 3, will be classified as Cohort 2 and will only be evaluated for safety."

[5] Sponsor comment: "OPA titres ≥LLOQ replaced the analyses for OPA titres ≥ 1:8."

above the LLOQ are considered accurate and their values reported. Values below the LLOQ or denoted as below limit of quantitation were set to 0.5*LOD for analysis.

Type I error is not adjusted for multiple comparisons within each group. Calculations of type I error relate only to the primary immunogenicity analysis.

*6.1.1.1.10. Immunogenicity Analysis*

Data from Groups 3 and 4 needed to be bridged to data from a population in which Prevenar has shown immunogenicity, as well as effectiveness in post licensure studies and in which 13vPnC is licensed (that is, infants and toddlers). A comparison to serotype specific IgG geometric means concentrations (GMCs) measured 1 most post-vaccination in this study was compared to corresponding data from a historical cohort, Study 6096A1-3005. Study 6096A1-3005 included approximately 1050 13vPnC-vaccinated subjects contributing data to the evaluable post-toddler immunogenicity analyses. In addition, the study included a 7vPnC control arm. The Prevenar control group from 6096A1-3005 was used for IgG GMC comparisons with 13vPnC in this study for the 7 common serotypes in Group 3 as this provides a direct link to Prevenar immunogenicity. The data from Group 4 was then compared to Group 3 OPA responses.

IgG and OPA responses have been shown to be concordant when determined 1 month after administration of 13vPnC in a 3 dose infant series, after a toddler dose, and after a single dose given to adults 50 years and older.

The primary analysis of IgG concentrations for Group 3 was a non-inferiority (NI) comparison to anti-capsular IgG data from Wyeth study 6096A1-3005. For each of the original 7 serotypes included in Prevenar, the ratio of the GMCs comparing Group 3 to results from 7vPnC-3005 were computed. For each of the additional serotypes included in Prevenar13 (1, 3, 5, 6A, 7F and 19A), the ratio of the GMCs comparing Group 3 to results from 13vPnC-3005 were computed. Two sided-95% confidence intervals were estimated by back transformation of the confidence intervals for the difference in means of the logarithmically transformed assay results based on the Student t-distribution. The criteria for NI for a given serotype were met if the lower limit of the 2-sided 95% CI for the GMR (Group 3 relative to 6096-3005) is greater than 0.5 (i.e. no greater than 2 fold). Additional analyses were considered in an overall evaluation of the merits of a given serotype that fails the primary NI criterion such as:

- Assessment of the relative margin of failure;
- Assessment of the elicitation of specific OPA antibody; and
- Review and comparison of the reverse cumulative distribution curves (RCDCs) embodying the overall antibody response distribution across the entire study population.

A similar analysis will be performed to compare the IgG data from Group 4 to data from Wyeth study 6096A1-3005. This will constitute a secondary analysis for Group 4.

*6.1.1.1.11. Proportion of subjects achieving defined levels*

The confidence interval for the single proportions were computed using the F distribution. These proportions were multiplied by 100 for presentation in tables. The confidence internal using the F distribution is described in Collett[6] and implemented in SAS PROC FREQ.

*Pneumococcal antibody concentrations*

For the pneumococcal IgG concentrations, the proportion of subjects achieving an antibody concentration ≥0.35µg/mL and ≥1.0 µg/mL before and after the first vaccination were computed for each blood sample.

[6]Collett, D. (1991), Modelling Binary Data, London: Chapman & Hall, pp 23-25

*6.1.1.1.12. Geometric means*

Within each age group, geometric means of the pneumococcal IgG antibody concentrations (GMCs) were calculated at each visit that has a blood draw. Two-sided 95% confidence intervals will be constructed by back transformation of the confidence internals for the mean of the logarithmically transformed assay results computed using the Student t distribution. GMFRs in antibody concentration (post-vaccination/pre-vaccination) were summarised by geometric means and 95% confidence intervals, also computed using the logarithmically transformed assay results.

*6.1.1.1.13. Reverse cumulative distribution curves*

Reverse Cumulative Distribution Curves were presented graphically by age group for each serotype-specific pneumococcal IgG antibody concentration before and after vaccination. Data from Study 6096A1-3005 will also be presented on the same plot.

Evaluator Comment: This study involved multiple analyses of the 13 serotypes in the 13vPnC. No adjustment was made for multiplicity. Given the high number of tests performed, the risk of false-positive results is high. Many of the results beyond the primary and secondary analysis should be viewed as exploratory analysis only.

*6.1.1.1.14. Participant flow*

**Table 1: Study Flowchart**

| Visit Number | 1 | 2 | 3 |
|---|---|---|---|
| **Study Interval** | Vaccination 1 | Post-vaccination Follow-up | Telephone follow-up |
| **Visit Window** | ≥5 years - < 18 years | 28 – 42 days | 165-210 days |
| **Informed consent** | x | | |
| **Medical history and examination** | x | | |
| **temperature** | x | | |
| **Blood sample** | x | x | |
| **13vPnC administered** | x | | |
| **Adverse event collection** | x | x | x |
| **Assess acute reactions (e-diary)** | Days 1-7 | | |
| **Review e-diary data** | | x | |

*6.1.1.1.15. Major protocol violations/deviations*

In Group 3, 22 subjects were withdrawn from the study due to loss to follow-up (6); failure to return (5); parent/legal guardian request (5); protocol violation (5) and "other" reason (1 subject uncooperative). In Group 4, 5 subjects were withdrawn due to failure to return (2); lost to follow-up (1); protocol violation (1); and "other" (1 unable to obtain blood sample).

Evaluator Comment: Withdrawal and loss-to-follow-up are within acceptable limits.

*6.1.1.1.16. Baseline data*

Demographic data for the study subjects is presented below.

**Table 2: Study Characteristics**

| | Vaccine Group | |
|---|---|---|
| | **Group 3 n (%)** | **Group 4 n (%)** |
| Consented | 299 (100) | 299 (100) |
| Enrolled | 299 (100) | 299 (100) |
| Vaccinated | 294 (98.3) | 298 (99.7) |
| Completed | 277 (22) | 294 (98.3) |
| Withdrawn | 22 (7.4) | 5 (1.7) |
| Reason for withdrawal | | |
| Failed to return | 5 (1.7) | 2 (0.7) |
| Lost to follow-up | 6 (2.0) | 1 (0.3) |
| Protocol violation | 5 (1.7) | 1 (0.3) |
| Parent/legal guardian request | 5 (1.7) | 0 (0.0) |
| Other | 1 (0.3) | 1 (0.3) |
| Blood sample drawn<br>Pre-vaccination<br>Post-vaccination | <br>277 (92.6)<br>293 (98.0) | <br>295 (98.7)<br>293 (98.0) |
| All-available immunogenicity | 295 (98.7) | 298 (99.7) |
| Evaluable immunogenicity | 272 (91.0) | 286 (95.7) |

Of the 5 subjects who were not vaccinated in Group 3, 4 subjects withdrew consent (specific terms include "withdrew consent", "subject uncooperative" and "patient refused vaccination". In Group 4, one subject was not vaccinated because study personnel were unable to draw blood from the subject. Compliance with e-diaries was high, with e-diaries being transmitted by 98.6% of subjects in Group 3 and by 99.3% of subjects in Group 4. Most subjects completed 75% or more of the e-diary days. Compliance remained high throughout the 7 day monitoring period.

The demographic characteristics of all 634 subjects who were screened for the study are presented below. In Group 3 and Group 4, respectively, the majority of subjects were White (66.9% and 77.9%) and non-Hispanic and non-Latino (91.3% and 91.3%). In Group 3 and Group 4, the percentages of males were 48.2% and 54.5%, respectively. In Group 3, age at enrolment ranged from 5-10 years, with the mean age at enrolment of 7.4 years. In Group 4, age at enrolment ranged from 10 to 18 years, with the mean age at enrolment of 13.7 years.

**Table 3: Demographic Data**[7]

| | Vaccine Group | |
|---|---|---|
| | **Group 3 n (%)** | **Group 4 n (%)** |
| Sex Male | 129 (47.4) | 161 (56.3) |
| Race White | 186 (68.4) | 223 (78.0) |
| Black, African American<br>Other | 69 (25.4)<br>12 (4.4) | 51 (17.8)<br>6 (2.1) |
| Age at first dose, *years* (SD) | 7.4 (1.3) | 13.7 (2.1) |
| *Min, max* | 5.0, 10.0 | 10.0, 18.0 |
| Weight at enrolment, *kg (SD)* | 28.4 (8.9) | 58.5 (17.9) |
| *Min, max* | 15.2, 66.8 | 23.1, 130.0 |
| Asthma | 52 (17.4) | 52 (17.4) |
| Psychiatric disorder | 36 (12) | 64 (21.4) |

Evaluator Comment: Demographic data is reasonable – the lack of Asian subjects in terms of Australian demographics is worth noting although there is no evidence to suggest that Asian children react differently to the pneumococcal vaccines. The mean weights at enrolment seem high (28.4kg Group 3 and 58.5kg Group 4); this is probably reflective of the state of child health in the US, with a high prevalence of overweight and obese children. It may also be a good reflection of mean Australian child weights. It is unlikely that weight would play a significant role in immunogenicity. Approximately 17% subjects had a diagnosis of Asthma; this is consistent with rates of childhood asthma in Australia and, in addition, provides some justification for comments made in the PI.

[7] Sponsor comment: "Representative of the US population

#### *6.1.1.2. Results for the primary immunogenicity outcome*

##### *6.1.1.2.1. IgG geometric means*

The primary immunogenicity objective was to demonstrate non-inferiority, based on IgG concentrations, 1 month after 13vPnC vaccination in the Group 3 (subjects ≥5 years to <10 years) confirmatory cohort compared to the post-toddler responses in the 7vPnC group from study 6096A1-3005 for the 7 common serotypes and compared to the post-toddler responses in the combined 13vPnC groups from Study 6096A1-3005 for the 6 additional serotypes. The criterion for non-inferiority for a given serotype was met if the lower limit of the 2-sided 95% CI for the ratio of GMCs (Group 3 confirmatory cohort relative to study 6096A1-3005) was >0.05.

**Table 4: Comparison of Pneumococcal IgG GMC (µg/mL) post vaccination – *Evaluable Immunogenicity Population***

| | 13vPnC Group 3c (Study 3011) | | | 7vPnC (Study 3005) | | | Ratio |
|---|---|---|---|---|---|---|---|
| **Serotype** | **n** | **GMC** | **95% CI** | **n** | **GMC** | **95% CI** | |
| 7vPnC | | | | | | | |
| 4 | 169 | 8.45 | 7.24, 9.87 | 173 | 2.79 | 2.45, 3.18 | 3.03 (2.48, 3.71) |
| 6B | 171 | 53.56 | 45.48, 63.07 | 173 | 9.47 | 8.26, 10.86 | 5.66 (4.57, 6.99) |
| 9V | 171 | 9.51 | 8.38, 10.78 | 173 | 1.97 | 1.77, 2.19 | 4.83 (4.10, 5.70) |
| 14 | 169 | 29.36 | 24.78, 34.78 | 173 | 8.19 | 7.31, 9.18 | 3.58 (2.93, 4.39) |
| 18C | 171 | 8.23 | 7.13, 9.51 | 173 | 2.33 | 2.05, 2.65 | 3.53 (2.91, 4.29) |
| 19F | 171 | 17.58 | 14.95, 20.67 | 173 | 3.31 | 2.87, 3.81 | 5.31 (4.29, 6.58) |
| 23F | 169 | 11.26 | 9.79, 12.95 | 173 | 4.49 | 3.86, 5.23 | 2.51 (2.04, 3.08) |

The serotype-specific GMCs were higher in Group 3 in this study compared to the 7vPnC group from Study 6096A1-3005 for all of the 7 common serotypes. The serotype-specific geometric mean ratios ranged from 2.51 for serotype 23F to 5.66 for serotype 6B.

**Table 5: Comparison of Pneumococcal IgG GMC (µg/mL) post-vaccination – *Evaluable Immunogenicity Population***

| | 13vPnC Group 3c (Study 3011) | | | 13vPnC (Study 3005) | | | Ratio |
|---|---|---|---|---|---|---|---|
| **Serotype** | **n** | **GMC** | **95% CI** | **n** | **GMC** | **95% CI** | |
| Additional | | | | | | | |
| 1 | 171 | 3.57 | 3.05, 4.18 | 1068 | 2.90 | 2.75, 3.05 | 1.23, (1.07, 1.42) |
| 3 | 171 | 2.38 | 2.07, 2.74 | 1065 | 0.75 | 0.72, 0.79 | 3.17 (2.78, 3.62) |
| 5 | 171 | 5.52 | 4.82, 6.32 | 1068 | 2.85 | 2.72, 2.98 | 1.94 (1.71, 2.20) |
| 6A | 169 | 21.51 | 18.15, 25.51 | 1063 | 7.11 | 6.78, 7.46 | 3.03 (2.64, 3.47) |
| 7F | 170 | 6.24 | 5.49, 7.08 | 1067 | 4.39 | 4.18, 4.61 | 1.42 (1.24, 1.62) |
| 19A | 170 | 17.18 | 15.01, 19.67 | 1056 | 8.44 | 8.05, 8.86 | 2.03 (1.78, 2.32) |

Evaluator Comment: The primary analysis compares GMC between a historical post-toddler cohort (Study 3039-3005) and Group 3. Serotypes within the 7vPnC vaccine were compared to the control arm of 7vPnC as it provides a direct link to Prevenar immunogenicity. The 13vPnC serotypes were compared to the 13vPnC historical cohort. This seems unnecessarily confusing and it is not clear why the 13vPnC historical cohort was not used for all comparisons. The results suggest that the vaccine is significantly more effective in Study 6096A1-3011, with significantly higher GMCs. It is not clear why the effect of the vaccine is more pronounced in this group.

#### *6.1.1.3. Results for other immunogenicity outcomes*

The secondary outcome was the analysis of Group 4 OPA data. The objective was to demonstrate non-inferiority of the immune responses to the 13 serotypes in 13vPnC in the Group 4 cohort compared to the Group 3 cohort, as measured by OPA titres 1 month after vaccination. OPA titres for Group 4 were declared non-inferior to those for Group 3 if lower limit of the 2-sided, 95% CI for GMR was >0.5 (2-fold criterion). The criterion was met for all 7 common serotypes and for 6[8] of the additional serotypes. Serotype 3 did not fulfil the criteria (lower-limit of 95% CI = 0.48).

[8] Sponsor comment: "This should read and for 5 of the 6 additional serotypes."

**Table 6: Comparison of Pneumococcal OPA GMTs post-vaccination – *Evaluable Immunogenicity Population.* Table continued across two pages.**

| | Group 4 | | | Group 3 | | | Ratio |
|---|---|---|---|---|---|---|---|
| **Serotype** | **n** | **GMT** | **95% CI** | **n** | **GMT** | **95% CI** | |
| 7vPnC | | | | | | | |
| 4 | 188 | 6912 | 6101, 7831 | 181 | 4629 | 4017, 5334 | 1.5 (1.24, 1.80) |
| 6B | 183 | 14224 | 12316, 16427 | 178 | 14496 | 13164, 17083 | 0.9 (0.78, 1.15) |
| 9V | 186 | 4485 | 4001, 5027 | 180 | 4733 | 4203, 5328 | 0.9 (0.80, 1.12) |
| 14 | 187 | 6894 | 6028, 7884 | 176 | 4759 | 4120, 5497 | 1.4 (1.19, 1.76) |
| 18C | 182 | 6263 | 5436, 7215 | 175 | 8815 | 7738, 10041 | 0.7 (0.59, 0.86) |
| 19F | 184 | 2280 | 1949, 2668 | 178 | 1559 | 1293, 1879 | 1.5 (1.15, 1.86) |
| 23F | 187 | 3808 | 2255, 4323 | 176 | 3245 | 2819, 3736 | 1.2 (0.97, 1.42) |
| Additional | | | | | | | |
| 1 | 189 | 319 | 271, 376 | 179 | 187 | 160, 219 | 1.7 (1.35, 2.13) |
| 3 | 181 | 114 | 100, 129 | 178 | 202 | 181, 226 | 0.6 (**0.48**, 0.67) |
| 5 | 183 | 336 | 270, 418 | 178 | 491 | 426, 565 | 0.7 (0.53, 0.89) |
| 6A | 182 | 9928 | 8457, 11655 | 178 | 7514 | 6351, 8891 | 1.3 (1.05, 1.67) |
| 7F | 185 | 6584 | 5829, 7436 | 178 | 10334 | 9099, 11737 | 0.6 (0.53, 0.76) |
| 19A | 187 | 1276 | 1132, 1439 | 180 | 1180 | 1048, 1329 | 1.1 (0.91, 1.28) |

Evaluator Comment: The secondary analysis for Group 4 shows non-inferiority of 13vPnC vaccine in the ≥10 to <18 years age group compared to Group 3 (≥5 to <10

years). Given the number of tests being undertaken it is possible that some serotypes were found to be significant (non-inferior) by chance. Likewise, it is possible that serotype 3 was found to not be non-inferior, by chance. However, the trend in results suggests that overall the 13vPnC in the Group 4 age group is non-inferior to the vaccine immunogenicity in Group 3.

*6.1.1.3.1. Proportion of subjects achieving pre-specified IgG concentrations*

The proportion of subjects (that is, responders) in Group 3 who had IgG concentrations ≥0.35 µg/mL 1 month after vaccination with 13vPnC for the evaluable immunogenicity population was 100% for the 7 common serotypes, and ranged from 98.2% to 100% for the 6 additional serotypes in Group 3. Before vaccination, the percentage of subjects with IgG concentrations ≥0.35 µg/mL ranged from 54.0% to 100% (lowest for serotype 4; highest for serotype 6B) for the 7 common serotypes, and from 58.9% to 100% (lowest for serotype 1; highest for serotype 19A) for the 6 additional serotypes in Group 3. Results for the all-available immunogenicity population were similar to those observed for the evaluable immunogenicity population before and after vaccination in Group 3.

**Table 7: Group 3 Subjects Achieving Pneumococcal IgG Antibody Concentrations ≥0.35 µg/mL - *Evaluable Immunogenicity Population***

| | Group 3 (pre-vaccination) | | | Group 3 (post-vaccination) | | |
|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **%, 95% CI** | **N** | **n** | **%, 95% CI** |
| 7vPnC | | | | | | |
| 4 | 251 | 119 | 47.4 (41.1, 53.8) | 259 | 259 | 100.0 (98.6, 100.0) |
| 6B | 262 | 262 | 100.0 (98.6, 100.0) | 261 | 261 | 100.0 (98.6, 100.0) |
| 9V | 262 | 242 | 92.4 (88.5, 85.3) | 261 | 261 | 100.0 (98.6, 100.0) |
| 14 | 261 | 168 | 64.4 (58.2, 70.2) | 259 | 259 | 100.0 (98.6, 100.0) |
| 18C | 260 | 173 | 66.5 (60.4, 72.2) | 261 | 261 | 100.0 (98.6, 100.0) |
| 19F | 257 | 251 | 97.7 (95.0, 99.1) | 260 | 260 | 100.0 (98.6, 100.0) |
| 23F | 262 | 256 | 97.2 (95.1, 99.2) | 258 | 258 | 100.0 (98.6, 100.0) |
| Additional | | | | | | |
| 1 | 232 | 124 | 53.4 (46.8, 60.0) | 261 | 259 | 99.2 (97.3, 99.9) |
| 3 | 248 | 199 | 80.2 (74.7, 85.0) | 261 | 258 | 98.9 (96.7, 99.8) |
| 5 | 258 | 254 | 98.4 (96.1, 99.6) | 261 | 261 | 100.0 (98.6, 100.0) |
| 6A | 263 | 262 | 99.6 (97.9, 100.0) | 259 | 259 | 100.0 (98.6, 100.0) |

| | Group 3 (pre-vaccination) | | | Group 3 (post-vaccination) | | |
|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **%, 95% CI** | **N** | **n** | **%, 95% CI** |
| 7F | 253 | 191 | 75.5 (69.7, 80.7) | 259 | 259 | 100.0 (98.6, 100.0) |
| 19A | 261 | 261 | 100.0 (98.6, 100.0) | 260 | 260 | 100.0 (98.6, 100.0) |

n = number of subjects with an antibody concentration ≥0.35µg/mL for the given serotype.

**Table 8: Group 3 Subjects Achieving Pneumococcal IgG Antibody Concentrations ≥1.0 µg/mL - *Evaluable Immunogenicity Population***

| | Group 3 (pre-vaccination) | | | Group 3 (post-vaccination) | | |
|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **%, 95% CI** | **N** | **n** | **%, 95% CI** |
| 7vPnC | | | | | | |
| 4 | 251 | 47 | 18.7 (14.1, 24.1) | 259 | 258 | 99.6 (97.9, 100.0) |
| 6B | 262 | 251 | 95.8 (92.6, 97.9) | 261 | 261 | 100.0 (98.6, 100.0) |
| 9V | 262 | 173 | 66.0 (59.9, 71.7) | 261 | 260 | 99.6 (97.9, 100.0) |
| 14 | 261 | 85 | 32.6 (26.9, 38.6) | 259 | 259 | 100.0 (98.6, 100.0) |
| 18C | 260 | 83 | 31.9 (26.3, 38.0) | 261 | 261 | 99.2 (97.3, 100.0) |
| 19F | 257 | 222 | 86.4 (81.6, 90.3) | 260 | 260 | 100.0 (98.6, 100.0) |
| 23F | 262 | 204 | 77.9 (72.3, 82.7) | 258 | 258 | 100.0 (98.6, 100.0) |
| Additional | | | | | | |
| 1 | 232 | 78 | 33.6 (27.6, 40.1) | 261 | 239 | 91.6 (87.5, 94.6) |
| 3 | 248 | 145 | 58.5 (52.1, 64.7) | 261 | 210 | 80.5 (75.1, 85.1) |
| 5 | 258 | 227 | 88.0 (83.4, 91.7) | 261 | 253 | 96.9 (94.1, 98.7) |
| 6A | 263 | 249 | 94.7 (91.2, 97.1) | 259 | 259 | 100.0 (98.6, 100.0) |
| 7F | 253 | 132 | 52.2 (45.8, 58.5) | 259 | 255 | 98.5 (96.1, 99.6) |
| 19A | 261 | 255 | 97.7 (95.1, 99.2) | 260 | 260 | 100.0 (98.6, 100.0) |

n = number of subjects with an antibody concentration ≥1.0µg/mL for the given serotype.

Evaluator Comment: Most subjects seem to have already acquired immunity from serotypes 5, 6A and 19A pre-vaccination. The ability of the study to show immunogenicity for these serotypes is therefore limited.

**Table 9: Group 4 Subjects Achieving Pneumococcal IgG Antibody Concentrations ≥0.35 µg/mL**

| | Group 4 (pre-vaccination) | | | Group 4 (post-vaccination) | | |
|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **%, 95% CI** | **N** | **n** | **%, 95% CI** |
| 7vPnC | | | | | | |
| 4 | 250 | 108 | 43.2 (37.0, 49.6) | 285 | 284 | 99.6 (98.1, 100.0) |
| 6B | 276 | 270 | 97.8 (95.3, 99.2) | 283 | 283 | 100.0 (98.7, 100.0) |
| 9V | 275 | 245 | 89.1 (84.8, 92.5) | 284 | 283 | 99.6 (98.1, 100.0) |
| 14 | 272 | 153 | 56.3 (50.1, 62.2) | 284 | 281 | 98.9 (96.9, 99.8) |
| 18C | 276 | 181 | 65.6 (59.6, 71.2) | 281 | 278 | 98.9 (96.9, 99.8) |
| 19F | 260 | 233 | 89.6 (85.3, 93.0) | 281 | 281 | 100.0 (98.7, 100.0) |
| 23F | 275 | 243 | 88.4 (94.0, 91.9) | 280 | 279 | 99.6 (98.0, 100.0) |
| Additional | | | | | | |
| 1 | 257 | 182 | 70.8 (64.8, 76.3) | 284 | 282 | 99.3 (97.5, 99.9) |
| 3 | 269 | 222 | 82.5 (77.5, 86.9) | 283 | 283 | 97.2 (94.5, 98.8) |
| 5 | 277 | 274 | 98.9 (96.9, 99.8) | 284 | 284 | 100.0 (98.7, 100.0) |
| 6A | 274 | 271 | 98.9 (96.8, 99.8) | 284 | 284 | 100.0 (98.7, 100.0) |
| 7F | 271 | 218 | 80.4 (75.2, 85.0) | 284 | 284 | 100.0 (98.7, 100.0) |
| 19A | 279 | 278 | 99.6 (98.0, 100.0) | 284 | 284 | 100.0 (98.7, 100.0) |

n = number of subjects with an antibody concentration ≥0.35µg/mL for the given serotype.

**Table 10: Group 4 Subjects Achieving Pneumococcal IgG Antibody Concentrations ≥1.0µg/mL**

| | Group 4 (pre-vaccination) | | | Group 4 (post-vaccination) | | |
|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **%, 95% CI** | **N** | **n** | **%, 95% CI** |
| 7vPnC | | | | | | |
| 4 | 250 | 58 | 23.2 (18.1, 28.9) | 285 | 260 | 91.2 (87.3, 94.2) |
| 6B | 276 | 243 | 88.0 (83.6, 91.6) | 283 | 283 | 100.0 (98.7, 100.0) |
| 9V | 275 | 181 | 65.8 (59.9, 71.4) | 284 | 273 | 96.1 (93.2, 98.1) |
| 14 | 272 | 92 | 33.8 (28.2, 39.8) | 284 | 267 | 94.0 (90.6, 96.5) |

| | Group 4 (pre-vaccination) | | | Group 4 (post-vaccination) | | |
|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **%, 95% CI** | **N** | **n** | **%, 95% CI** |
| 18C | 276 | 103 | 37.3 (31.6, 43.3) | 281 | 262 | 93.2 (89.6, 95.9) |
| 19F | 260 | 167 | 64.2 (58.1, 70.1) | 281 | 280 | 99.6 (98.0, 100.0) |
| 23F | 275 | 193 | 70.2 (64.4, 75.5) | 280 | 271 | 96.8 (94.0, 98.5) |
| Additional | | | | | | |
| 1 | 257 | 110 | 42.8 (36.7, 49.1) | 284 | 272 | 95.8 (92.7, 97.8) |
| 3 | 269 | 145 | 53.9 (47.7, 60.0) | 283 | 219 | 77.4 (72.1, 82.1) |
| 5 | 277 | 245 | 88.4 (84.1, 92.0) | 284 | 278 | 97.9 (95.5, 99.2) |
| 6A | 274 | 255 | 93.1 (89.4, 95.8) | 284 | 284 | 100.0 (98.7, 100.0) |
| 7F | 271 | 140 | 51.7 (45.5, 57.7) | 284 | 278 | 97.9 (95.5, 99.2) |
| 19A | 279 | 267 | 95.7 (92.6, 97.8) | 284 | 283 | 99.6 (98.1, 100.0) |

Evaluator Comment: Most subjects seem to have already acquired immunity to most of the serotypes present in the 13vPnC vaccine with at least 40% of subjects having antibody concentrations ≥ 1.0µg/mL prior to vaccination. Serotypes 5, 6A and 19A had antibody concentrations ≥ 1.0µg/mL in over 85% of the study population pre-vaccine. The ability of the study to show immunogenicity for these serotypes is therefore limited.

*6.1.1.3.2. IgG Reverse Cumulative Distribution Curves (RCDCs)*

RCDCs were generated for IgG concentrations for each of the 13 serotypes. RCDCs for post-vaccination IgG antibody concentrations were displayed on the same plot for the Group 3 exploratory cohort and the Group 3 confirmatory cohort in this study, along with data from study 6096A1-3005. With the exception of serotypes 1 and 7F, the curves for the Group 3 exploratory and confirmatory cohorts were higher, generally throughout the range of IgG concentrations, than the curves for study 6096A1-3005. For serotypes 1 and 7F, the curves for the Group 3 cohorts were similar to the curve for study 6096A1-3005. RCDCs were also plotted with both pre and post vaccination IgG concentrations for Group 3, Group 3 exploratory cohort, and Group 3 confirmatory cohort. The curves show an increase in each of the serotype-specific IgG concentrations after the study vaccine was administered.

Evaluator Comment: Results are exploratory only and do not form part of the evaluation for the extension of age indication.

## 6.2. Nasopharyngeal carriage

### 6.2.1. Pivotal efficacy studies

#### *6.2.1.1. Study 6096A1-3006*

##### *6.2.1.1.1. Study design, objectives, locations and dates*

This was a Phase III, randomised, active-controlled, double-blind, multi-site study in healthy infants. The study was designed as a parallel-group study in which subjects were randomly assigned to 2 groups in a 1:1 ratio to receive either 13cPnC or 7vPnC.

The study was conducted in Israel from 11 February 2008 through 8 August 2011.

##### *6.2.1.1.2. The primary objective was:*

To demonstrate that 13vPnC reduces newly identified nasopharyngeal **acquisition** of *S. pneumoniae* serotypes 6A and 19A combined compared with 7vPnC from 1 month after the infant series to 24 months of age.[9]

##### *6.2.1.1.3. Secondary objectives:*

To assess whether 13vPnC reduces the **prevalence** of nasopharyngeal colonisation with *S. pneumoniae* serotypes 6A and 19A as a group compared with 7vPnC at 18 months of age.

To assess whether 13vPnC reduces the **prevalence** of nasopharyngeal colonisation with *S. pneumoniae* serotypes 6A and 19A as a group compared with 7vPnC from 1 month after the infant series to 24 months of age.[10]

Evaluator Comment: In addition to the primary and secondary objectives, this study included numerous exploratory outcomes which have not been assessed as part of this evaluation.

##### *6.2.1.1.4. Inclusion and exclusion criteria*

Inclusion criteria

Subjects were required to meet all of the following inclusion criteria:

- Aged 2 months (42-98 days) at time of enrolment;
- Available for entire study period and whose parent/legal guardian could be reached by telephone;
- Healthy infant as determined by medical history, physical examination and judgement of the investigator;
- Parent/legal guardian had to be able to complete all relevant study procedures during study participation.

Exclusion criteria

Subjects were excluded if any of the following criteria were met:

- Previous vaccination with licensed or investigational pneumococcal vaccine;
- A previous anaphylactic reaction to any vaccine or vaccine-related component;
- Contraindication to vaccination with a pneumococcal conjugate vaccine;

[9] Serotype 6A' (serotypes 6A and 6C combined) was evaluated instead of 6A. Serotype 6A has been recently recognised to include both 6A and the immunologically similar 6C. Nasopharyngeal acquisition of serotypes 6A' and 19A combined meant acquisition of either 6A' OR 19A.
[10] The prevalence of nasopharyngeal colonisation with serotypes 6A' and 19A as a group meant prevalence of either 6A' or 19A.

- Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection;
- Known or suspected immune deficiency or suppression including treatment with systemic steroids, anti-metabolites, chemotherapy and immunomodulatory agents;
- History of culture proven invasive disease caused by *S. pneumoniae*;
- Major known congenital malformation or serious chronic disorders;
- Significant neurologic disorder including congenital neurological disease in siblings of the subject or history of seizure including febrile seizure, or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorder. Does not include resolving syndromes due to birth trauma such as Erb palsy;
- Receipt of blood products or gamma-globulin (including hepatitis B immunoglobulin and monoclonal antibodies, for example Synagis);
- Participation in another investigational or interventional trial. Participation in purely observational studies was acceptable;
- Infant who was a direct descendant (child or grandchild) or a member of the study site personnel.

*6.2.1.1.5. Temporary delaying vaccine administration*

The following conditions were temporary or self-limiting and a subject could be vaccinated once the condition(s) had been resolved and no other exclusion criteria were met:

- Current febrile illness (axillary temperature greater than or equal to 38.0), or other acute illness within 48 hours before study vaccine administration;
- Subject received any live vaccine within the previous 28 days (with the exception of enterally administered vaccines, which were allowed at any time). Loves vaccines administered by the parenteral route could be given on the same day as the study vaccine;
- Subject was less than 3 days into a course of antibiotic therapy (excluding topical antibiotics) for other acute illness.

Evaluator Comment: Inclusion and Exclusion criteria are appropriate.

*6.2.1.1.6. Study treatments*

Subjects were assigned to receive either 13vPnC or 7vPnC for all doses. Four doses of study vaccine 13vPnC or 7vPnC were to be administered at approximately 2, 4 and 6 months of age (infant series) and 12 months of age (toddler dose).

Each subject was to receive 1 dose (0.5 mL) of either 13vPnC or 7vPC at each of the 4 vaccination visits. All study vaccines were to be administered only by the investigator or medically qualified member of the investigator's staff.

According to the national paediatric schedule subjects also received HBV at 0, 1, 6 and 7 months, DTaP-IPV-PRP-T at 2, 4, 6 and 12 months, MMR at 12 months and HAV at 18, 24 months.

*6.2.1.1.7. Efficacy variables and outcomes*

The main comparison was the nasopharyngeal culture findings in subjects receiving 13vPnC relative to the culture findings in subjects receiving 7vPnC. New acquisitions over time and prevalence of carriage at pre-specified time points were also evaluated.

The efficacy variables were:

- Nasopharyngeal swabs cultured for *S. pneumoniae* isolates were collected at 2, 4, 6, 7, 12, 13, 18 and 24 months and serotyped and tested for antimicrobial sensitivity;

- Semi-quantitative analysis of *S. pneumoniae* growth on the nasopharyngeal swabs;
- Blood samples were collected at 7 months and 13 months and serum concentration of serotype-specific polysaccharide IgG binding antibodies using ELISA for the 13 pneumococcal serotypes contained in the 13vPnC were measured;
- Functional antibody titres for the 13 pneumococcal serotypes contained in the 13vPnC using OPA assays using the serum.

Evaluator Comment: In addition to the main efficacy variables, several 'epidemiology' variables were collected including childcare attendance, breastfeeding, socioeconomic characteristics. It is not clear how these variables were used in the main efficacy analysis.

*6.2.1.1.8. Randomisation and blinding methods*

Subjects were prospectively, randomly assigned (1:1 ratio) to receive either 13vPnC infant series/ toddler dose OR 7vPnC infant series/toddler dose based on a randomised schedule prepared by the sponsor.

Allocation of subjects to treatment groups was performed through a manual randomisation system. Randomisation envelopes were used in sequential order at each enrolling site to assign the subject's randomisation number and a treatment letter.

This was a double blind study. The database was to remain blinded until all data had been received for all subjects and all data queries had been resolved. The laboratory staff where the cultures, serotyping and antibiotic sensitivity assays were conducted, were blinded to treatment codes, as were the sponsor staff that performed the serum immunoglobulin G (IgG) and opsonophagocytic activity (OPA) assays.

*6.2.1.1.9. Analysis populations*

For nasopharyngeal culture analyses, 2 analysis populations were defined; evaluable and all-available. The evaluable culture population was the primary analysis population.

*6.2.1.1.10. Evaluable culture population*

The evaluable culture population included all subjects who:

- were eligible for the study
- were randomised
- were 41-99 days of age, inclusive, on the day of first vaccination
- received the vaccine to which they were randomised at all doses (when vaccinated)
- had at least 1 valid nasopharyngeal swab for the proposed analysis
- received no prohibited vaccines
- had no other protocol violations as determined by the medical monitor

*6.2.1.1.11. All-available culture population*

The all-available culture population included all subjects who had at least one valid nasopharyngeal swab result related to a proposed analysis

*6.2.1.1.12. Sample size*

Approximately 1,864 subjects were planned to achieve 820 evaluable subjects per group. This planned enrolment was divided between the 2 cohorts as follows:

- Cohort 1 (subjects enrolled with the first set of treatment codes: Up to approximately 700 subjects (350 subjects per group);

- Cohort 2 (subjects enrolled with the second set of treatment codes: up to approximately 1164 subjects (582 subjects per group).

A total of 3, 624 subjects were recruited into the study. 1,863 subjects received the 3-dose infant series (n=930 13vPnC, n=933 7vPnC) and 1,761 subjects received the toddler series (n=833 13vPnC, n=878 7vPnC).

Evaluator Comment: No power calculations were included in the sample size analysis; however, the sample size appears large enough to detect a result.

*6.2.1.1.13. Statistical methods*

For nasopharyngeal cultures, a newly identified acquisition was defined based upon observation of a positive culture during the observation visits if one was not positive at baseline. There were two definitions of baseline applied:

- As per the statistical analysis plan (SAP), baseline was defined as before AND during the infant immunisation series (that is, visits 1-3 corresponding to 2-6 months of age). The observation period consisted of all visits thereafter (7 to 24 months of age).
- Ad-hoc baseline was defined as the post-infant series visit (that is, visit 4 at 7 months of age). This baseline definition corresponds to findings on population-protection for pneumococcal conjugate vaccines. The observation period for this new acquisition analysis consisted of all visits thereafter (that is, visits 5 to8 corresponding to 12 to 24 months of age).

Prevalence of carriage for a serotype at any given visit was defined as the proportion of positive findings relative to the total number of non-missing findings. Prevalence of carriage for a combination of serotypes at any given visit was defined as the proportion of positive combinations relative to the total number of non-missing combinations.

The primary endpoint was the proportion of subjects with a new acquisition for either serotype 6A + 6C (hereafter denoted 6A') **and/or** 19A (serotype 6A' or 19 combined) from 1 month after the infant series to 24 months of age. Statistically significantly lower differences between vaccine groups were demonstrated if the upper bound of the 2-sided 95% CI if the rate ratio was < 1.

Secondary endpoints were the proportion of cultures testing positive (prevalence of carriage) for serotypes 6A' **or** 19A as a group, measured at each interval from 1 month after the infant series to 24 months of age (at 7, 12, 13, 18 and 24 months of age).

There were a number of exploratory endpoints for nasopharyngeal cultures that related to the acquisition of serotypes contained in 13vPnC, tested at different age points.

Exploratory endpoints included:

- Testing for nasopharyngeal carriage (positive cultures) measured at 7, 12, 13, 18 and 24 months of age for a range of *S. pneumoniae* serotype combinations;
- Correlation between nasopharyngeal acquisition for *S. pneumoniae* serotypes with post-infant IgG;
- Comparison of immune response between 13vPnC and 7vPnC as measured by IgG concentration.

*6.2.1.1.14. Participant flow*

**Table 11: Study Flowchart**

| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Visit ID | 2-Month Visit | 4-Month Visit | 6-Month Visit | 7-Month Visit | 12-Month Visit | 13-Month Visit | 18-Month Visit | 24-Month Visit |
| Study Interval | Vaccination 1 | Vaccination 2 | Vaccination 3 | Postinfant Series | Vaccination 4 | Posttoddler Series | 18 Month Visit | 24 Month Visit |
| Visit Window | 42 to 98 Days of Age | 42 to 75 Days After Visit 1 | 42 to 75 Days After Visit 2 | 28 to 70 Days After Visit 3, | 365 to 425 Days of Age | 28 to 56 Days After Visit 5 | 17 to 19 Months of Age | 23 to 25 Months of Age |
| Informed consent | X | | | | | | | |
| Review inclusion/exclusion criteria | X | | | | | | | |
| Medical history and physical examination | X | | | | | | | |
| Clinical evaluation to confirm eligibility, collect epidemiology data and report AEs as appropriate. | X | X | X | X | X | X | X | X |
| Randomization | X | | | | | | | |
| Axillary temperature | X | X | X | | X | | | |
| Collect nasopharyngeal swab | X | X | X | X | X | X | X | X |
| 13vPnC or 7vPnC administration and 30 minute observation | X | X | X | | X | | | |
| Collect blood sample | | | | X | | X | | |

*6.2.1.1.15. Major protocol violations/deviations*

There were no major protocol violations/deviations.

*6.2.1.1.16. Baseline data*

The majority of the randomised subjects met the criterion for inclusion in the all-available culture population in the 13vPnC (930, 99.8%) and 7vPnC (934, 100%) vaccine group. Two subjects (0.1%) in the trial were excluded from the all-available culture population, each for no nasopharyngeal culture results at any visit. The majority of randomised subjects also met the criteria for inclusion in the evaluable culture population in the 13vPnC (881, 94.5%) and 7vPnC (873, 93.5%) vaccine groups. 112 subjects (6.0%) were excluded from the evaluable culture population. The most frequent reason for exclusion from the evaluable culture population was that the subject did not receive all the pneumococcal study vaccinations (103 subjects, 5.5%).

The two vaccine groups were similar with respect to demographic characteristics in the evaluable culture population. Epidemiological data (child care, breastfeeding, siblings, smoking history) was assessed through regression models with independent variables for treatment group (13vPnC versus 7vPnC) and found that there were no significant differences between cohorts.

**Table 12: Study Demographic Characteristics**

| | Vaccine Group (as Randomized) | | | | | |
|---|---|---|---|---|---|---|
| | 13vPnC N=932 | | 7vPnC N=934 | | Total N=1866 | |
| | n | % | n | % | n | % |
| Sex | | | | | | |
| Female | 474 | 50.9 | 471 | 50.4 | 945 | 50.6 |
| Male | 458 | 49.1 | 463 | 49.6 | 921 | 49.4 |
| Race | | | | | | |
| White | 905 | 97.1 | 909 | 97.3 | 1814 | 97.2 |
| Black or African American | 27 | 2.9 | 24 | 2.6 | 51 | 2.7 |
| Asian | 0 | 0.0 | 1 | 0.1 | 1 | 0.1 |
| Ethnicity | | | | | | |
| Jewish | 611 | 65.6 | 610 | 65.3 | 1221 | 65.4 |
| Bedouin | 318 | 34.1 | 322 | 34.5 | 640 | 34.3 |
| Other | 3 | 0.3 | 2 | 0.2 | 5 | 0.3 |
| Gestational age (months) | | | | | | |
| n | 931 | | 934 | | 1865 | |
| Mean (SD) | 9.0 (0.4) | | 9.0 (0.4) | | 9.0 (0.4) | |
| Median | 9.0 | | 9.0 | | 9.0 | |
| Min, max | 6.7, 9.7 | | 6.7, 9.7 | | 6.7, 9.7 | |
| Age at enrollment (months) | | | | | | |
| Mean (SD) | 2.2 (0.3) | | 2.2 (0.3) | | 2.2 (0.3) | |
| Median | 2.1 | | 2.1 | | 2.1 | |
| Min, max | 1.4, 3.2 | | 1.4, 3.2 | | 1.4, 3.2 | |
| Weight at enrollment (kg) | | | | | | |
| n | 930 | | 934 | | 1864 | |
| Mean (SD) | 5.2 (0.7) | | 5.2 (0.7) | | 5.2 (0.7) | |
| Median | 5.1 | | 5.2 | | 5.2 | |
| Min, max | 2.8, 7.4 | | 2.6, 7.7 | | 2.6, 7.7 | |
| Head circumference at enrollment (cm) | | | | | | |
| n | 931 | | 932 | | 1863 | |
| Mean (SD) | 38.7 (1.3) | | 38.8 (1.4) | | 38.7 (1.4) | |
| Median | 38.8 | | 39.0 | | 39.0 | |
| Min, max | 32.0, 42.0 | | 31.0, 42.5 | | 31.0, 42.5 | |

Note: The data are combined across the cohorts.

#### *6.2.1.2. Results for the primary immunogenicity outcome*

Results of the primary analysis showed that the proportion of subjects with newly identified nasopharyngeal (NP) acquisitions of *S. pneumoniae* serotypes 6A' (serotypes 6A + 6C) and/or 19A was statistically significantly lower in the 13vPnC group (20.0%) than in the 7vPnC group (36.0%) from 1 month after the infant series to 24 months of age.

**Table 13: Comparison of Subjects with a New Acquisition by Serotype or Combination Measured 1 Month After the Infant Series to 24 Months of Age: Evaluable Culture Population**

| | 13vPnC | | | | 7vPnC | | | |
|---|---|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **% (95% CI)** | | **N** | **n** | **% (95% CI)** | **Rate Ratio** |
| 6A' or 19A | 881 | 176 | 20.0 (17.4, 22.8) | | 873 | 314 | 36.0 (32.8, 39.3) | 0.56 (0.47, 0.65) |

N = number of subjects with at least 1 determinate nasopharyngeal culture result n = number of subjects with at least 1 new acquisition of any of the given serotypes or combinations

#### *6.2.1.3. Results for other immunogenicity outcomes*

The proportion of subjects with new acquisition of single serotypes 1, 6A', 6A, 6C, 7F, and 19A was significantly lower in the 13vPnC group than in the 7vPnC group. For serotype 3, no difference was observed in the proportion with NP acquisition in 13vPnC and 7vPnC recipients. Assessment of colonisation by serotype 5 was not possible because of insufficient events.

**Table 14: Comparison of Subjects with a New Acquisition by Serotype or Combination Measured 1 Month After the Infant Series to 24 Months of Age: Evaluable Culture Population. Continued across two pages.**

| | 13vPnC | | | 7vPnC | | | |
|---|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **% (95% CI)** | **N** | **n** | **% (95% CI)** | **Rate Ratio** |
| 7vPnC | | | | | | | |
| 4 | 872 | 4 | 0.5 (0.1, 1.2) | 864 | 5 | 0.6 (0.2, 1.3) | 0.79 (0.18, 3.29) |
| 6B | 821 | 43 | 5.4 (3.9, 7.2) | 804 | 60 | 7.5 (5.7, 9.5) | 0.72 (0.49, 1.05) |
| 9V | 589 | 17 | 2.0 (1.2, 3.1) | 862 | 17 | 2.0 (1.2, 3.1) | 1.00 (0.49, 1.05) |
| 14 | 842 | 50 | 5.9 (4.4, 7.8) | 841 | 37 | 4.4 (3.1, 6.0) | 1.35 (0.89, 2.07) |
| 18C | 869 | 15 | 1.7 (1.0, 2.8) | 583 | 15 | 1.8 (1.0, 2.9) | 0.98 (0.47, 2.06) |
| 19F | 833 | 66 | 7.9 (6.2, 10.0) | 831 | 101 | 12.2 (10.0, 14.6) | 0.65 (0.48, 1.39) |
| 23F | 843 | 37 | 4.4 (3.1, 6.0) | 824 | 26 | 3.2 (2.1, 4.6) | 1.39 (0.85, 2.31) |

**Table 15: Comparison of Subjects with a New Acquisition by Serotype or Combination Measured 1 Month After the Infant Series to 24 Months of Age: Evaluable Culture Population. Continued.**

| | 13vPnC | | | 7vPnC | | | |
|---|---|---|---|---|---|---|---|
| **Serotype** | **N** | **n** | **% (95% CI)** | **N** | **n** | **% (95% CI)** | **Rate Ratio** |
| Additional | | | | | | | |
| 1 | 880 | 0 | 0.0 (0.0, 0.4) | 872 | 8 | 0.9 (0.4, 1.8) | 0.00 (NE, 0.44) |
| 3 | 871 | 16 | 1.8 (1.1, 3.0) | 863 | 16 | 1.9 (1.1, 3.0 | 0.99 (0.48, 2.06) |
| 5 | 880 | 1 | 0.1 (0.0, 0.6) | 872 | 2 | 0.2 (0.0, 0.8) | 0.50 (0.02, 5.54) |
| 6A | 821 | 63 | 7.7 (5.9, 9.7) | 806 | 106 | 13.2 (10.9, 15.7) | 0.58 (0.43, 0.78) |
| 6C | 867 | 23 | 2.7 (1.7, 4.0) | 855 | 51 | 6.0 (4.5, 7.8) | 0.44 (0.27, 0.71) |
| 7F | 879 | 3 | 0.3 (0.1, 1.0) | 869 | 11 | 1.3 (0.6, 2.3) | 0.27 (0.04, 0.90) |
| 19A | 832 | 105 | 12.6 (10.4, 5.1) | 830 | 190 | 22.9 (20.1, 25.9) | 0.55 (0.44, 0.68) |
| | | | | | | | |
| 6A’ | 876 | 79 | 9.0 (7.2, 11.1) | 873 | 151 | 17.3 (14.8, 20.0) | 0.52 (0.40, 0.67) |
| Vaccine sero. | 881 | 360 | 40.9 (37.6, 44.2) | 873 | 499 | 57.2 (53.8, 60.5) | 0.71 (0.65, 0.79) |
| Non-vaccine | 881 | 665 | 75.5 (72.5, 78.3) | 873 | 609 | 69.8 (66.6, 72.8) | 1.08 (1.02, 1.15) |

N = number of subjects with at least 1 determinate nasopharyngeal culture result
n = number of subjects with at least 1 new acquisition of any of the given serotypes or combinations

Evaluator Comment: Results are consistent with what would be expected based on vaccine effects; there was no real difference found in new acquisition of serotypes present in the 7vPnC vaccine but a statistically significant difference found in the new acquisition of serotypes present in the 13vPnC vaccine. Low absolute numbers detected in serotypes 1, 5 and 7F and broad confidence intervals make interpreting the clinical significance of results, particularly in these serotypes difficult. No difference was detected in the acquisition of non-vaccine serotypes between groups (RR 1.08 (1.02, 1.15)); this is a reassuring result suggesting that non-vaccine serotypes do not necessarily

replace vaccine serotypes in nasopharyngeal carriage (although this statement is highly speculative).

All other results related to new nasopharyngeal acquisition were exploratory only and have not been included in this report as they are not considered to be relevant to the decision-making process.

*6.2.1.3.1. Nasopharyngeal prevalence (secondary immunogenicity outcome)*

Comparisons of the prevalence of 6A' or 19A between 13vPnC and 7vPnCat at 7, 12, 13, 18 and 24 months of age demonstrated significantly lower prevalence (upper limit of 95% CI of the odds ratio was less than 1) compared with the 7vPnC vaccine group at 7, 12, 13, 18 and 24 months of age. These results were also observed for the all-available culture population.

**Table 16: Comparison of Prevalence of *S. pneumoniae* Positive Nasopharyngeal Culture Measured at 7 months of Age – *Evaluable Culture Population.***

| | 13vPnC (N = 855) | | 7vPnC (N = 856) | | |
|---|---|---|---|---|---|
| **Serotype** | **n** | **% (95% CI)** | **n** | **% (95% CI)** | **Odds Ratio** |
| 6A' or 19A | 64 | 7.3 (5.6, 9.2) | 95 | 10.9 (8.9, 13.2) | 0.6 (0.5, 0.9) |
| 7vPnC | | | | | |
| 4 | 2 | 0.2 (0.0, 0.8) | 2 | 0.2 (0.0, 0.8) | 1.0 (0.1, 7.0) |
| 6B | 48 | 5.4 (4.0, 7.2) | 39 | 4.5 (3.2, 6.1) | 1.2 (0.8, 1.9) |
| 9V | 4 | 0.5 (0.1, 1.2) | 4 | 0.5 (0.1, 1.2) | 1.0 (0.2, 4.0) |
| 14 | 13 | 1.5 (0.8, 2.5) | 12 | 1.4 (0.7, 2.4) | 1.1 (0.5, 2.4) |
| 18C | 4 | 0.5 (0.1, 1.2) | 9 | 1.0 (0.5, 2.0) | 0.4 (0.1, 1.4) |
| 19F | 24 | 2.7 (1.8, 4.0) | 27 | 3.1 (2.1, 4.5) | 0.9 (0.5, 1.5) |
| 23F | 14 | 1.6 (0.9, 2.7) | 22 | 2.5 (1.6, 3.8) | 0.6 (0.3, 1.2) |
| Additional | | | | | |
| 1 | 0 | 0.0 (0.0, 0.4) | 1 | 0.1 (0.0, 0.6) | 0.0 (0.0, ∞) |
| 3 | 6 | 0.7 (0.3, 1.5) | 2 | 0.2 (0.0, 0.8) | 3.0 (0.6, 14.8) |
| 5 | 0 | 0.0 (0.0, 0.4) | 0 | 0.0 (0.0, 0.4) | NE (NE) |
| 6A | 30 | 3.4 (2.3, 4.8) | 49 | 5.6 (4.2, 7.4) | 0.6 (0.4, 0.9) |
| 6C | 7 | 0.8 (0.3, 1.6) | 8 | 0.9 (0.4, 1.8) | 0.9 (0.3, 2.4) |
| 7F | 0 | 0.0 (0.0. 0.4) | 2 | 0.2 (0.0, 0.8) | 0.0 (0.0, ∞) |
| 19A | 27 | 3.1 (2.0, 4.4) | 38 | 4.4 (3.1, 5.9) | 0.7 (0.4, 1.1) |

| | 13vPnC (N = 855) | | 7vPnC (N = 856) | | |
|---|---|---|---|---|---|
| **Serotype** | **n** | **% (95% CI)** | **n** | **% (95% CI)** | **Odds Ratio** |
| 6A' | 37 | 4.2 (3.0, 5.7) | 57 | 6.5 (5.0, 8.4) | 0.6 (0.4, 1.0) |
| Vaccine sero. | 178 | 20.2 (17.6, 23.0) | 212 | 24.3 (21.5, 27.3) | 0.8 (0.6, 1.0) |
| Non-vaccine | 228 | 25.9 (23.0, 28.9) | 239 | 27.4 (24.5, 30.5) | 0.9 (0.7, 1.1) |

N = number of subjects with at least 1 determine nasopharyngeal culture result for any of the given serotypes or combinations
n= number of subjects with at least 1 *S. pneumoniae*-positive culture for any of the given serotypes or combinations

Evaluator Comment: For simplicity, the 7 month data is the only data presented however, figures at 12, 13, 18 and 24 months followed similar trends. Prevalence of *S. pneumoniae*-positive swabs fluctuated over the 18 month period, although trends stayed consistent. The results are equivocal; there was no difference observed for any serotype contained in both the 7vPnC and the 13vPnC. Absolute numbers for the additional 13vPnC were small in both groups making interpretation of odds ratios difficult. The combined analysis for serotypes "6A' or 19" showed a statistically significant result with the upper limit of the 95% confidence interval being less than 1 (upper confidence interval of 0.9 for 7, 12, 13, 18 and 24 months being 0.9). However, limitations of the study, possibilities for the introduction of bias and low and fluctuating absolute numbers make interpreting this (secondary outcome) analysis difficult.

### 6.2.2. Study 6096A1-3010

#### *6.2.2.1. Study design, objectives, locations and dates*

This was a Phase III, multicentre, open-label study to evaluate the immunogenicity and safety of 13vPnC and the impact of 13vPnC on the incidence of IPD and NP colonisation in healthy Alaskan native children in the YK Delta region of Alaska.

The study was conducted at 1 main and 23 satellite sites (remote village clinics) in the state of Alaska by obtaining IPD data from existing IPD surveillance systems and NP colonisation data from an ongoing NP colonisation study (Alaska Area 2008-09-029) that began in February 2008 in Alaska.

The primary objective of this study was:

- To assess the impact of 13vPnC on the incidence of IPD in the YK Delta region due to the 13 vaccine *S. pneumoniae* serotypes.

The secondary objectives of this study were:

- To assess the overall impact of 13vPnC on the incidence of IPD in the YK Delta region due to any *S. pneumoniae* serotypes
- To assess the impact of 13vPnC on the incidence of IPD due to *S. pneumoniae* serotypes 1, 3, 5, 6A, 7F and 19A in the YK Delta region
- To assess the impact of 13vPnC on the incidence of IPD due to *S. pneumoniae* serotype 19A in the YK Delta region

- To assess the impact of 13vPnC on the incidence of IPD due to non-vaccine *S. pneumoniae* serotypes in the YK Delta region
- To assess the impact of 13vPnC on NP colonisation in the YK Delta region
- To assess the pneumococcal immune responses induced by 13vPnC when measured 1 month after the infant series (Groups 1, 2 and 3)
- To assess the pneumococcal immune responses induced by 13vPnC when measured 1 month after the toddler dose (Groups 1, 2 and 3)
- To assess the pneumococcal immune responses induced by 13vPnC in children aged ≥12 months who transitions from Prevenar (7vPnC) to 13vPnC 1 month after completion of the relevant catch-up dose(s)

Exploratory objectives were:

- To assess the level of OPA produced by the 13vPnC serotypes
- To assess the pneumococcal immune responses induced by 13vPnC at alternate levels
- To assess the correlation of OPA and enzyme-linked immunosorbent assay (ELISA) values for each of the 13vPnC serotypes

*6.2.2.1.1. Inclusion and exclusion criteria*

Subjects were enrolled in the study if they satisfied all of the following inclusion criteria:

- Male or female subjects aged ≥42 days (6 weeks) through <5 years at the time of enrolment;
- Available for the entire study period and the parents(s)/legal guardian(s) could be reached by telephone;
- Healthy child as determined by medical history, physical examination, and judgement of the investigator or a medically qualified designee;
- Parent(s)/legal guardian(s) able to complete all relevant study procedures during study participation.

Subjects were excluded from study participation if they met ANY of the following criteria:

- Previous anaphylactic reaction to any vaccine or vaccine-related component;
- Contraindication to vaccination with pneumococcal vaccine;
- Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection;
- Major known congenital malformation;
- Significant neurological disorder or significant evolving disorders (such as encephalopathy, hydrocephalus), a history of seizures (including uncontrolled epilepsy/infantile) or other significant disorders. Does not include resolving birth trauma;
- Participation in another investigational or interventional trial.

Inclusion criteria for Immunogenicity Study Participants included:

- Parent(s)/legal guardian(s) willing to complete a supplemental informed consent form permitting blood to be taken from the subject;
- Subject has to reside in the Bethel, Alaska area.

Exclusion criteria for Immunogenicity Study Participants:

- Receipt of blood products or gamma globulin within the last 3 months;

- Known or suspected immune deficiency or suppression.

*6.2.2.1.2. Study treatments*

Subjects received 1 dose (0.5 mL) of 13vPnC at each of the vaccination visits according to the protocol-defined study groups based on age and prior vaccination history:

- Group 1: (6 weeks to <10 months) received 4 doses (3 infant series, 1 toddler dose) with no prior 7vPnC exposure;
- Group 2: (<12 months) received 3 doses (2 infant series, 1 toddler dose) and 1 prior dose of 7vPnC;
- Group 3: (<12 months) received 2 doses (1 does infant series, 1 toddler dose) and had 2 prior doses of 7vPnC;
- Group 4: (>12 months to 2 years) 2 doses (up to 60 days apart) and up to 4 prior doses of 7vPnC;
- Group 5: (2 to 5 years) 1 dose with up to 4 prior doses of 7vPnC.

Concomitant Vaccines were given according to the national paediatric schedule and were not stipulated by protocol.

*6.2.2.1.3. Efficacy variables and outcomes*

The main efficacy variables were:

- Cases of IPD due to any pneumococcal serotype contained in the 13vPnC measured through the CDC surveillance network;
- Pneumococcal vaccination rates measured via CDC;
- Microbial resistance of IPD cases measured by CDC;
- Nasopharyngeal carriage (serotype).

Other efficacy outcomes included:

Participation in the immunogenicity portion of the study was optional. Efficacy variables collected for this portion of the study included:

- Serum concentrations of anticapsular IgG for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) expressed as μg/mL measured via blood samples taken one month after vaccination;
- Functional antibody activity measure using an OPA assay for each of the 13 pneumococcal serotypes.

*6.2.2.1.4. Randomisation and blinding methods*

This was an open-label study and all eligible subjects received 13vPnC according to protocol-defined study groups based on age and prior vaccination history at enrolment.

There was no randomisation or blinding.

*6.2.2.1.5. Analysis populations*

Surveillance data from the YK delta were used for the IPD and NP carriage analysis.

Immunogenicity analyses were conducted for the evaluable immunogenicity population and the all-available immunogenicity population. The evaluable immunogenicity population included all subjects who met the inclusion criteria and had the required number of blood draws for the analysis. The all-available immunogenicity population had at least 1 valid and determinate assay result.

*6.2.2.1.6. Sample size*

13vPnC was offered to all YK Delta region children aged 6 weeks to <5 years (Alaskan native children). The estimated number of subjects who received investigational 13vPnC is outlined below.

The rate of IPD caused by 13vPnC serotypes in the YK Delta region of subjects <5 years of age during 2006 and 2007, assuming a birth cohort size of 600 subjects, was 19 cases per 3,000 subjects (316 cases/100,000 person/year). It was expected that the rate in the YK Delta region during a 2 year post-13vPnC vaccination period would be reduced by 85% compared with baseline; this would result in 3 cases per 3,000 subjects (50 cases/100,000 persons/year). There was an 89% power to detect this reduction in rates using a Fisher exact test at an alpha level of 0.05 (2-sided test).

At the completion of the study there were 373 Alaskan native children immunised and available for analysis.

Evaluator Comment: This study failed to recruit the number of subjects anticipated due to reluctance by the community to participate in a study with an 'experimental' vaccine. The ability to detect an 85% reduction in IPD incidence was based on recruitment (and vaccination) of 2,500 children. It is not clear what results will be possible with a study of only 373 subjects (13vPnC coverage rate of 19%).

Statistical methods

The CDC has an existing IPD surveillance system and NP colonisation study and was responsible for data collection and analysing this data. Statistical analysis of the immunogenicity and safety data were the responsibility of the sponsor.

Invasive pneumococcal disease

The primary variable was the incidence rate (case/number at risk) of IPD due to any serotype contained in 13vPnC in subjects residing in the YK Delta region. The cases of IPD were collected over 1 to 2 years and compared with the incidence of IPD in the 2 to3 years prior to introduction of 13vPnC in the YK Delta region (baseline). Additionally, the incidence was compared with a time period before the introduction of Prevenar in the YK Delta region.

Secondary variables included the following:

- Incidence of IPD due to any *S. pneumoniae* serotype;
- Incidence of IPD due to 6 new additional serotypes;
- Incidence of IPD due to 19A;
- Incidence of IPD due to non-vaccine serotypes.

The primary analysis was completed for subjects aged <5 years. Additional analyses were undertaken for subjects aged <2 years and other age groupings in children and adults.

The proportion of residents with IPD at baseline and after the introduction of 13vPnC in the YK Delta region were to be computed along with exact, 2-sided 95% confidence intervals (CIs). Two (2)-sided 95% CIs were also to be computed for the risk difference for post-13vPnC introduction rates as compared to baseline. A mid-P (midp) test of significance was to be used to compare the baseline rates with the YK Delta region post-13vPnC introduction rates (2-sided test, alpha=0.05).

Nasopharyngeal carriage

Characterisation of serotypes and antimicrobial resistance patterns of *S. pneumoniae* carriage was to be completed for the YK Delta region using data from an ongoing NP colonisation investigator-originated study that began in February 2008 in Alaska. The primary endpoint was

the proportion of subjects with NP carriage of the 13vPnC serotypes, summarised for subjects aged <2 years, < 5 years and other age groupings in children and adults.

The proportion of residents with NP carriage for separate pneumococcal serotypes was to be tabulated for a 1 year period prior to and 3 to 4 years after the introduction of 13vPnC to the YK Delta region. The proportion of subjects with NP carriage of the 13vPnC serotypes was of primary interest in this analysis.

Immunogenicity analysis

The primary immunogenicity endpoint for each of the pneumococcal serotypes was the proportion of subjects achieving a serotype-specific IgG antibody concentration ≥0.35µg/mL measured 1 month after the infant series (Groups 1, 2 and 3), 1 month after the toddler dose (Groups 1, 2 and 3) and 1 month after completion of the relevant catch-up dose(s) (Group 4 and 5), the proportion of subjects with IgG antibody concentration ≥0.35 µg/mL prior to vaccination with 13vPnC. Choice of IgG antibody concentration was based on the World Health Organisation (WHO) guideline for the evaluation of pneumococcal serotypes and the WHO Expert Committee on Biological Standardisation.

Secondary and exploratory endpoints included:

- The proportion of subjects achieving a serotype-specific IgG antibody concentration ≥1.0µg/mL measured 1 month after the infant series (Groups 1, 2 and 3), toddler series (Groups 1, 2 and 3) and pre-vaccination and 1 month after completion of the relevant catch-up dose(s) (Groups 4, 5).
- Serotype-specific levels of OPA achieved in each group for each of the pneumococcal serotypes and correlation of OPA and ELISA values for each of the 13vPnC serotype.

Tabular summaries of immunogenicity data were produced for the evaluable immunogenicity population and the all-available immunogenicity population; graphical presentation of immunogenicity data was to be produced only for the evaluable immunogenicity population. The number of samples collected was expected to be small and descriptive statistics and CIs less precise. The ability to draw conclusions regarding this exploratory analysis was anticipated to be limited however, analysis included proportion of subjects with IgG concentrations ≥0.35 µg/mL, GMC, RCDC and OPA activity analysis.

Evaluator Comment: Statistical analysis was based on significantly more subjects being available for analysis. Results should be therefore interpreted with caution.

*6.2.2.1.7. Participant flow*

It was originally anticipated that 2,500 subjects in this region of Alaska would be enrolled. Information on enrolment was provided via radio public service announcement, meetings with local tribal leaders and medical clinics. Enrolment was severely limited by a combination of factors; logistical reasons, fear of participation in investigational trials with experimental vaccine, remoteness of areas with limited access to village sites, availability of licensed 7vPnC vaccine and weather restrictions. The most prevalent limitation was concerns regarding research participation and use of an experimental vaccine.

Some 1,365 subjects were screened and/or parents approached about study participation; of these children 60 did not enrol or show up for a visit and 500 had delayed screening/participation for a variety of reasons. A total of 373 subjects were consented and enrolled (n=151, Group 1; n=51, Group 2; n=25, Group 3; n=67 Group 4; n=79, Group 5) and 3 subjects were consented and screened only. Of the 373 enrolled subjects, 354 completed the study. Enrolment started in January 2009 and finished in March 2010, when Prevenar13 became commercially available. A total of 19 subjects were withdrawn from the study.

Many subjects categorised as 'completers' did not, in fact, receive all protocol vaccinations, as when 13vPnC became commercially available in the region, vaccination under the protocol ceased. Accordingly, data for the later doses are available for increasingly smaller numbers of subjects.

**Table 17: Disposition of Subjects**

| | Vaccine Group (as Enrolled) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Screened Only n (%) | 13vPnC Group 1 n (%) | 13vPnC Group 2 n (%) | 13vPnC Group 3 n (%) | 13vPnC Group 4 n (%) | 13vPnC Group 5 n (%) | Total n (%) |
| Consented[a] | 3 (100.0) | 151 (100.0) | 51 (100.0) | 25 (100.0) | 67 (100.0) | 79 (100.0) | 376 (100.8) |
| Enrolled[b] | 0 (0.0) | 151 (100.0) | 51 (100.0) | 25 (100.0) | 67 (100.0) | 79 (100.0) | 373 (100.0) |
| Vaccinated – Group 1 | | | | | | | |
| Dose 1 | 0 (0.0) | 151 (100.0) | - | - | - | - | 151 (100.0) |
| Dose 2 | 0 (0.0) | 112 (74.2) | - | - | - | - | 112 (74.2) |
| Dose 3 | 0 (0.0) | 74 (49.0) | - | - | - | - | 74 (49.0) |
| Toddler Dose | 0 (0.0) | 15 (9.9) | - | - | - | - | 15 (9.9) |
| Vaccinated – Group 2 | | | | | | | |
| Dose 1 | 0 (0.0) | - | 51 (100.0) | - | - | - | 51 (100.0) |
| Dose 2 | 0 (0.0) | - | 41 (80.4) | - | - | - | 41 (80.4) |
| Toddler Dose | 0 (0.0) | - | 23 (45.1) | - | - | - | 23 (45.1) |
| Vaccinated – Group 3 | | | | | | | |
| Dose 1 | 0 (0.0) | - | - | 25 (100.0) | - | - | 25 (100.0) |
| Toddler Dose | 0 (0.0) | - | - | 16 (64.0) | - | - | 16 (64.0) |
| Vaccinated – Group 4 | | | | | | | |
| Dose 1 | 0 (0.0) | - | - | - | 66 (98.5) | - | 66 (98.5) |
| Dose 2 | 0 (0.0) | - | - | - | 49 (73.1) | - | 49 (73.1) |
| Vaccinated – Group 5 | 0 (0.0) | - | - | - | - | 79 (100.0) | 79 (100.0) |
| Completed | 0 (0.0) | 141 (93.4) | 48 (94.1) | 23 (92.0) | 63 (94.0) | 79 (100.0) | 354 (94.9) |
| Withdrawn | 0 (0.0) | 10 (6.6) | 3 (5.9) | 2 (8.0) | 4 (6.0) | 0 (0.0) | 19 (5.1) |
| Reason for withdrawal | | | | | | | |
| Parent/Legal Guardian Request | 0 (0.0) | 3 (2.0) | 2 (3.9) | 2 (8.0) | 2 (3.0) | 0 (0.0) | 9 (2.4) |
| Adverse event | 0 (0.0) | 3 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.8) |
| Death | 0 (0.0) | 2 (1.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.5) |
| Investigator request | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (3.0) | 0 (0.0) | 2 (0.5) |
| Other | 0 (0.0) | 1 (0.7) | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.5) |
| Failed to Return | 0 (0.0) | 1 (0.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) |

a. The values in this row are used as the denominators for percentages for screened only.
b. The values in this row are used as the denominators for percentages for vaccine groups.
Program ID: Study 6096A1-3010/CP CS_DISP.SAS. Runtime ID: 08FEB2011 20:34
Source: Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3010/Reports, Tables, and Figures/Conduct/Conduct_Final.zip/cs_disp.htm

Evaluator Comment: The poor enrolment rate in addition to the significantly reduced numbers of children completing the study protocol raise questions about the robustness of the study results, in particular the immunogenicity data is likely to be severely underpowered.

*6.2.2.1.8. Major protocol violations/deviations*

Of the 227 enrolled study subjects who received 13vPnC in the infant series (Groups 1, 2 and 3), 20 (8.8%) subjects were included in the all-available and evaluable infant immunogenicity populations.

Of the 227 subjects enrolled in Groups 1, 2 and 3 a total of 10 (4.4%) subjects were included in the all-available and evaluable toddler immunogenicity populations.

Of the 146 enrolled study subjects (Groups 4 and 5), 23 (15.8%) subjects were included in the all-available immunogenicity population and 13 (8.9%) in the evaluable immunogenicity population. Reasons for exclusion from the evaluable population were as follows: 8 (5.5%) subjects had no valid and determinate assay result; 4 (2.7%) subjects did not receive all pneumococcal study vaccinations; 1 (0.7%) subject had a post vaccination blood draw >56 days after the last scheduled vaccination; and 1 (0.7%) subject had a protocol violation categorised as "other" (one subject did not have baseline blood sample obtained prior to study vaccine administration).

Evaluator Comment: Only 13 (8.9%) of enrolled subjects were available for the evaluable immunogenicity population and 23 (15.8%) in the all-available immunogenicity population. Interpreting results from the immunogenicity population is impossible.

*6.2.2.1.9. Baseline data*

Demographic characteristics for all subjects (n=373) are as follows; overall, 48.7% of the subjects were male and 51.3% were female. Groups were similar with respect to race and ethnicity. Most subjects were American Indian or Alaskan native (89.6%) and characterised as non-Hispanic and non-Latino (98.4%).

The evaluable infant immunogenicity population (Groups 1, 2 and 3) consisted of 11 males and 9 females. Two (2) subjects identified as White, 16 as American Indian or Alaska Native and 2 as 'other'. The evaluable toddler immunogenicity population (Groups 1, 2 and 3) consisted of 5 males and 5 females; of these 6 identified American Indian or Alaska Native as their ethnicity with two identifying as white and two 'other'.

The evaluable immunogenicity population (Groups 4 and 5) consisted of 8 females and 5 males; 11 identified as American Indian or Alaskan Native.

Medical history characteristics for all subjects were generally consistent with illnesses/conditions commonly seen in the age groups represented in this study. There were 13 subjects with carnitine palmitoyltransferase deficiency, a genetic condition common in native northern Alaskan populations considered to be mild in severity and not related to any other medical conditions. There was one subject enrolled with cardiac failure (Group 2), pulmonary valve stenosis (Group 1) and encephalopathy (Group 5).

Evaluator Comment: The demographic profile for the groups seems balanced. Given the low study numbers, a large proportion of the children have coexisting medical conditions (15/373). This may have been due to inadvertent selection bias as parents already in regular contact with medical services may have been less reluctant to enrol their children in a clinical trial.

### *6.2.2.2. Results for the primary efficacy outcome*

The primary objective was to assess the impact of 13vPnC on the incidence of IPD in the YK Delta region due to the 13 vaccine *S. pneumoniae* serotypes. During the study period (January 2009 – March 2010) approximately 10% of children <5 years of age in the YK Delta region were vaccinated with 13vPnC. After commercial introduction of the vaccine, there was a rapid uptake such that by March 2011, approximately 90% children had received at least 1 dose of 13vPnC.

Cases of IPD caused by serotypes in 13vPnC (caused by 7F and 19A) in YK Delta region children <5 years of age, appeared to decline in 2009 and 2010. In 2009, the number of cases in children aged <5 years was unusually low. In 2010, the number of cases due to both 13vPnC and non-13vPnC serotypes increased but rates of both remained lower than those documented prior to the availability of 13vPnC. After commercial introduction of 13vPnC there was 1 documented

case of IPD due to serotype 19A in an unvaccinated child and 1 documented case in a study participant that was due to a serotype not included in the vaccine (16F). There were no cases of IPD in children <5 years of age in the YK Delta region in the first 3 months of 2011.

Overall the rate of IPD caused by 13vPnC serotypes dropped from 237.9/100,000 (31 cases) in the pre vaccine period to 85.3/100,000 (6 cases) during the study period (that is, the period beginning with the date of immunisation of the first child with 13cPnC under the study protocol, January 30 2009 through 1 year post state wide introduction following commercialisation 31 March 2011. A substantial decline in children in the rest of Alaska did not occur until the year vaccine was introduced state wide (2010).

Evaluator Comment: The unexpected drop in IPD incidence in YK Delta in 2009 unfortunately clouds the interpretation of the results. The drop from 186.1 cases/100,000 years to 93.9 cases/100,000 years cannot be explained by the vaccination of less than 10% of the YK Delta target population. There also appears to have been a higher than expected number of IPD cases in 2007 (284.3 cases/100,000 persons). An adjusted average annual incidence pre vaccine would be a more helpful baseline figure and could include data from the previous 5 years to average annual fluctuations (and dips) in IPD.

Both the YK Delta and Alaska cohorts showed a decrease in the incidence of IPD cases in 2010, with a further decrease in 2011. The roll-out of the 13vPnC vaccine commenced in March 2010 and the drop in both may be due to vaccine up-take or alternatively due to cyclical variations in IPD incidence.

It is not clear why YK Delta data was compared to 'all Alaska'; a more helpful comparator in terms of determining the efficacy in American Indian and Alaskan native children would have been to compare the YK Delta region with another region with a high native population, or alternatively limit the Alaska dataset to people identifying as American Indian/Native Alaskan.

Stabilisation of non-13vPnC IPD infections is reassuring; data from 2012 showing stabilisation of IPD cases at the level seen in 2011 would provide further reassurance of efficacy.

#### *6.2.2.3. Results for other efficacy outcomes*

##### *6.2.2.3.1. Nasopharyngeal carriage*

The impact of vaccination with 13vPnC on NP colonisation was assessed by containing NP colonisation data from an ongoing NP colonisation investigator-originated proposal study that began in February 2008 in Alaska. NP swabs are collected among children residing in four villages in the YK Delta region, in addition to villages in other regions and three urban clinics. Data is currently available from 2008 to 2010; the study is ongoing.

Eight villages were visited; four villages in the YK Delta region, 2 villages in Bristol Bay and 2 villages in Norton Sound. Swabs were also taken from 2 urban medical centres in Anchorage. In villages participating in the YK Delta region clinical trial, the proportion of children <5 years of age carrying any of the 6 additional serotypes in 13vPnC decreased from 30% in 2008-2009 to16% in 2010 ($p<0.002$). During this same period, there was no significant difference in carriage of any of the 6 additional serotypes in 13vPnC in populations which did not begin to use13vPnC until licensure in 2010. The decrease in carriage in the YK Delta region population occurred in a setting where only 19% of the population <5 years of age had received > 1 dose of13vPnC vaccine.

**Table 18: Proportion of Carriage of Typeable Pneumococci Comprised of the 6 Additional Serotypes in 13vPnC, Children <5 Years of Age, Alaska**

| Population | 13vPnC Coverage (March, 2010) | | 13vPNC additional serotypes/pneumococci carriers | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 2008 | | 2009 | | 2010 | |
| YK Delta | 47/245 | 19% | 55/184 | 30% | 58/193 | 30% | 25/152 | 16% |
| Rural and Urban | 14/445 | 3% | 27/135 | 20% | 59/234 | 25% | 74/285 | 26% |

Carriage data from persons 18 years and older in the village populations participating in the clinical trial suggests a decrease in the 6 additional serotypes in 13vPnC amongst the adult population. NP colonisation decreased from 23% in 2008 to 2009 (26% in 2008, 20% in 2009) to 12% in 2010 ($p<0.02$). Carriage among adults in villages not participating in the clinical trial introduction rose slightly from 18% (19% in 2008, 18% in 2009) to 21% but this difference was not statistically significant.

**Table 19: Proportion of Carriage of Typeable Pneumococci Comprised of the 6 Additional Serotypes in 13vPnC, Adult Population (18 years and older), Alaska**

| Population | 13vPNC additional serotypes/pneumococci carriers | | | | | |
|---|---|---|---|---|---|---|
| | 2008 | | 2009 | | 2010 | |
| YK Delta | 38/147 | 26% | 25/128 | 20% | 16/133 | 12% |
| Rural Alaska | 4/21 | 19% | 7/40 | 18% | 17/81 | 21% |

The significant decrease in carriage of the 6 additional serotypes in 13vPnC in children and adults in the early vaccine introduction area and no corresponding decrease in carriage in neighbouring rural or urban areas not receiving the vaccine clearly suggest an impact of the vaccine on carriage. This occurred with only 19% of children in the high-risk area having received 1 dose or more of vaccine, suggesting a herd immunity effect.

Evaluator Comment: There are no references ranges provided for any results. Given the low absolute numbers, particularly in the rural Alaskan adult population, it is likely that the reference ranges would be wide. The comparison of the pre and post-vaccine NP carriage rates for YK Delta adult cohort were made between the average of the 2008 to2009 data and the 2010 data. It is not clear why this decision was made rather than a comparison between 2009 and 2010 annual figures. It is possible that the former analysis gave more favourable statistical results.

There have been several studies published showing herd immunity associated with use of the 7vPnC vaccine. These studies have looked at IPD incidence and showed a decrease in 7vPnC serotype disease following the introduction of the vaccine. There is sufficient evidence to show *S. pneumoniae* vaccination has a herd immunity effect, however, establishing whether this is due to NP carriage reduction or the immune effects of the vaccine itself has not been established.

*6.2.2.3.2. Immunogenicity results*

Blood samples were collected from subjects in the immunogenicity subset 1 month after completion of the infant series and toddler dose and before vaccination and 1 month after completion of catch-up dose regimens in children aged ≥12 months. Serum concentrations of anti-capsular immunoglobulin G were determined for each blood sample. The number of immunogenicity samples collected was very small and ability to draw any conclusions from any of the analysed data is limited.

The number of samples collected was Group 1 – 11, Group 2 – 6 and Group 3 – 3. Almost 100% of samples obtained antibody concentrations ≥0.35 μg/mL for all serotypes presented in 13vPnC. For the catch-up toddler series there were 4 subjects in Group 4 and 8 in Group 5. The proportion of subjects achieving antibody concentrations ≥0.35 μg/mL pre-vaccination ranged from 50 to 100%, following the 13vPnC catch-up dose all subjects antibody concentrations for all serotypes ≥0.35 μg/mL.

Evaluator Comment: The number of subjects who were available for the immunogenicity component of the study is too small to make any valuable addition to the discussion. The remaining results of OPA, RCDC data have not been reviewed as they are exploratory only.

## 6.3. Other efficacy studies

None.

## 6.4. Analyses performed across trials (pooled analyses and meta-analyses)

No data was pooled across trials.

No data was pooled across trials.

### 6.4.1. Evaluator's conclusions on clinical efficacy (immunogenicity) for extension of Age indication (age 6 to 17 years)

The pivotal efficacy study (6096A1-3011) assessed the safety and immunogenicity of Prevenar13 in children aged 5-17 years. The primary immunogenicity analysis involved a complex design that compared Group 3 (children aged 5 to 10 years) against a historical cohort of similarly aged children who received Prevenar or Prevenar13. For this analysis IgG titres were used as an indicator of immunogenicity. Immunogenicity in the oldest cohort (aged 10 to 17 years) was assessed by comparing Group 3 and Group 4 OPA GMTs (secondary outcome). In addition to these results, numerous calculations were performed assessing antibody titres, pre and post-vaccination antibody levels, OPA GMTs and RCDC. A major limitation of the study is the ability to show immunogenicity in an older cohort of children who have already acquired immunity to many of the serotypes available in the vaccine.

The key immunogenicity findings were:

- The serotype-specific GMCs were higher in the cohort of children aged 5 to 10 years who received 13vPnC (Group 3) compared to a similarly aged historical cohort who received 7vPnC. The serotype-specific geometric mean ratios for the 7vPnC serotypes ranged from 2.51 for serotype 23F to 5.66 for serotype 6B.
- The serotype-specific GMCs were higher in the cohort of children aged 5 to 10 years who received 13vPnC (Group 3) compared to a similarly aged historical cohort who received 13vPnC. The serotype-specific geometric mean ratios for 13vPnC serotypes ranged from 1.23 for serotype 1 to 3.17 for serotype 19A.

- For Group 4 (children aged 10 to 17 years) immunogenicity data was based on OPA GMTs comparisons between 13vPnC data from Group 3. All serotypes were found to be non-inferior except for serotype 3 where the lower limit of the 95% CI for the ratio between OPA GMTs was 0.48.
- Sensitivity analysis (comparison between the evaluable and all-available immunogenicity populations) generally confirmed the results.
- Results for the IgG antibody titres for both Group 3 and 4 showed that for all serotypes subjects achieved IgG titres ≥0.35 μg/mL post-vaccination (98.9% to 100.0%).
- The majority of subjects in Group 3 also had IgG antibody titres ≥1.0 μg/mL for the 13vPnC serotypes. Serotype 3 had the lowest number of subjects with titres ≥1.0 μg/mL with 80.5%.
- Pre-vaccination IgG titres for 13vPnC serotypes for Group 4 suggested that many subjects had already been exposed to the 13vPnC pneumococcal serotypes with the proportion of subjects with IgG concentrations ≥0.35 μg/mL pre-vaccination being between 43 to 99%. The proportion of subjects with pre-vaccination antibody titres ≥1.0 μg/mL was also high (23 to 96%).

Based on the key immunogenicity findings, the vaccine shows immunogenicity for the age Group 10 to 17 years although many children, particularly in the older age group are likely to have already come into contact with the serotypes present in the vaccine.

### 6.5. Evaluator's conclusions on clinical efficacy (immunogenicity) for PI change

Two pivotal studies (3006, 3010) and one post-marketing surveillance study (ACTIV) provide evidence to support the PI change.

Study 3006 was a Phase III, randomised, active-controlled, double-blind, multi-site study in healthy infants. The study was designed as a parallel-group study in which subjects were randomly assigned to 2 groups in a 1:1 ratio to receive either 13cPnC or 7vPnC. The study was generally well designed and implemented and found that there was a statistically significant difference in NP colonisation of 13vPnC serotypes between the two groups (7vPnC versus 13vPnC). In particular, the study showed a reduction in the colonisation of 19A and 6A' serotypes. A number of other analyses were performed, however, the study was not powered to detect a difference in these tests and they should be viewed as exploratory results only.

Study 3010 was a Phase III, multicentre, open-label study to evaluate the immunogenicity and safety of 13vPnC and the impact of 13vPnC on the incidence of IPD and NP colonisation in healthy Alaskan native children in the YK Delta region of Alaska. Unfortunately due to cultural factors and the timing of the implementation of the 13vPnC vaccine, the study suffered severely from poor subject recruitment. The immunogenicity portion of the study is based on a handful of cases and no conclusions can be drawn from this data. The surveillance data is also limited by poor study numbers. In addition, an unusually low prevalence of IPD in the Yukon Delta population in 2009 makes interpreting the change in serotype prevalence overtime difficult. Overall this study adds very little weight to the evidence presented in Study 3006.

ACTIV is an ongoing post market surveillance study assessing the prevalence of 13vPnC serotypes in NP swabs of subjects presenting with acute otitis media. The study found a statistically significant decrease in the prevalence of 13vPnC serotypes, particularly serotype 19A amongst children presenting with acute otitis media following the introduction of Prevenar 13. This study is the only study to directly support the PI change. Although the results provide some evidence to support the hypothesis that Prevenar 13 reduces the carriage of *S. pneumoniae* serotypes present in the 13vPnC vaccine, it is not sufficient on its own. The study should ideally be supported by more robust studies in the form of randomised controlled trial,

or alternatively long term (5 year) follow-up data from post-market studies from a cross-section of the global community.

# 7. Clinical safety

## 7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

### 7.1.1. Pivotal efficacy studies

In the pivotal efficacy study (6069A1-3011), the following safety data were collected:

- Local reactions (redness, swelling and tenderness);
- Systemic events (including fever, decreased appetite, irritability, increased sleep, decreased sleep and hives [urticaria]) and the use of antipyretic medications to prevent or treat symptoms. Adverse events were recorded via an e-diary for 7 days after vaccination. A 6 month follow-up telephone interview recorded any newly diagnosed chronic medical conditions as AEs.
- All SAEs were reported from the time of enrolment through the 6-month follow-up.

Local reactions were assessed by a severity scale. For tenderness the range was; no discernible tenderness, tenderness present or tenderness interfering with limb movement. For redness and swelling, the parent/legal guardian measured the actual size of the reaction with a calliper and recorded the measurement (range 1-14 caliper units). A calliper unit represented 0.5 cm. The measurements for redness and swelling were categorised as absent (no redness or swelling present), mild (1-4 caliper units), moderate (5-14 caliper units) or severe (>14 caliper units).

Temperature was collected at bedtime daily for 7 days after vaccination and at any time during the 7 days that fever was suspected. Temperature was measured and recorded to 1 decimal place and then categorised according to the following terms and scale:

- Absent <38.0ºC;
- Mild ≥38 ºC to <39 ºC;
- Moderate ≥39 ºC to <40 ºC;
- Severe >40.0ºC.

### 7.1.2. Pivotal studies that assessed safety as a primary outcome

No studies assessed safety as a primary outcome.

### 7.1.3. Dose-response and non-pivotal efficacy studies

#### *7.1.3.1. Study 6096A1-3010*

Measures of reactogenicity (solicited local reactions and systemic events) were collected for 7 days after 13vPnC vaccination. Adverse events were collected for all subjects from day of consent until the final study follow-up telephone call, scheduled at 6 months after the last 13vPnC vaccination.

#### *7.1.3.2. Study 6096A1-3006*

Adverse events, specifically medically important adverse events, adverse events resulting in withdrawal, adverse events associated with antibiotic use (excluding topical antibiotics) and severe adverse events were collected. AEs were recorded from the signing of the informed consent form to the last study visit.

#### *7.1.3.3. Other studies evaluable for safety only*

None.

## 7.2. Patient exposure

Subject exposure for all cases was the standard dose of either 13vPnC or 7vPnC. For the pivotal study (6096A1-3011), all subjects received a single toddler series dose.

## 7.3. Adverse events

### 7.3.1. All adverse events (irrespective of relationship to study treatment)

#### *7.3.1.1. Pivotal study (6096A1-3011)*

##### *7.3.1.1.1. Severe or life-threatening adverse events*

Two subjects in Group 3 experienced severe or life-threatening adverse events (AEs): 1 subject had appendicitis and 1 subject had an eye injury. Neither of these were considered related to study vaccine. There were no severe or life-threatening AEs in Group 4.

##### *7.3.1.1.2. Adverse events*

The incidence of AEs occurring through approximately 1 month after vaccination was similar in Group 3 (19.4%) and in Group 4 (24.2%). In both vaccine groups, the most frequently reported types of AEs were Infections and infestations (10.2% in Group 3 and10.4% in Group 4). Nervous system disorders were reported for slightly more subjects in Group 4 (14, 4.7%) than in Group 3 (5, 1.7%). The most frequently reported individual AEs in Group 3 were cough (10 subjects, 3.4%), vomiting (8 subjects, 2.7%), pyrexia (7 subjects, 2.4%) and pharyngitis streptococcal (6 subjects, 2.0%). The most frequently reported individual AEs in Group 4 were headache (10 subjects, 3.4%), cough (5 subjects, 1.7%), pharyngitis (5 subjects, 1.7%), influenza (5 subjects, 1.7%), oropharyngeal pain (5 subjects, 1.7%) and sinusitis (5 subjects, 1.7%). AEs after vaccination were generally consistent with childhood illnesses common in the respective age categories of Groups 3 and 4.

At the 6 month follow-up telephone contact, only newly diagnosed chronic medical conditions and SAEs were to be reported. The incidence of AEs reported at 6 months was 2.4% in Group 3 and 1.7% in Group 4. In both vaccine groups, the types of AEs reported most frequently were respiratory, thoracic and mediastinal disorders (asthma, bronchial hyper-reactivity, rhinitis allergic).

Evaluator Comment: SAE and AE reporting is consistent with childhood illness/injury expected in these age groups. The higher incidence of neurological adverse events is consistent with differences in age between Groups 3 and 4.

##### *7.3.1.1.3. Vaccine related AEs*

The incidence of AEs related to vaccination occurring through approximately 1 month after vaccination was identical in Group 3 (3 subjects, 1.0%) and Group 4 (3 subjects, 1.05). The related AE of headache was reported by 2 subjects in Group 3 and by 2 subjects in Group 4. All other AEs were reported by 1 subject in a Group 4 (diarrhoea, nausea and vomiting, back pain, dizziness, injection site pain and pruritus).

##### *7.3.1.1.4. Local reactions*

At least 1 local reaction was reported within 7 days of vaccine administration for 89.6% of subjects in Group 3 and for 90.5% of subjects in Group 4. The most frequent local reaction during this interval was tenderness, which occurred in 86.8% of subjects in Group 3 and 89.0% of subjects in Group 4. Most local reactions were mild or moderate in severity. The percentage of subjects reporting significant tenderness was higher in Group 4 (43.8%) than in Group 3

(19.5%). Severe redness was reported by 7 (3.3%) subjects in Group 3 and by 4 (1.9%) subjects in Group 4. Severe swelling was reported by 7 (3.3%) subjects in Group 3 and 4 (1.9%) subjects in Group 4.

**Table 20: Subjects Reporting Local Reactions within 7 Days, Safety Analysis**

| Local Reaction | Group 3 | | | Group 4 | | |
|---|---|---|---|---|---|---|
| | N | n | % | N | n | % |
| Tenderness | | | | | | |
| Any | 265 | 230 | 86.8 | 283 | 252 | 89.0 |
| Significant | 221 | 43 | 19.5 | 242 | 106 | 43.8 |
| Swelling | | | | | | |
| Any | 226 | 85 | 77 | 233 | 86 | 36.9 |
| Mild | 220 | 48 | 75 | 221 | 50 | 22.6 |
| Moderate | 219 | 48 | 76 | 226 | 48 | 21.2 |
| Severe | 211 | 7 | 73 | 214 | 4 | 1.9 |
| Redness | | | | | | |
| Any | 233 | 100 | 81 | 232 | 70 | 30.2 |
| Mild | 226 | 63 | 79 | 226 | 48 | 21.2 |
| Moderate | 218 | 48 | 77 | 221 | 31 | 14.0 |
| Severe | 212 | 7 | 73 | 213 | 4 | 1.9 |
| Any local reaction | 270 | 242 | 96 | 285 | 258 | 90.5 |

N = number of subjects reporting 'yes' for at least 1 day or 'no' for all days
n = number of subjects reporting the specific characteristic

The highest incidence of tenderness occurred on Days 1 and 2 for both groups. The highest incidence of redness and swelling occurred on Days 2 and 3. The mean duration of local reactions was similar in the two vaccine groups with a mean duration of 2.4 (standard deviation (SD) 1.8) in Group 3 and 2.9 (SD 1.7) for Group 4 for tenderness. Duration of reaction for redness and swelling were similar and did not extend beyond 3 days.

*7.3.1.1.5. Systemic events*

The percentage of subjects with any systemic event was similar in Group 3 (47.2%) and Group 4 (51.4%). The percentages of subjects with the 3 most frequent systemic events (irritability, decreased appetite and increased sleep) were also similar in Group 3 (31.2%, 22.9% and 21.2% respectively). Decreased sleep occurred for a higher percentage of subjects in Group 4 (18.8%) than Group 3 (5.7%). Urticaria occurred for 4 (1.9%) subjects in Group 3 and 3 (1.4%) subjects in Group 4.

Most cases of fever were mild in both age groups. There was one case of severe fever (>40) in both groups. In Group 3, 45.1% of subjects reported use of antipyretic medications to treat *or* prevent symptoms and 15.9% subjects reported use of antipyretic medications to treat *and* prevent symptoms; in Group 4 the corresponding rates were 33.1% and 13.1%.

The incidence of systemic events and use of antipyretic medications was generally highest on Day 1, Day 2 and Day 3 in both age groups; most reports of systemic events declined thereafter,

although there was a slight increase in incidence at the end of the week. The mean duration of systemic events was similar in both groups and did not exceed 3.0 days.

Evaluator Comment: Local reactions and systemic events associated with vaccination are consistent with the incidence of these events with general vaccinations.

#### *7.3.1.2. Other studies*

##### *7.3.1.2.1. Study 6096A1-3010*

*Study related AEs:* In Group 1, 51 AEs were reported in subjects after doses 1-3 of the infant series. The most common reported categories were 'Infection and infestation' and 'General disorders and administration site conditions'. AEs that occurred in >1 subject were pyrexia, respiratory syncytial virus bronchiolitis, pneumonia, influenza, pneumonia respiratory syncytial viral, bronchiolitis, urinary tract infection, convulsion and pneumonia aspiration. Some 13 of these events were considered to be vaccine related; 9 (6.0%) subjects after dose 1 and in 2 (1.85%) subjects after dose 2. The events were pyrexia and injection site erythema. Results were similar in Group 2 and 3. In Group 3 there were two severe AEs which were considered to be vaccine related; 1 subject had apnoea following dose 1 and another subject had a breath holding event following the toddler dose.

In Group 4 there were three AEs reported in 2 (3.0%) subjects following dose 1, all in the category of Infection and infestations (abscess, influenza and pneumonia) and 2 AEs were reported in 2 (4.1%) subjects following dose 2 (lymphadenitis and rash macula-papular). There were no AEs reported in Group 5.

*Local Reactions:* At least one local reaction was reported in 41.5% of subjects in Group 4 and 50.6% of subjects in group 5. The most frequent reported reaction was tenderness, in 32.3% of subjects in Group 4 and in 48.1% of subjects in Group 5; followed by redness (15.4% and 13.0%, respectively) and swelling (7.8% in both groups). Significant tenderness (interfered with limb movement) was reported in 2 (3.2%) subjects in Group 4 and 7 (9.1%) subjects in Group 5; and both severe redness and severe swelling were reported in 1 (1.6%) subjects in Group 4 and 2 (2.6%) subjects in Group 5.

The number of subjects reporting any local reactions within 7 days of dose 2 (Group 4 only) was 37.5% subjects. The most frequent reaction was tenderness (reported in 36.7%), followed by swelling (10.4%) and redness (6.1%). Significant tenderness was reported in 10.2% of subjects.

*Systemic Events:* Systemic events (fever, decreased appetite, irritability, increased sleep, decreased sleep and hives) and use of antipyretic medication to treat or prevent symptoms were collected daily for 7 days after each 13vPnC vaccination (2 doses for Group 4 and 1 dose for Group 5). At least 1 systemic event was reported in 85.2% of subjects in Group 4 and 66.7% of subjects in Group 5. The most frequently reported event was irritability, reported in 53.0% and 41.6% of subjects, respectively. Mild fever was reported in 42.9% of subjects in Group 4 and in 27.7% of subjects in Group 5; moderate fever in 20.7% and 11.6% respectively, and severe fever (>40) in 7.1% and 0.0%, respectively). There were 2 cases of hives; although neither case was reported as related to vaccination. Antipyretic medication was given to 65.2% and 46.8% of subjects, respectively, with treatment of symptoms being the most common reason.

##### *7.3.1.2.2. Study 6096A1-3006*

*Severe and Life-Threatening Adverse Events:* The incidence of severe AEs was comparable between the 13vPnC group (0.3%) and the 7vPnC group (0.2%) for the infant series (p=0.687). Severe AEs in the 13vPnC group were sudden death, otitis media and apparent life threatening event (3 events, 1 in each group). Severe events of meningococcal infection and pertussis (1 subject each) were reported in subjects receiving 7vPnC. These events were not thought to be related to the study vaccines.

Post-infant series, 3 subjects (0.3%) in the 13vPnC group and 2 subjects (0.2%) in the 7vPnC group reported severe AEs after the infant series. Severe AEs of developmental delay and gastroenteritis were reported by 1 subject in each of the vaccine groups. A severe AE of infantile spasm was reported by 1 subject in the 13vPnC group. Post-toddler dose there was one severe AE of otitis media reported in 1 subject (0.1%) in the 13vPnC group after the toddler dose.

*Infant Series:* All AEs occurring from dose 1 of the infant series through to the 1 month blood draw were recorded. The incidence of AEs was similar in the 13vPnC group (51.8%) and in the 7vPnC group (49.7%). In both vaccine groups, the most frequently reported types of AEs were Infection and infestations (25.7% in the 13vPnC group and 23.4% in the 7vPnC group) and General disorders and administration site conditions (24.9% in the 13vPnC group and 21.9% in the 7vPnC group).

The most frequently reported individual AEs in both vaccine groups were pyrexia (24.0% in the 13vPnC group and 21.1% in the 7vPnC group) and otitis media (18.0% in the 13vPnC group and 15.0% in the 7vPnC group). Pharyngitis was reported in 1.3% of subjects in the 13vPnC group and 2.7% of subjects in the 7vPnC group (p=0.045). All other AEs occurred in <3% of subjects. One event of sudden death, which was not related to vaccine administration, was reported in the 13vPnC group (0.1%).

There was no difference in the incidence of AEs reported for each dose of vaccine. In the 13vPnC group, the incidence of AEs was 20.0%, 26.9% and 31.0% for dose 1, dose 2 and dose 3, respectively. In the 7vPnC group, the incidence of AEs was 18.0%, 25.5% and 27.1% for dose 1, dose 2 and dose 3, respectively.

*Toddler Dose:* The incidence of AEs reported during the toddler dose (from the toddler dose through the blood draw 1 month after the toddler dose) was similar in the 13vPnC group (27.7%) and 7vPnC group (28.0%). The most frequently reported types of AEs in both vaccine groups were Infections and infestations (16.3% in the 13vPnC group and 17.8% in the 7vPnC group) and General disorders and administration site conditions (10.8% in the 13vPnC group and 11.0% in the 7vPnC group). The incidence of individual AEs was also similar between vaccine groups with otitis media (10.5% in the 13vPnC group and 10.7% in the 7vPnC group) being the most frequently reported AEs. T here was a statistically significant different between the 2 vaccine groups in the incidence of upper respiratory tract infection (p=0.012); however this finding involved a small number of subjects (2 subjects in the 13vPnC group (0.02%) and 11 subjects in the 7vPnC group (1.3%).

### 7.3.2. Treatment-related adverse events (adverse drug reactions)

#### *7.3.2.1. Pivotal study*

##### *7.3.2.1.1. After Vaccination*

The incidence of AEs related to vaccination occurring through approximately 1 month after vaccination was identical in Group 3 (3 subjects, 1.0%) and in Group 4 (3 subjects, 1.0%). The related AE of headache was reported by 2 subjects in Group 3 and by 2 subjects in Group 4. All other related AEs were reported by 1 subject in each group (diarrhoea, nausea, vomiting, pyrexia and pruritus, back pain, dizziness and nausea).

##### *7.3.2.1.2. 6-month follow-up*

There were no related AE reported in either group at the 6-month follow-up contact.

#### *7.3.2.2. Other studies*

##### *7.3.2.2.1. Study 6096A1-3010*

Treatment-related adverse events are not specified for this study.[11]

##### *7.3.2.2.2. Study 6096A1-3006*

In the infant series, the overall incidence of related AEs was similar in the 13vPnC group (28.7%) and the 7vPnC group (26.0%). The type of related AEs which occurred most frequently in both vaccine groups was general disorders and administration site conditions (22.0% in the 13vPnC group and 19.8% in the 7vPnC group). The most frequently reported related individual AEs were pyrexia (21.3% in the 13vPnC group and 19.2% in the 7vPnC group) and restlessness (10.4% in the 13vPnC group and 9.5% in the 7vPnC group).

In the toddler series, the overall incidence of related AEs was similar in the 13vPnC group (10.1%) and the 7vPnC group (9.3%) for the toddler dose. The most frequently reported types of AEs were in the category of General disorders and administration site conditions (9.2% in the 13vPnC group and 9.2% in the 7vPnC group). Pyrexia was the most commonly reported related individual AE in the 13vPnC group (8.7%) and the 7vPnC group (7.9%).

**Table 21: Related Adverse Events – *Infant Series***

| | 13vPnC (n = 930) | | | 7vPnC (n = 933) | | | |
|---|---|---|---|---|---|---|---|
| **System / Preferred Term** | **N** | **%** | **No. Events** | **N** | **%** | **No. Events** | **p-value** |
| Any event | 267 | 28.7 | 403 | 243 | 26.0 | 355 | 0.212 |
| Gastrointestinal disorders | 1 | 0.1 | 1 | 0 | 0.0 | 0 | 0.499 |
| (diarrhoea) | | | | | | | |
| General disorders | 205 | 22.0 | 272 | 185 | 19.8 | 251 | 0.255 |
| Injection site erythema | 4 | 0.4 | 4 | 2 | 0.2 | 2 | 0.452 |
| Injection site swelling | 14 | 1.5 | 14 | 10 | 1.1 | 11 | 0.421 |
| Pyrexia | 198 | 21.3 | 254 | 179 | 19.2 | 238 | 0.273 |
| Nervous system disorders | 5 | 0.5 | 5 | 2 | 0.2 | 2 | 0.287 |
| Febrile convulsion | 0 | 0.0 | 0 | 1 | 0.1 | 1 | >0.99 |
| Somnolence | 5 | 0.5 | 5 | 1 | 0.1 | 1 | 0.124 |
| Psychiatric disorders | 97 | 10.4 | 124 | 89 | 9.5 | 102 | 0.537 |
| (restlessness) | | | | | | | |
| Skin and subcutaneous tissue | 1 | 0.1 | 1 | 0 | 0.0 | 0 | 0.499 |
| (rash) | | | | | | | |

[11] Sponsor comment: "Related AEs were reported for the study. Majority occurred during infant series for Groups 1.2, and 3 and were all reports of fever. For Group 4, there was 1 related AE of rash."

**Table 22: Related Adverse Events – *Infant Series***

| | 13vPnC (n = 882) | | | 7vPnC (n = 875) | | | p-value |
|---|---|---|---|---|---|---|---|
| **Any event** | **89** | **10.1** | **98** | **81** | **9.3** | **86** | **0.573** |
| General disorders | 81 | 9.2 | 87 | 72 | 8.2 | 74 | 0.499 |
| Gait disturbance | 1 | 0.1 | 1 | 0 | 0.0 | 0 | >0.99 |
| Injection site erythema | 3 | 0.3 | 3 | 1 | 0.1 | 1 | 0.625 |
| Injection site swelling | 5 | 0.6 | 5 | 3 | 0.3 | 3 | 0.726 |
| Oedema peripheral | 1 | 0.1 | 1 | 1 | 0.1 | 1 | >0.99 |
| Pyrexia | 77 | 8.7 | 77 | 69 | 7.9 | 69 | 0.546 |
| Psychiatric disorders (restlessness) | 11 | 1.2 | 11 | 11 | 1.3 | 11 | >0.99 |
| Skin and subcutaneous tissue (rash) | 0 | 0.0 | 0 | 1 | 0.1 | 1 | 0.498 |

N = number of subjects reporting at least 1 event
No. Event = multiple events may be reported by 1 subject

Evaluator Comment: Studies 6096A1-3010 and 6096A1-3006 contain safety data for the <5 year age group. This data is not relevant to the extension of indications. No safety issue has been raised with the reported information.

### 7.3.3. Deaths and other serious adverse events

#### *7.3.3.1. Pivotal study*

There were no deaths. One (1) SAE was reported approximately 1 month after vaccination in Group 3. The subject reported severe appendicitis; it was not considered to be related to the vaccine. There were no SAE reported in Group 4 through to 1 month after vaccination. There was one SAE reported at the 6 month follow-up contact for 1 subject in Group 4 (moderate asthma) reported on Day 161. This SAE was not considered to be related to study vaccine. There were no SAE reported at 6 months for Group 3.

#### *7.3.3.2. Other studies*

##### *7.3.3.2.1. Study 6096A1-3010*

There were two deaths during the study in Group 1. One subject died 20 days after receiving 1 dose of 13vPnC. The death was attributed to cardio-pulmonary failure secondary to pneumonia. No autopsy was performed. The second death occurred 85 days after receiving 1 dose of 13vPnC. An autopsy was performed and the death was attributed to sudden infant death syndrome. Both deaths were considered by the investigator and medical monitors to be not related to the protocol or study vaccine.

One subjects in Group 1 experienced life-threatening hyponatraemia, convulsion and respiratory failure after dose 2. The SAEs were not considered related to vaccination. There were 36 SAEs reported in Group 1. The majority of SAEs were in the category Infections and infestations (pneumonia, RSV bronchiolitis, influenza, urinary tract infection) and convulsion.

Four (4) SAEs were reported in 2 (3.9%) subjects in Group 2; both SAEs were in the category of Infection and infestation. Four (4) SAEs were reported in Group 4. All SAEs were in the category of Infections and infestations (abscess, influenza, pneumonia) and Lymphatic disorders (lymphadenitis). There were no SAEs reported in group 5.

*7.3.3.2.2. Study 6096A1-3006*

There was one study death. One (1) subjects in the 13vPnC vaccine group died during the infant series. On Day 7 after dose 1 of the infant series, the subject died at home. The death certificate issued by a physician diagnosed sudden death of unknown cause. No autopsy was performed. The death was no considered related to study vaccine. Eleven SAEs were reported in subjects in Group 3. SAEs in the category of Infections and infestations, Respiratory, Thoracic and mediastinal disorders were seen.

Evaluator Comment: Studies 6096A1-3010 and 6096A1-3006 contain safety data for the <5 year age group. This data is not relevant to the extension of indications. No safety issue has been raised with the reported information.

### 7.3.4. Discontinuation due to adverse events

#### *7.3.4.1. Pivotal study*

There were no discontinuations.

#### *7.3.4.2. Other studies*

*7.3.4.2.1. Study 6096A1-3010*

In Group 1, 2 subjects died after receiving 1 dose of 13vPnC. One death occurred 20 days after vaccination, the other occurred 85 days after, by which time the subject was considered to be in the 6-month follow-up period. Neither death was considered to be vaccine related. Three (3) additional subjects in Group 1 were withdrawn from the study due to convulsions.

There were no discontinuations from vaccination or the study due to AEs in Groups 2, 3, 4 or 5.

*7.3.4.2.2. Study 6096A1-3006*

During the infant series, 5 subjects in the 13vPnC group and 6 subjects in the 7vPnC group experienced AEs that led to withdrawal from the study. None of the AEs that led to withdrawal were considered to be related to vaccine administration.

In the 13vPnC group, the AEs that led to withdrawal during the infant series included sudden death (1 subject), food allergy (1 subject), cardiac failure congestive (1 subject) and convulsion (2 subjects). In the 7vPnC group, AEs that led to withdrawal during the infant series included cerebral infarction (1 subject) and convulsion (2 subjects). With the expectation of food allergy, all met the criteria for SAEs. With the exception of sudden death and of cerebral infarction, all AEs that led to withdrawal resolved. Following the infant series six subjects were withdrawn for AEs (2 subjects, 13vPnC and 4 subjects, 7vPnC). None of the withdrawals were thought to be related to study vaccine. One subject from the 13vPnC group was withdrawn following the toddler series.

Evaluator Comment: Studies 6096A1-3010 and 6096A1-3006 contain safety data for the <5 year age group. This data is not relevant to the extension of indications. No safety issue has been raised with the reported information.

## 7.4. Laboratory tests

### 7.4.1. Haematology, liver function, kidney function, other chemical analysis

#### *7.4.1.1. Pivotal studies*

No data.

#### *7.4.1.2. Other studies*

No data.

## 7.5. Postmarketing experience

Two studies were presented in the sponsor's Clinical Safety Summary with postmarket data.

The ACTIV Surveillance Study is a national surveillance study of pneumococcal NP colonisation in children with acute otitis media (AOM). It was initiated in France with the licensing of 7cPnC and extended for 13vPnC which was introduced into France between June and September 2010.

The study enrolled 943 infants between October 2010 and May 2011 with AOM; 651 received at least 1 dose of 13vPnC and 285 received 7vPnC only; 7 children were not vaccinated.

Among children vaccinated with at least 1 dose of 13vPnC, overall pneumococcal colonisation and colonisation by the 6 additional serotypes not in 7vPnC were significantly lower when compared with that of children exclusively vaccinated with 7vPnC (53.9% versus 64.6%, p=0.002, and 9.5% versus 20.7%, p<0.001, respectively). There were also significantly lower colonisation rates of serotypes 19A, 7F and 6C.

The sponsor concludes that in young children (<2 years of age) with AOM 13vPnC has an impact on overall pneumococcal colonisation, as well colonisation of individual serotypes 19A, 7F and 6C.

A second postmarket study looked at NP colonisation in children <5 years in Atlanta, Georgia. NP colonisation was assessed prior to the introduction of 13vPnC (2009) and after vaccine introduction (July 2010-September 2011). A total of 776 children who presented to an emergency department were enrolled in the study. Results from 3 time periods were compared and susceptibility of isolates to antimicrobial agents were evaluated.

Prior to 13vPnC introduction 31% of children <5 years were colonised with *S. pneumoniae;* 22% of isolates were 13vPnC-type, mostly serotype 19A. Of the 776 children enrolled after 13vPnC introduction 225 (29%) were colonised with *S. pneumoniae,* with serotype 19A making up 18% of serotypes isolated. Overall *S. pneumoniae* colonisation rates were unchanged throughout the study but the rate of colonisation of serotype 19A declined from 26.7% (period 1) to 11.9% (period 2) to 4.4% (period 4), p=0.0047. Colonisation rates for 13vPnC serotypes combined declined significantly from 30% (period 1) to 15.3% (period 2) to 4.4% (period 3), p=0.0006.

The sponsor concludes that after introduction of 13vPnC, 13vPnC-ytpe serotypes significantly declined in young children, primarily due to a decline in serotype 19A.

The study was implemented in 2009, prior to the introduction of the 13vPnC vaccine. At baseline less than 31% of children were colonised with *S pneumoniae;* 22% of isolates were 13vPnC-type, mostly serotype 19A.

## 7.6. Evaluator's overall conclusions on clinical safety

Safety data is available from all three studies submitted with this application; however, only data from Study 6096A1-3011 (pivotal study) is relevant to the extension of age indication.

Study 6069A1-3011 was a phase-three open-label study.

Safety endpoints were assessed through an e-diary, filled out nightly for 7 days following vaccination and a 6 month follow-up telephone interview. There are numerous inherent problems with patient-reported outcome (PRO) data, particularly for its potential for selection bias. PRO and in particular e-diaries rely on patient motivation to obtain relevant outcome data; subjects with 'events' are more likely to report and therefore the potential for selection bias is high. Such selection bias would be more likely to favour 'adverse event' reporting so, if anything,

results would not favour the vaccine. In Study 6096A1-3011, this type of selection bias seems to have been minimised as there was 75% compliance with the e-diary with no obvious difference in reporting rates between groups.

Local reactions seem to have been consistent with known AE reporting across other vaccines.

Headaches and gastroenteritis seem to be rare, but important, adverse events associated with the vaccine in this age group. These events have been added to the PI for this age group which is appropriate.

Overall the safety evaluation for this vaccine in the age groups 5 to 18 years seems appropriate.

# 8. First round benefit-risk assessment

## 8.1. First round assessment of benefits

The benefits of an extension to the age indication are:

- Increased coverage for older children at increased risk of pneumococcal disease for example, children with predisposing medical conditions
- Increased coverage for older children in 'at risk' populations for example, Aboriginal and Torres Strait Islanders

## 8.2. First round assessment of risks

The risks of an extension of age indication:

- Burden of disease from pneumococcal disease less in older age groups; inherent risks of vaccination (local reactions, systemic reactions) may not be justified when underlying burden of disease so small
- Many children >10 years have already been exposed to pneumococcal serotypes present in 13vPnC vaccine. Immunogenicity data is therefore difficult to interpret.

## 8.3. First round assessment of benefit-risk balance

The benefit-risk balance of an extension of age indication, given the proposed usage, was favourable.

# 9. First round recommendation regarding authorisation

The evaluator recommended the extension of age indication for Prevenar 13.

There is insufficient evidence presented to show that Prevenar 13 reduces the rate of carriage of pneumococcal serotypes present in the 13vPnC vaccine. There is some evidence to suggest that 13vPnC vaccination prevents colonisation of 13vPnC. This statement was already provided in the PI; the evaluator's recommendation was that this statement *not* be changed to carriage.

# 10. Clinical questions

## 10.1. Immunogenicity

1. In the primary analysis the index group (Group 3) had significantly better GMC results compared to the Study 3005 7vPnC and 13vPnC GMC results. In all cases the ratio of geometric mean concentrations was substantially higher than the non-inferiority cut-off level of 0.5 (lower limit of the 2-sided 95% CI). Why does the 13vPnC vaccine seem to be performing so much better in this group of children, the expectation would be for the vaccines to be substantially equivalent?
2. Two different cohorts of children were used for the comparator in the primary analysis; what was the rationale behind this decision, why wasn't the Study 3005, 13vPnC population used for all serotypes? Please provide calculations and analysis of the 7vPnC serotypes with this group of children.
3. No power calculations were included in the sample size calculations for Study 3006. Please provide evidence that the study was adequately powered to detect a difference between groups.
4. All results from Study 3006 and 3010 relate to new NP acquisition of *S. pneumoniae* serotypes. What evidence is there to support the link between reduction in NP acquisition and reduction in NP carriage at a population level?
5. Study 3006 found a 3% difference between NP acquisition of Serotype 6A' or 19A (OR 0.6, 95%CI 0.5, 0.9), what is the clinical significance of this result?
6. Results from Study 3010 "Proportion of Carriage of Typeable Pneumococci Comprised of 6 Additional Serotypes in 13vPnC Children <5 Years of Age" and "Proportion of Carriage of Typeable Pneumococci Comprised of 6 Additional Serotypes in 13vPnC Adult Population" do not have reference ranges included. Please provide 95% CI reference ranges for the percentages provided for all years (March, 2010, 2008, 2009 and 2010).
7. For Study 3010, the comparison for pre and post-vaccine NP carriage rates for YK Delta adult cohort were made between the average of the 2008 to 2009 data and the 2010 data. What was the justification for performing the analysis this way?
8. The incidence of IPD in the YK Delta population dropped unexpectedly in 2009. This may have been due to natural annual variance. What is the likely effect or association of a decrease in seasonal IPD on the nasopharyngeal carriage rates of pneumococci?

# 11. Second round evaluation of clinical data submitted in response to questions

## 11.1. Question 1

*In the primary analysis the index group (Group 3) had significantly better GMC results compared to the study 3005 7vPnC and 13vPnC GMC results. In all cases the ratio of geometric mean concentrations was substantially higher than the non-inferiority cut-off level of 0.5 (lower limit of the 2 sides 95%CI). Why does the 13vPnC vaccine seem to be performing so much better in this group of children, the expectation would be for the vaccines to be substantially equivalent?*

The sponsor states that higher immune responses were seen in the index group as they were previously vaccinated with 7vPnC. In addition, higher immune responses in older children are expected due to a mature immune system.

The sponsor's answer provided adequate explanation for the difference in results seen.

### 11.2. Question 2

*Two different cohorts of children were used for the comparator in the primary analysis; what was the rationale behind this decision, why wasn't the Study 3005, 13vPnC population used for all serotypes? Please provide calculation and analysis of the 7vPvC serotypes with this group of children.*

The comparison with Study 3005 allowed bridging of the two populations (infants and children 6 weeks to 5 years) and represented the largest and most robust dataset for comparison with the infants and children vaccinated in Study 3011.

The sponsor's response was considered to be adequate.

### 11.3. Question 3

*No power calculations were included in the sample size calculations for Study 3006; please provide evidence that the study was adequately powered to detect a difference between groups.*

Power calculations are provided by the sponsor, sample sizes of 820 subjects per group would provide at least 90% power to show that the reduction of new acquisitions (6A and 19A combined) 1 year after the toddler dose in subjects receiving 13vPnC is statistically significantly greater than the reduction in subjects receiving 7vPnC, assuming a 2-sided type I error rate of 0.05 and a dropout rate of at most 12%.

**Table 23. Power to detect reduction in 6A or 19A carriage with type 1 error rate=0.05 and 820 subjects/group**

| Assumed Carriage Rate in 7vPnC | Power for Detecting Reduction of | | | |
|---|---|---|---|---|
| | 27.5% | 30% | 40% | 50% |
| 0.30 | 96% | 98 | >99% | >99% |
| 0.24 | **90%** | 94% | >99% | >99% |
| 0.2 | 82% | 88% | >99% | >99% |
| 0.15 | 67% | 75% | 95% | >99% |

### 11.4. Question 4

*All results from Study 3006 and 3010 related to NP acquisition of S. pneumoniae serotypes. What evidence is there to support the link between reduction in NP acquisition and reduction in NP carriage at a population level?*

The sponsor provided a recent paper[12] (Simell et al, 2012) that provides a review of the evidence supporting pneumococcal carriage at the individual level as an immediate and necessary precursor to pneumococcal disease. The review suggests that there is a casual link between carriage and disease.

The sponsor defines *acquisition* and *colonisation* in a similar manner to Simell et al. that is; *acquisition* is the time when a pneumococcal strain establishes itself within the host, and *ongoing NP colonisation* describes carriage.

According to the sponsor, Study 3006 showed significant reduction in NP acquisition. The impact of the vaccine on prevalence (carriage) was a significantly lower NP prevalence in the 13vPnC group than in the 7vPnC group for 6A, 6C and 19A combined. For single serotypes,

[12] Simell B et al (2012). The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines 11: 841-855.

13vPnC recipients had significantly lower levels of 6A and 19A. There was no statistically significant difference between the common serotypes, with the exception of serotype 19F which had a lower prevalence in the 13vPnC group compared with the 7vPnC group.

The sponsor concluded that *"a similar correlation between acquisition and carriage should exist in the general population with the use of 13vPnC in paediatric vaccination programs."*

Evaluator Comment: Study 3006 found that 13vPnC reduced the acquisition of serotypes, as well as, the ongoing prevalence of serotypes 6A, 6C and 19A combined, and serotype 19F at an individual level. Prevalence data was secondary analysis and the study was not powered to detect this result, however, the results support the hypothesis that a decrease in 13vPnC serotypes acquisition and carriage are both associated with Prevenar13.

Study 3010 suffered from poor study recruitment and results from this study should be seen as exploratory.

The post-market study, ACTIV, found a reduction in the carriage of 13vPnC serotypes in French children vaccinated exclusively with the 13vPnC vaccine compared to children exclusively vaccinated with the 7vPnC.

The sponsor asked the TGA to draw a link between the individual data provided in Study 3006 and the post-market population data provided in the ACTIV study. Drawing this link provides evidence that 13vPnC may reduce the carriage of serotypes 6A, 6C and 19A. This link is also supported by the article by Simell et al.[13] However, from the evidence provided the link should be considered as an association only and not a causal pathway.

### 11.5. Question 5

Question removed on agreement with sponsor and evaluator.

### 11.6. Question 6

*Results from Study 3010 "Proportion of Carriage of Typeable Pneumococci Comprised of 6 Additional Serotypes in 13vPnC children <5 Years of Age" and "Proportion of Carriage of Typeable Pneumococci Comprised of 6 Additional Serotypes in 13vPncC Adult Population" do not have reference ranges included. Please provide 95% CI reference ranges for the percentages provided for all years (March 2010, 2008, 2009 and 2010).*

The data was analysed by the CDC's Arctic Investigation Program and the summary provided to the sponsor did not contain the reference ranges and 95% CI requested by the evaluator.

### 11.7. Question 7

*For Study 3010, the comparison for pre and post-vaccine NP carriage rates for YK Delta adult cohort were made between the average of the 2008 to2009 data and the 2010 data. What was the justification for performing the analysis this way?*

The sponsor stated that averages were used to establish a stable baseline; however, it did not make a significant difference to the results due to low variability between 2008 and 2009 data.

[13] Simell B et al (2012). The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines 11: 841-855.

## 11.8. Question 8

*The incidence of IPD in the YK Delta population dropped unexpectedly in 2009. This may have been due to natural annual variance. What is the likely effect or association of a decrease in seasonal IPD on the nasopharyngeal rates of pneumococci?*

The sponsor suggested that seasonal differences were mitigated by conducting the cross-sectional carriage surveys annually at the same time, and in the same villages and clinic sites, where a cross section of the population was enrolled for NP swab collection. Data could then be compared to trends in serotype specific disease rates using the ongoing invasive pneumococcal disease (IPD) surveillance operated by CDC in Alaska.

Evaluator Comment: The effect of seasonal variation in disease may still have been a factor in the results presented in Study 3010, which compared only 4 years of data. Long-term trends will detect any seasonal variation in the Alaskan group over time (10 years), however, the potential interaction of seasonal variation and the vaccine effectiveness cannot be separated over such a short time period

## 11.9. Second round benefit-risk assessment

### 11.9.1. Second round assessment of benefits

The answers provided by the sponsor to questions raised at the end of Round 1 served to clarify the clinical trial data and did not affect the benefits previously described. Accordingly, the benefits of 13vPnC are unchanged from those identified in the *First Round Assessment of benefits*.

### 11.9.2. Second round assessment of risks

The answers provided by the sponsor to questions raised at the end of Round 1 served to clarify the clinical trial data and did not affect the benefits previously described. Accordingly, the risks of 13vPnC are unchanged from those identified in *First Round Assessment of risks*.

### 11.9.3. Second round assessment of benefit-risk balance

The benefit-risk balance of an extension of age indication, given the proposed usage, was considered to be favourable.

## 11.10. Second round recommendation regarding authorisation

The key immunogenicity findings presented show that for the age Group 10 to 17 years the 13vPnC is likely to be effective in eliciting an immune response to the 13vPnC serotypes. Many children in this age group are likely to have already come into contact with the serotypes present, however; children without previous contact are likely to mount a strong response to the serotypes. In addition, the safety profile of the vaccine in this age group shows that children aged 10 to 17 years may experience mild-moderate, self-limiting adverse events similar to those associated with many vaccines. The balance of risks to benefits of the vaccine is favourable and the evaluator recommended that the age indication be extended to include this age group.

The sponsor provided three studies to support their proposal to update the PI to introduce the concept that 13vPnC reduced NP disease by decreasing the NP carriage of 13vPnC serotypes. Study 3006 provides individual data showing that 13vPnC vaccination decreases acquisition of 6A, 6C and 19A combined individually and may decrease carriage of 13vPnC serotypes when compared to children vaccinated with 7vPnC. Study 3010 was intended to provide population data showing a link between vaccination and decreased carriage rates, however the study suffered from poor recruitment and the results reported should be considered exploratory only.

A post-market surveillance study shows reduction of 13vPnC serotype carriage in children with otitis media following the introduction of 13vPnC however, no individual data exists.

It was not clear to the evaluator whether individual data from one study and population data from a second is sufficient to draw a causal link between 13vPnC vaccine and carriage of 13vPnC serotypes. There is almost certainly an association between 13vPnC vaccine, acquisition of 13vPnC serotypes and carriage of 13vPnC serotypes. However, association does not prove causation and in the absence of more concrete data the evaluator was reluctant to approve the suggested PI changes.

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6232 8605
**http://www.tga.gov.au**