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Committee for Medicinal Products for Human Use (CHMP)

# CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended.

## Prevenar 13

(Pneumococcal saccharide conjugated vaccine, adsorbed)

Procedure No. EMEA/H/C/001104

P46 049 & 050

**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# I. INTRODUCTION

On August 7, 2012 the MAH submitted completed paediatric studies for Prevenar 13, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Prevenar 13 and that there is no consequential regulatory action.

# II. SCIENTIFIC DISCUSSION

## II.1 Information on the pharmaceutical formulation used in the studies

The formulation used in the studies was the same as the currently approved formulation

## II.2 Clinical aspects

### 1. Introduction

The MAH submitted final reports for:

- **6096A1-3024**: Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine Given With DTaP Compared to Open- Label DTaP in Healthy Japanese Infants
- **6096A1-1000**; A Phase 1 Open-label Study to Assess the Safety and Tolerability of a Single Dose of 13-valent Pneumococcal Conjugate Vaccine in Healthy Chinese Adults, Children and Infants.

### 2. Clinical studies

**6096A1-3024**: **Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine Given With DTaP Compared to Open- Label DTaP in Healthy Japanese Infants**

- **Description**

Study 6096A1-3024-JA (B1851056) was conducted in Japan and was a Phase 3, parallel-group, randomized, active-controlled, double-blind, multicenter trial in infants and toddlers to evaluate the immunogenicity, safety, and tolerability of subcutaneous 13vPnC given with diphtheria, tetanus, acellular pertussis vaccine (DTaP) compared to subcutaneous 7vPnC given with DTaP or DTaP alone in healthy infants. Subjects were randomized in a 1:1:1 ratio to receive 13vPnC and concomitant DTaP (Group 1), 7vPnC and concomitant DTaP (Group 2), or DTaP (Group 3).

- **Methods**

- Objective(s)

  Primary Immunologic Objectives:
  - To demonstrate that the immune responses to the 13 pneumococcal conjugates (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 13-valent pneumococcal conjugate vaccine (13vPnC) are noninferior to the immune responses induced by 7-valent pneumococcal conjugate vaccine (7vPnC) when measured 1 month after the infant series.
  - To assess whether the immune responses as measured by serum antibody responses to diphtheria toxoid, tetanus toxoid, pertussis toxoid (PT), and filamentous hemagglutinin (FHA) induced by diphtheria, tetanus, acellular pertussis vaccine (DTaP) given with 13vPnC were comparable to the immune responses induced by DTaP given alone when measured 1 month after the infant series.

  Primary Safety Objectives:

- To evaluate the acceptability of the safety profile of 13vPnC and 7vPnC given with DTaP as measured by the incidence rates of local reactions, systemic events, and adverse events (AEs).

Secondary:

- To demonstrate that the immune responses to the 13 pneumococcal conjugates (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 13vPnC are noninferior to the immune responses induced by 7vPnC when measured 1 month after the toddler dose.
- To describe antibody responses to the 13 pneumococcal conjugates after the toddler dose compared to antibody responses before the toddler dose and after the infant series within each of Groups 1 and 2.
- To assess whether the immune responses as measured by serum antibody responses to diphtheria toxoid, tetanus toxoid, PT, and FHA induced by DTaP given with 13vPnC were comparable to the immune responses induced by DTaP given alone when measured 1 month after the toddler dose.

Exploratory:

- In subjects that received ActHIB: To describe the immune responses as measured by serum antibody responses to Haemophilus influenza type b (Hib) induced by ActHIB given concomitantly with 13vPnC when measured 1 month after the infant series and after the toddler dose.

- Study design

This was a Phase 3, parallel-group, randomized, active-controlled, double-blind, multicenter trial to evaluate the immunogenicity, safety, and tolerability of 13vPnC given with DTaP compared to 7vPnC given with DTaP or DTaP alone in healthy infants.
Subjects were randomized in a 1:1:1 ratio to receive 13vPnC and concomitant DTaP, 7vPnC and concomitant DTaP, or DTaP. Administration of the pneumococcal conjugate vaccines (13vPnC and 7vPnC) in the 13vPnC+DTaP group and the 7vPnC+DTaP group was blinded due to the identical appearance of the vaccines. DTaP was administered open-label.
In this study, the subjects in the 13vPnC+DTaP, 7vPnC+DTaP and the DTaP groups received 3 doses of their assigned study vaccine during the infant series and another toddler dose. In the infant series, dose 1 of the study vaccines was given at 3 to 6 months of age, dose 2 of the study vaccines was given 4 to 8 weeks after dose 1, and dose 3 of the study vaccines was given 4 to 8 weeks after dose 2. The toddler dose of the study vaccines was given at 12 to 15 months of age. In addition, subjects in the DTaP group received 3 catch-up doses of Prevenar (commercial product of 7vPnC for Japan, with catch-up dose 1 given approximately 1 month after dose 3 of the infant series, catch-up dose 2 given approximately 1 month after catch-up dose 1, and catch-up dose 3 given approximately 1 month after the toddler dose.

- Study population /Sample size

  Main Criteria for Inclusion: Subjects eligible to participate in the study were healthy (as determined by medical history, physical examination, and judgment of the investigator) infants between ≥3 months and ≤6 months of age at the time of enrollment. Parent/legal guardian had to be able to complete all relevant study procedures during study participation, and was expected to be available for the duration of the trial.
  Subjects were ineligible to participate in the study if they had previously been vaccinated with any licensed or investigational pneumococcal, diphtheria, tetanus, or pertussis vaccine, had a previous anaphylactic reaction to any vaccine or vaccine-related component, contraindication to vaccination with a pneumococcal conjugate, diphtheria, tetanus, or pertussis vaccine, had a bleeding diathesis, had a known or suspected immune deficiency or suppression, had a history of culture-proven invasive disease caused by *S pneumoniae*, or had any of the other exclusion criteria specified in the protocol.

  Sample size was powered to confirm the noninferiority of immune responses to the 13 pneumococcal conjugates induced by 13vPnC relative to the immune responses induced by 7vPnC and was estimated based upon the proportions of responders for the pneumococcal serotypes for both the 7 common serotypes and the 6 additional serotypes and the IgG geometric mean concentration (GMC) ratio for the 7 common serotypes, which are referred

from the data for Wyeth studies 6096A1-3003-JA (Japan study), 6096A1-010-KP (Korea study), and 6096A1-3004-TW (Taiwan study).
A sample size of 160 evaluable subjects per group was estimated to provide at least 81% power to declare noninferiority for all primary endpoints (power = 0.932 * 0.923 * 0.94 = 0.809%). Assuming a dropout rate of about 10%, 178 subjects per group (534 total) were planned to be enrolled to ensure that 160 subjects per group were evaluable.
Sample size estimation was also considered to provide appropriate precision from the clinical viewpoint for the proportion of responders for each antigen induced by DTaP. Vaccination of 160 subjects in each group was to provide 7.0%, 6.5%, 5.7%, and 4.6% precision (the lower bound of the 2-sided 95% confidence interval [CI] is 73.0%, 78.5%, 84.3%, and 90.4%) from estimates of the proportion of responders of 80%, 85%, 90%, and 95%, respectively.

- Treatments
  Subjects received 1 dose of either 13vPnC+DTaP, 7vPnC+DTaP, or DTaP depending on treatment assignment at each of the 4 vaccination visits. Subjects in the DTaP group received 1 dose of Prevenar at each of the 3 catch-up dose vaccination visits.
  Investigational products were administered subcutaneously by injecting 0.5 mL at each dose. The pneumococcal conjugate vaccine (13vPnC, 7vPnC, or Prevenar) was administered in the left arm and DTaP was administered in the right arm.

- Outcomes/endpoints
  **Immunogenicity Evaluations**: Blood samples (approximately 5 mL) were collected before the first vaccination of investigational product, at 1 month (28 to 42 days) after the infant series, before the toddler dose, and 1 month (28 to 42 days) after the toddler dose.

  Pneumococcal antibody response was assessed in the 13vPnC+DTaP and 7vPnC+DTaP groups. Using enzyme-linked immunosorbent assay (ELISA), serum concentrations of anticapsular immunoglobulin G (IgG) that were elicited by each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and 7 pneumococcal serotypes (4, 6B, 7F, 9V, 14, 18C, 19F, and 23F) were determined in subjects for each blood sample. Assays of serum opsonophagocytic activity (OPA) that was elicited by the 13 pneumococcal serotypes were performed on blood samples obtained 1 month after the infant series and 1 month after the toddler dose for subjects with an adequate amount of serum. This study used the improved microcolony assay for determination of OPA. The new microcolony OPA (mcOPA) assay specified cutoff criteria for OPA assay data as the lower limit of quantification (LLOQ) for each serotype. In previous infant studies using the dribble OPA (dOPA) assay, an OPA serum response was determined using an OPA titer cut-off of 1:8 for all serotype-specific OPA assays. However, in both assay methods, an OPA titer is defined as the interpolated reciprocal serum dilution that results in complement mediated killing of 50% of the bacteria in each OPA assay.
  Antibody responses to the diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT and FHA) were measured in each serum sample for all 3 vaccine groups.

  **Safety Evaluations:**
  Local reactions (tenderness, redness, and swelling) at the site of injection of pneumococcal conjugate vaccine (13vPnC or 7vPnC) in the 13vPnC+DTaP and 7vPnC+DTaP groups and at the site of injection of DTaP in the DTaP group were monitored daily for 7 days after each vaccination in electronic diary (e-diary). Tenderness was recorded as no discernible tenderness, tenderness present, or tenderness interfered with limb movement. For redness and swelling, the parent/legal guardian measured the actual size of the reaction with a caliper. For analysis purposes, measurements recorded for redness and swelling were categorized as absent (no redness or swelling present), mild (1 to 4 caliper units), moderate (5 to 14 caliper units), or severe (>14 caliper units).

  Systemic events (fever, decreased appetite, irritability, increased sleep, decreased sleep, hives [urticaria], and the use of antipyretic medications to prevent or treat symptoms) were monitored daily for 7 days after each vaccination of investigational product (other than Prevenar for catch-up doses in the DTaP group) using an e-diary. Temperature was measured at bedtime daily and at any time during the 7 days that fever was suspected. Severity of fever was categorized as absent (<37.5°C), mild (☐37.5°C to ☐39.0°C), moderate >39.0°C to ☐40.0°C), or severe (☐40.0☐C) for analysis. Other systemic events were reported as present or absent.

Adverse events: AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The relation between an AE and study vaccine was categorized as related or not related. AE severity was categorized as mild, moderate, severe, or life threatening.

AEs were collected from the signing of the informed consent form (ICF) to at least 28 days after the administration of dose 3 of the infant series in all 3 vaccine groups and at least 28 days after the administration of catch-up dose 2 of 7vPnC in the DTaP group. AEs were also collected at the time of the toddler dose through at least 28 days after the toddler dose visit in all 3 vaccine groups and to at least 28 days after the administration of catch-up dose 3 of7vPnC in the DTaP group.

- Statistical Methods

  Immunogenicity Analysis Comparisons: To assess the pneumococcal immune responses induced by 13vPnC as measured by IgG concentrations, noninferiority comparisons were made directly between the 13vPnC+DTaP and 7vPnC+DTaP groups for the 7 serotypes common to 13vPnC and 7vPnC. For the 6 additional serotypes in 13vPnC, noninferiority comparisons were made between individual serotypes in the 13vPnC+DTaP group and the lowest response observed among the 7 common serotypes in the 7vPnC+DTaP group. For the 6 additional serotypes in 13vPnC, a direct comparison was also done to assess superiority. To assess the pneumococcal immune responses induced by 13vPnC as measured by OPA titers, the comparison was only constructed directly comparing 13vPnC+DTaP group to 7vPnC+DTaP group for all 13 serotypes.

  A primary immunological comparison for the pneumococcal conjugate vaccine was the proportion of subjects who achieved a serotype-specific IgG concentration ≥0.35 µg/mL 1 month after the infant series in subjects in the 13vPnC+DTaP group relative to the immune responses in subjects in the 7vPnC+DTaP group for the 7 common serotypes and the 6 additional serotypes. Another primary immunological comparison for the pneumococcal conjugate vaccine was the IgG geometric mean concentration (GMC) ratio 1 month after the infant series in subjects in the 13vPnC+DTaP group relative to the immune responses in subjects in the 7vPnC+DTaP group for the 7 common serotypes.

  A secondary immunological comparison was the IgG GMC ratio 1 month after the infant series in subjects in the 13vPnC+DTaP group relative to the immune responses in subjects in the 7vPnC+DTaP group for the 6 additional serotypes. Also, the comparisons of the proportion of subjects who achieved a serotype-specific IgG concentration ≥0.35 µg/mL and IgG GMC ratio 1 month after the toddler dose in subjects in the 13vPnC+DTaP group relative to the immune responses in subjects in the 7vPnC+DTaP group were secondary immunological comparisons.

  Other comparisons for 13vPnC+DTaP group relative to the immune responses in subjects in the 7vPnC+DTaP group were of the proportion of subjects with serotype-specific IgG concentration ≥0.15 µg/mL, the proportion of OPA titers ≥ the lower limit of quantification (LLOQ), and the geometric mean titers (GMTs) of OPA for each of the 13 serotypes.

  The immunological comparison of interest for diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT and FHA) was the responses in subjects in the 13vPnC+DTaP group relative to the responses in subjects in the DTaP group for each antigen following the infant series. The primary endpoints for diphtheria toxoid, tetanus toxoid, PT and FHA were the proportions of subjects achieving a predetermined antibody level measured 1 month after the infant series. Proportions were also calculated following the toddler dose. Antigen-specific GMCs/ GMTs after the infant series and after the toddler dose were also assessed.

  Immunogenicity Analysis Methods: Within each 13vPnC+DTaP group and 7vPnC+DTaP group, the GMCs of pneumococcal IgG and the GMTs of OPA were calculated. The IgG antibody concentrations and OPA antibody titers were logarithmically transformed for analysis. Two (2)-sided 95% confidence intervals (CIs) were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results, computed using the Student t distribution. IgG GMC ratios (13vPnC+DTaP / 7vPnC+DTaP) and their corresponding 2-sided 95% CIs will be calculated. The geometric mean fold rises (GMFRs) in IgG antibody concentration (measured from before the toddler dose to after the toddler dose and measured

after the infant series to after the toddler dose) and in OPA titres (measured from after the infant series to after the toddler dose) were summarized by geometric means and 95% CIs. For each serotype after infant series and after toddler dose, noninferiority was declared if the lower CI for the IgG GMC ratio was >0.5. Superiority was declared if the lower CI for the IgG GMC ratio was >1.0. Although not prespecified by the SAP or the protocol, the same criterion for superiority as was used in previous infant studies was used in this study.

Within each 13vPnC+DTaP group and 7vPnC+DTaP group, the proportion of subjects achieving an IgG concentration ≥0.35 µg/mL for each of the 13 pneumococcal serotypes was calculated for each serotypes and their exact, 2-sided 95% CIs for the proportions were calculated. The CI for the single proportions was computed using the F distribution. The differences in proportions (13vPnC+DTaP – 7vPnC+DTaP) and their corresponding 2-sided 95% CIs were calculated. For each serotype, noninferiority was declared if the lower CI for the difference was >-0.10. Superiority was declared if the lower CI for the difference was >0. Although not prespecified by the statistical analysis plan (SAP) or the protocol, the same criterion for superiority as was used in previous infant studies was used in this study.

Within each 13vPnC+DTaP group and 7vPnC+DTaP group, the LLOQ for OPA titers was used to compute the proportion of subjects with OPA titers ☐ LLOQ for each serotype, along with exact, 2-sided 95% CI.

Within each group and for each DTaP antigen separately, the proportion of subjects achieving at least a prespecified antibody concentration was computed for each blood sample. The prespecified antibody levels for each antigen are diphtheria 0.1 international unit (IU)/mL; tetanus, 0.01 IU/mL; PT, 5 ELISA units (EU)/mL; and FHA, 5 EU/mL. The differences in proportions (13vPnC+DTaP – DTaP) and their corresponding 2-sided 95% CIs were calculated after the infant series and after the toddler dose. Antigen-specific GMCs/ GMTs and their corresponding 2-sided 95% CIs were calculated after the infant series and the toddler dose.

- **Results**

  - Recruitment/ Number analysed
    Four (4) analysis populations were defined: evaluable infant immunogenicity, all available infant immunogenicity, evaluable toddler immunogenicity, and all-available toddler immunogenicity. The evaluable infant immunogenicity population was the primary immunogenicity analysis population in this study. The evaluable infant immunogenicity population comprised subjects who were eligible for the study, received all 3 study vaccinations with the correct study vaccine(s) for their group, had at least 1 valid and determinate assay result after the third vaccination, had their blood drawn after vaccination within the required time frame, and had no major protocol violations. The reasons for exclusion of subjects from the all-available infant and evaluable infant
    immunogenicity populations are presented in Table 21.

## Table 21. All-Available and Evaluable Immunogenicity Populations – Infant Series

| | Vaccine Group (as Randomized) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP | | 7vPnC+DTaP | | DTaP (Catch-up 7vPnC) | | Total | |
| | n[a] | % | n[a] | % | n[a] | % | n[a] | % |
| Randomized[b] | 183 | 100.0 | 184 | 100.0 | 184 | 100.0 | 551 | 100.0 |
| All-available infant immunogenicity population | 181 | 98.9 | 178 | 96.7 | 179 | 97.3 | 538 | 97.6 |
| Subjects excluded from the all-available infant immunogenicity population | 2 | 1.1 | 6 | 3.3 | 5 | 2.7 | 13 | 2.4 |
| Did not collect blood sample after the infant series | 2 | 1.1 | 5 | 2.7 | 3 | 1.6 | 10 | 1.8 |
| Randomized but not vaccinated | 0 | 0.0 | 1 | 0.5 | 1 | 0.5 | 2 | 0.4 |
| Did not ship the blood sample after the infant series, regardless of collection of the sample | 0 | 0.0 | 0 | 0.0 | 1 | 0.5 | 1 | 0.2 |
| Evaluable infant immunogenicity population | 177 | 96.7 | 176 | 95.7 | 175 | 95.1 | 528 | 95.8 |
| Subjects excluded from the evaluable infant immunogenicity population[c] | 6 | 3.3 | 8 | 4.3 | 9 | 4.9 | 23 | 4.2 |
| Not in all-available infant immunogenicity population | 2 | 1.1 | 6 | 3.3 | 5 | 2.7 | 13 | 2.4 |
| Blood draw <28 or >42 days after the infant series | 1 | 0.5 | 1 | 0.5 | 3 | 1.6 | 5 | 0.9 |
| Did not ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met, at the infant series | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 | 3 | 0.5 |
| Administration of nonlive vaccine within 7 days or live vaccine within 28 days before giving of test article vaccine(s) at the infant series | 1 | 0.5 | 0 | 0.0 | 0 | 0.0 | 1 | 0.2 |
| At least one vaccination of the pneumococcal conjugate vaccine with less than 0.5 mL at the infant series | 1 | 0.5 | 0 | 0.0 | 0 | 0.0 | 1 | 0.2 |
| Use of blood products or gamma-globulin (including hepatitis B immunoglobulin and monoclonal antibodies, eg, Synagis) at the infant series | 0 | 0.0 | 0 | 0.0 | 1 | 0.5 | 1 | 0.2 |

a. n = Number of subjects with the specified characteristic.
b. The values in this row are used as the denominators for percentages.
c. Subjects may have been excluded for more than 1 reason.

The evaluable toddler immunogenicity population comprised subjects who were eligible for the study, received all 4 study vaccinations with the correct study vaccine(s) for their group, had at least 1 valid and determinate assay result after the fourth vaccination, had their blood drawn after vaccination within the required time frame, and had no major protocol violations. The reasons for exclusion of subjects from the all-available toddler and evaluable toddler immunogenicity populations are presented in Table 22.

**Table 22. All-Available and Evaluable Immunogenicity Populations – Toddler Dose**

| | Vaccine Group (as Randomized) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP | | 7vPnC+DTaP | | DTaP (Catch-up 7vPnC) | | Total | |
| | n[a] | % | n[a] | % | n[a] | % | n[a] | % |
| Randomized[b] | 183 | 100.0 | 184 | 100.0 | 184 | 100.0 | 551 | 100.0 |
| All-available toddler immunogenicity population | 162 | 88.5 | 162 | 88.0 | 169 | 91.8 | 493 | 89.5 |
| Subjects excluded from the all-available toddler immunogenicity population | 21 | 11.5 | 22 | 12.0 | 15 | 8.2 | 58 | 10.5 |
| Did not collect blood sample after the toddler dose | 21 | 11.5 | 21 | 11.4 | 14 | 7.6 | 56 | 10.2 |
| Randomized but not vaccinated | 0 | 0.0 | 1 | 0.5 | 1 | 0.5 | 2 | 0.4 |
| Evaluable toddler immunogenicity population | 158 | 86.3 | 155 | 84.2 | 163 | 88.6 | 476 | 86.4 |
| Subjects excluded from the evaluable toddler immunogenicity population[c] | 25 | 13.7 | 29 | 15.8 | 21 | 11.4 | 75 | 13.6 |
| Not in all-available toddler immunogenicity population | 21 | 11.5 | 22 | 12.0 | 15 | 8.2 | 58 | 10.5 |
| Did not collect blood sample for post-toddler dose <28 or >42 days after the toddler dose[d] | 0 | 0.0 | 5 | 2.7 | 4 | 2.2 | 9 | 1.6 |
| Did not receive toddler vaccination at 12 to 15 months of age | 2 | 1.1 | 1 | 0.5 | 2 | 1.1 | 5 | 0.9 |
| Did not ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met, at the infant series | 1 | 0.5 | 1 | 0.5 | 0 | 0.0 | 2 | 0.4 |
| Administration of nonlive vaccine within 7 days or live vaccine within 28 days before giving of test article vaccine(s) at the infant series | 1 | 0.5 | 0 | 0.0 | 0 | 0.0 | 1 | 0.2 |

a. n = Number of subjects with the specified characteristic.
b. The values in this row are used as the denominators for percentages.
c. Subjects may have been excluded for more than 1 reason.
d. Not within protocol-specified time frame

The demographic characteristics of the evaluable infant and toddler populations were similar to those of all subjects with respect to sex, race, racial designation, and weight at enrollment. The mean ages were 4.1 months at dose 1, 5.2 months at dose 2, and 6.4 months at dose 3. The mean age at the toddler dose was 13.4 months.

- Efficacy results

  Infant series

  Before vaccination, the percentage of subjects with IgG concentrations ≥0.35 µg/mL for the 7 common serotypes ranged from 0.6% (serotype 4) to 33.9% (serotype 14) in the 13vPnC+DTaP group and ranged from 0.6% (serotype 4) to 27.8% (serotype 14) in the 7vPnC+DTaP group. Before vaccination, the percentage of subjects with IgG concentrations ≥0.35 µg/mL for the 6 additional serotypes ranged from 1.1% (serotype 1) to 41.5% (serotype 19A) in the 13vPnC+DTaP group and ranged from 1.1% (serotype 1) to 43.2% (serotype 19A) in the 7vPnC+DTaP group.

  The direct comparison of the proportion of subjects who achieved IgG concentrations ≥0.35 µg/mL 1 month after the infant series between subjects who received 13vPnC+DTaP and subjects who received 7vPnC+DTaP is presented in Table 23 for the evaluable infant immunogenicity population. The noninferiority criterion was met for all 7 common serotypes.

**Table 23. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Infant Series – Evaluable Infant Immunogenicity Population**

| | Vaccine Group (as Randomized) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | | 7vPnC+DTaP (Group 2) | | | | Difference Group 1 – Group 2 | |
| Serotype | N[a] | n[b] | % | (95% CI[c]) | N[a] | n[b] | % | (95% CI[c]) | Difference[d] | (95% CI[e]) |
| 7vPnC | | | | | | | | | | |
| 4 | 174 | 174 | 100.0 | (97.9, 100.0) | 176 | 176 | 100.0 | (97.9, 100.0) | 0.0 | (-2.2, 2.1) |
| 6B | 177 | 173 | 97.7 | (94.3, 99.4) | 176 | 175 | 99.4 | (96.9, 100.0) | -1.7 | (-5.2, 1.1) |
| 9V | 175 | 175 | 100.0 | (97.9, 100.0) | 176 | 176 | 100.0 | (97.9, 100.0) | 0.0 | (-2.1, 2.1) |
| 14 | 176 | 176 | 100.0 | (97.9, 100.0) | 176 | 176 | 100.0 | (97.9, 100.0) | 0.0 | (-2.1, 2.1) |
| 18C | 176 | 176 | 100.0 | (97.9, 100.0) | 174 | 174 | 100.0 | (97.9, 100.0) | 0.0 | (-2.1, 2.2) |
| 19F | 177 | 175 | 98.9 | (96.0, 99.9) | 175 | 169 | 96.6 | (92.7, 98.7) | 2.3 | (-1.1, 6.3) |
| 23F | 176 | 172 | 97.7 | (94.3, 99.4) | 175 | 172 | 98.3 | (95.1, 99.6) | -0.6 | (-4.2, 2.9) |
| Additional | | | | | | | | | | |
| 1 | 176 | 176 | 100.0 | (97.9, 100.0) | 172 | 2 | 1.2 | (0.1, 4.1) | 98.8 | (95.9, 99.9) |
| 3 | 177 | 176 | 99.4 | (96.9, 100.0) | 156 | 7 | 4.5 | (1.8, 9.0) | 94.9 | (90.4, 97.8) |
| 5 | 177 | 176 | 99.4 | (96.9, 100.0) | 158 | 125 | 79.1 | (71.9, 85.2) | 20.3 | (14.2, 27.4) |
| 6A | 177 | 174 | 98.3 | (95.1, 99.6) | 174 | 141 | 81.0 | (74.4, 86.6) | 17.3 | (11.3, 23.9) |
| 7F | 176 | 176 | 100.0 | (97.9, 100.0) | 124 | 15 | 12.1 | (6.9, 19.2) | 87.9 | (80.8, 93.1) |
| 19A | 177 | 177 | 100.0 | (97.9, 100.0) | 176 | 171 | 97.2 | (93.5, 99.1) | 2.8 | (0.5, 6.5) |

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, Group 1 (13vPnC+DTaP) – Group 2 (7vPnC+DTaP), expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, Group 1 (13vPnC+DTaP) – Group 2 (7vPnC+DTaP), expressed as a percentage.

When comparing the proportions of subjects who achieved IgG concentrations ≥0.35 µg/mL for the 6 additional serotypes 1 month after the 13vPnC+DTaP infant series to the lowest response observed among the 7 common serotypes in the 7vPnC+DTaP (96.6% for serotype 19F) the noninferiority criterion was met for all of the 6 additional serotypes.

The direct comparison of IgG GMCs 1 month after the infant series between subjects who received 13vPnC+DTaP and subjects who received 7vPnC+DTaP is presented in Table 25 for the evaluable infant immunogenicity population. For the 7 common serotypes, the IgG GMCs were numerically lower in the 13vPnC+DTaP group than in the 7vPnC+DTaP group. However, the noninferiority criterion was met for all 7 common serotypes (lower limit of the 95% CI for the ratio >0.5).

**Table 25. Comparison of Pneumococcal IgG GMCs (µg/mL) After Infant Series – Evaluable Infant Immunogenicity Population**

| | Vaccine Group (as Randomized) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | Ratio Group 1 / Group 2 | |
| Serotype | n[a] | GMC[b] | (95% CI[c]) | n[a] | GMC[b] | (95% CI[c]) | Ratio[d] | (95% CI[e]) |
| 7vPnC | | | | | | | | |
| 4 | 174 | 9.40 | (8.48, 10.41) | 176 | 11.54 | (10.51, 12.67) | 0.81 | (0.71, 0.94) |
| 6B | 177 | 4.50 | (3.90, 5.21) | 176 | 5.71 | (4.93, 6.63) | 0.79 | (0.64, 0.97) |
| 9V | 175 | 5.04 | (4.52, 5.62) | 176 | 6.80 | (6.15, 7.52) | 0.74 | (0.64, 0.86) |
| 14 | 176 | 13.86 | (12.16, 15.80) | 176 | 16.79 | (15.03, 18.76) | 0.83 | (0.70, 0.98) |
| 18C | 176 | 5.30 | (4.75, 5.91) | 174 | 7.26 | (6.53, 8.08) | 0.73 | (0.63, 0.85) |
| 19F | 177 | 7.37 | (6.43, 8.46) | 175 | 8.38 | (7.17, 9.80) | 0.88 | (0.72, 1.08) |
| 23F | 176 | 3.64 | (3.16, 4.19) | 175 | 4.53 | (3.96, 5.18) | 0.80 | (0.66, 0.98) |
| Additional | | | | | | | | |
| 1 | 176 | 8.14 | (7.23, 9.18) | 172 | 0.03 | (0.02, 0.03) | 294.73 | (243.62, 356.57) |
| 3 | 177 | 4.90 | (4.43, 5.42) | 156 | 0.04 | (0.03, 0.05) | 132.55 | (106.35, 165.21) |
| 5 | 177 | 4.64 | (4.14, 5.20) | 158 | 0.94 | (0.79, 1.13) | 4.92 | (4.00, 6.04) |
| 6A | 177 | 4.71 | (4.15, 5.34) | 174 | 1.11 | (0.94, 1.32) | 4.23 | (3.42, 5.23) |
| 7F | 176 | 8.26 | (7.45, 9.17) | 124 | 0.08 | (0.06, 0.10) | 102.74 | (81.87, 128.93) |
| 19A | 177 | 8.56 | (7.67, 9.56) | 176 | 1.23 | (1.10, 1.38) | 6.94 | (5.92, 8.14) |

a. n = Number of subjects with a determinate IgG antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs, Group 1 (13vPnC+DTaP) to Group 2 (7vPnC+DTaP).
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 [13vPnC+DTaP] – Group 2 [7vPnC+DTaP]).

The direct comparison of OPA GMTs 1 month after the infant series between subjects who received 13vPnC+DTaP and subjects who received 7vPnC+DTaP is presented in Table 27 for the evaluable infant immunogenicity population. Although functional antibody response was intended to be descriptive and was not prespecified as a criterion of comparison, the lower limits of the 95% CI of GMRs exceeded 0.5 for all 7 common serotypes. In addition, the immune response was statistically significantly greater (lower limit of the 95% CI for the ratio >1.0) in the 13vPnC+DTaP group than in the 7vPnC+DTaP group for 2 of the 7 common serotypes (serotypes 6B and 19F). After the infant series, the majority of subjects achieved an OPA titer ≥ LLOQ for the 7 common serotypes in the 13vPnC+DTaP group (91.3% [serotype 9V] to 100% [serotypes 4, 14, and 18C]) and the 7vPnC+DTaP group (89.5% [serotype 19F] to 100% [serotypes 4 and 18C]). The differences in proportion of responders (13vPnC+DTaP – 7vPnC+DTaP) to each of the 7 common serotypes ranged from -1.8% (serotype 9V) to 9.8% (serotype 19F). Although functional antibody response was intended to be descriptive and was not prespecified as a criterion of comparison, the lower limits of the 95% CI exceeded –10% for all 7 common serotypes. In addition, the immune response in the 13vPnC+DTaP group was statistically significantly greater (lower limit of the 95% CI for the difference in proportions >0) than in the 7vPnC+DTaP group for serotype 19F.

**Table 27. Comparison of Pneumococcal OPA GMTs (titer) After Infant Series – Evaluable Infant Immunogenicity Population**

| | Vaccine Group (as Randomized) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | Ratio Group 1 / Group 2 | |
| Serotype | n[a] | GMT[b] | (95% CI[c]) | n[a] | GMT[b] | (95% CI[c]) | Ratio[d] | (95% CI[e]) |
| 7vPnC | | | | | | | | |
| 4 | 149 | 1298 | (1142.5, 1475.6) | 144 | 1242 | (1095.7, 1407.5) | 1.0 | (0.87, 1.25) |
| 6B | 139 | 4338 | (3504.0, 5370.0) | 132 | 2854 | (2104.5, 3870.3) | 1.5 | (1.05, 2.19) |
| 9V | 138 | 906 | (662.9, 1237.4) | 130 | 904 | (678.7, 1205.3) | 1.0 | (0.66, 1.53) |
| 14 | 149 | 3530 | (3041.5, 4097.3) | 142 | 4070 | (3399.1, 4873.5) | 0.9 | (0.69, 1.09) |
| 18C | 141 | 7414 | (6564.2, 8373.3) | 139 | 7240 | (6320.1, 8293.4) | 1.0 | (0.85, 1.23) |
| 19F | 136 | 470 | (397.2, 556.6) | 133 | 201 | (154.0, 261.4) | 2.3 | (1.72, 3.20) |
| 23F | 135 | 1944 | (1543.6, 2447.2) | 132 | 2103 | (1682.2, 2628.3) | 0.9 | (0.67, 1.27) |
| Additional | | | | | | | | |
| 1 | 174 | 186 | (161.9, 214.5) | 174 | 4 | (3.9, 4.2) | 45.9 | (39.80, 53.00) |
| 3 | 154 | 263 | (234.7, 293.8) | 156 | 4 | (4.0, 4.6) | 60.9 | (53.50, 69.34) |
| 5 | 172 | 128 | (111.4, 146.8) | 173 | 4 | NE | 32.0 | (27.86, 36.66) |
| 6A | 147 | 4882 | (4206.4, 5665.3) | 138 | 456 | (301.0, 691.3) | 10.7 | (6.97, 16.44) |
| 7F | 171 | 4224 | (3847.2, 4638.7) | 153 | 7 | (5.5, 9.9) | 570.7 | (425.99, 764.67) |
| 19A | 172 | 557 | (493.1, 628.9) | 167 | 9 | (7.3, 12.0) | 59.8 | (45.42, 78.70) |

Abbreviation: NE = Not estimable.

a. n = Number of subjects with a determinate OPA antibody titer for the specified serotype.

b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.

c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

d. Ratio of GMTs, Group 1 (13vPnC+DTaP) to Group 2 (7vPnC+DTaP).

e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 [13vPnC+DTaP] – Group 2 [7vPnC+DTaP]).

Toddler dose

Before the toddler dose, the percentage of subjects with IgG concentrations ≥0.35 µg/mL for the 7 common serotypes ranged from 84.2% (serotype 18C) to 97.5% (serotype 19F) in the 13vPnC+DTaP group and ranged from 83.0% (serotype 23F) to 98.7% (serotypes 4 and 14) in the 7vPnC+DTaP group. Before the toddler dose, the percentage of subjects with IgG concentrations ≥0.35 µg/mL for the 6 additional serotypes ranged from 72.2% (serotype 3) to 99.4% (serotypes 5 and 6A) in the 13vPnC+DTaP group and ranged from 1.3% (serotype 1) to 84.9% (serotype 19A) in the 7vPnC+DTaP group.

The direct comparison of the proportion of subjects who achieved IgG concentrations ≥0.35 µg/mL 1 month after the toddler dose between subjects who received 13vPnC+DTaP and subjects who received 7vPnC+DTaP is presented in Table 29 for the evaluable toddler immunogenicity population. The noninferiority criterion was met for all 7 common serotypes.

**Table 29. Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL After Toddler Dose – Evaluable Toddler Immunogenicity Population**

| | Vaccine Group (as Randomized) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | | 7vPnC+DTaP (Group 2) | | | | Difference Group 1 – Group 2 | |
| Serotype | N[a] | n[b] | % | (95% CI[c]) | N[a] | n[b] | % | (95% CI[c]) | Difference[d] | (95% CI[e]) |
| 7vPnC | | | | | | | | | | |
| 4 | 158 | 158 | 100.0 | (97.7, 100.0) | 154 | 154 | 100.0 | (97.6, 100.0) | 0.0 | (-2.4, 2.4) |
| 6B | 157 | 157 | 100.0 | (97.7, 100.0) | 153 | 153 | 100.0 | (97.6, 100.0) | 0.0 | (-2.4, 2.4) |
| 9V | 158 | 158 | 100.0 | (97.7, 100.0) | 153 | 153 | 100.0 | (97.6, 100.0) | 0.0 | (-2.4, 2.4) |
| 14 | 157 | 157 | 100.0 | (97.7, 100.0) | 152 | 152 | 100.0 | (97.6, 100.0) | 0.0 | (-2.4, 2.4) |
| 18C | 158 | 158 | 100.0 | (97.7, 100.0) | 151 | 151 | 100.0 | (97.6, 100.0) | 0.0 | (-2.4, 2.4) |
| 19F | 158 | 156 | 98.7 | (95.5, 99.8) | 154 | 153 | 99.4 | (96.4, 100.0) | -0.6 | (-3.9, 2.4) |
| 23F | 157 | 157 | 100.0 | (97.7, 100.0) | 153 | 153 | 100.0 | (97.6, 100.0) | 0.0 | (-2.4, 2.4) |
| Additional | | | | | | | | | | |
| 1 | 156 | 155 | 99.4 | (96.5, 100.0) | 149 | 5 | 3.4 | (1.1, 7.7) | 96.0 | (91.4, 98.5) |
| 3 | 158 | 157 | 99.4 | (96.5, 100.0) | 147 | 15 | 10.2 | (5.8, 16.3) | 89.2 | (82.9, 93.7) |
| 5 | 158 | 158 | 100.0 | (97.7, 100.0) | 153 | 133 | 86.9 | (80.5, 91.8) | 13.1 | (8.2, 19.5) |
| 6A | 157 | 157 | 100.0 | (97.7, 100.0) | 152 | 147 | 96.7 | (92.5, 98.9) | 3.3 | (0.6, 7.5) |
| 7F | 158 | 158 | 100.0 | (97.7, 100.0) | 103 | 18 | 17.5 | (10.7, 26.2) | 82.5 | (73.8, 89.3) |
| 19A | 158 | 158 | 100.0 | (97.7, 100.0) | 155 | 151 | 97.4 | (93.5, 99.3) | 2.6 | (0.1, 6.5) |

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.
d. Difference in proportions, Group 1 (13vPnC+DTaP) – Group 2 (7vPnC+DTaP), expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, Group 1 (13vPnC+DTaP) – Group 2 (7vPnC+DTaP), expressed as a percentage.

The direct comparison of IgG GMCs 1 month after the toddler dose between subjects who received 13vPnC+DTaP and subjects who received 7vPnC+DTaP is presented in Table 31 for the evaluable toddler immunogenicity population. For 5 of the 7 common serotypes (all except serotypes 6B and 19F), the IgG GMCs were numerically lower in the 13vPnC+DTaP group than in the 7vPnC+DTaP group. However, the noninferiority criterion was met for all 7 common serotypes.

**Table 31. Comparison of Pneumococcal IgG GMCs (µg/mL) After Toddler Dose – Evaluable Toddler Immunogenicity Population**

| | Vaccine Group (as Randomized) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | Ratio Group 1 / Group 2 | |
| Serotype | n[a] | GMC[b] | (95% CI[c]) | n[a] | GMC[b] | (95% CI[c]) | Ratio[d] | (95% CI[e]) |
| 7vPnC | | | | | | | | |
| 4 | 158 | 15.34 | (13.23, 17.79) | 154 | 16.35 | (14.19, 18.83) | 0.94 | (0.77, 1.15) |
| 6B | 157 | 17.05 | (14.47, 20.08) | 153 | 13.91 | (11.93, 16.21) | 1.23 | (0.98, 1.53) |
| 9V | 158 | 7.00 | (6.11, 8.03) | 153 | 8.64 | (7.54, 9.89) | 0.81 | (0.67, 0.98) |
| 14 | 157 | 19.70 | (17.69, 21.93) | 152 | 20.69 | (18.25, 23.47) | 0.95 | (0.81, 1.12) |
| 18C | 158 | 8.10 | (6.94, 9.47) | 151 | 9.88 | (8.64, 11.30) | 0.82 | (0.67, 1.01) |
| 19F | 158 | 16.73 | (14.20, 19.71) | 154 | 9.55 | (8.11, 11.26) | 1.75 | (1.39, 2.21) |
| 23F | 157 | 8.64 | (7.46, 10.01) | 153 | 10.00 | (8.61, 11.62) | 0.86 | (0.70, 1.07) |
| Additional | | | | | | | | |
| 1 | 156 | 13.96 | (11.94, 16.31) | 149 | 0.03 | (0.03, 0.04) | 406.19 | (318.76, 517.60) |
| 3 | 158 | 2.48 | (2.17, 2.85) | 147 | 0.07 | (0.06, 0.09) | 33.16 | (25.36, 43.37) |
| 5 | 158 | 11.10 | (9.83, 12.53) | 153 | 1.13 | (0.95, 1.34) | 9.82 | (7.99, 12.09) |
| 6A | 157 | 15.17 | (13.31, 17.30) | 152 | 2.98 | (2.45, 3.62) | 5.10 | (4.04, 6.44) |
| 7F | 158 | 10.90 | (9.54, 12.45) | 103 | 0.11 | (0.08, 0.14) | 102.00 | (78.27, 132.92) |
| 19A | 158 | 16.02 | (14.07, 18.25) | 155 | 2.31 | (2.01, 2.65) | 6.95 | (5.75, 8.39) |

a. n = Number of subjects with a determinate IgG antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs, Group 1 (13vPnC+DTaP) to Group 2 (7vPnC+DTaP).
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 [13vPnC+DTaP] – Group 2 [7vPnC+DTaP]).

*Assessor's comment: The response to serotype 3 in the 13vPnC+DTaT group was lower following the toddler dose compared to the response to the infant series, in contrast to all other serotypes.*

The direct comparison of OPA GMTs 1 month after the toddler dose between subjects who received 13vPnC+DTaP and subjects who received 7vPnC+DTaP is presented in Table 37 for the evaluable toddler immunogenicity population. Although functional antibody response was intended to be descriptive and was not prespecified as a criterion of comparison, the lower limits of the 95% CI of GMRs exceeded 0.5 for all 7 common serotypes. In addition, the immune response was statistically significantly greater (lower limit of the 95% CI for the ratio in GMCs >1.0) in the 13vPnC+DTaP group than in the 7vPnC+DTaP group for common serotype 19F.

**Table 37. Comparison of Pneumococcal OPA GMTs (titer) After Toddler Dose – Evaluable Toddler Immunogenicity Population**

| | Vaccine Group (as Randomized) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | Ratio Group 1 / Group 2 | |
| Serotype | n[a] | GMT[b] | (95% CI[c]) | n[a] | GMT[b] | (95% CI[c]) | Ratio[d] | (95% CI[e]) |
| 7vPnC | | | | | | | | |
| 4 | 136 | 2061 | (1746.0, 2433.6) | 137 | 1935 | (1640.8, 2281.7) | 1.1 | (0.84, 1.34) |
| 6B | 141 | 5310 | (4237.1, 6654.4) | 142 | 4556 | (3413.5, 6081.7) | 1.2 | (0.81, 1.68) |
| 9V | 138 | 2855 | (2455.1, 3319.9) | 137 | 2674 | (2321.0, 3079.7) | 1.1 | (0.87, 1.31) |
| 14 | 142 | 2840 | (2429.6, 3320.0) | 139 | 2833 | (2442.1, 3285.8) | 1.0 | (0.81, 1.24) |
| 18C | 136 | 11457 | (9603.4, 13668.2) | 138 | 12308 | (10501.7, 14426.0) | 0.9 | (0.74, 1.18) |
| 19F | 137 | 1053 | (876.7, 1265.7) | 133 | 399 | (310.9, 512.4) | 2.6 | (1.94, 3.59) |
| 23F | 144 | 3289 | (2717.2, 3981.7) | 143 | 3921 | (3157.2, 4870.4) | 0.8 | (0.63, 1.12) |
| Additional | | | | | | | | |
| 1 | 137 | 461 | (388.7, 547.0) | 140 | 4 | (3.9, 4.4) | 111.2 | (93.30, 132.61) |
| 3 | 129 | 354 | (321.4, 391.0) | 138 | 6 | (5.1, 7.2) | 58.7 | (48.10, 71.55) |
| 5 | 143 | 178 | (147.4, 214.3) | 143 | 4 | (3.9, 4.2) | 43.6 | (36.03, 52.70) |
| 6A | 135 | 5799 | (4938.7, 6808.4) | 135 | 1047 | (711.2, 1542.0) | 5.5 | (3.65, 8.40) |
| 7F | 130 | 2990 | (2593.2, 3447.8) | 132 | 7 | (5.3, 10.1) | 407.1 | (286.66, 578.09) |
| 19A | 139 | 1287 | (1109.0, 1494.1) | 138 | 24 | (17.3, 34.5) | 52.7 | (36.27, 76.61) |

a. n = Number of subjects with a determinate OPA antibody titer for the specified serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.
d. Ratio of GMTs, Group 1 (13vPnC+DTaP) to Group 2 (7vPnC+DTaP).
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 [13vPnC+DTaP] – Group 2 [7vPnC+DTaP]).

*Assessor's comment: The lower IgG GMT response to serotype 3 following the toddler dose compared to the response to the infant series was not seen for the OPA GMTs.*

After the toddler dose, the majority of subjects achieved an OPA titer ≥ LLOQ for the 7 common serotypes in the 13vPnC+DTaP group (98.6% [serotype 6B] to 100%) [serotypes 4, 9V, 14, and 18C]) and the 7vPnC+DTaP group (95.5% [serotype 19F] to 100%).% [serotypes 4, 9V, 14, and 18C]). The differences in proportion of responders (13vPnC – 7vPnC) to each of the 7 common serotypes ranged from 0.0% (serotypes 4, 9V, 14 and 18C) to 3.8% (serotype 19F). Although functional antibody response was intended to be descriptive and was not prespecified as a criterion of comparison, the lower limits of the 95% CI for the differences in proportion of responders exceeded –10% for all 7 common serotypes.

After the toddler dose, the majority of subjects achieved an OPA titer ≥ LLOQ for the 6 additional serotypes in the 13vPnC+DTaP group (95.1% [serotype 5] to 100% [serotypes 1, 3, 6A, 7F, and 19A]). After the toddler dose, the percentage of subjects achieving an OPA titer ≥ LLOQ for the 6 additional serotypes ranged from 0.7% (serotype 5) to 88.9% (serotype 6A) in the 7vPnC+DTaP group. The differences in proportion of responders (13vPnC+DTaP – 7vPnC+DTaP) to each of the 6 additional serotypes ranged from 11.1% (serotype 6A) to 98.6% (serotype 1). The immune response in the 13vPnC+DTaP group was statistically significantly greater (lower limit of the 95% CI for the difference in proportions >0) than in the 7vPnC+DTaP group for all 6 additional serotypes. In the 7vPnC+DTaP group, there was a high

percentage of subjects achieving an OPA titer ≥ LLOQ (88.9%) for serotype 6A, consistent with crossreactivity of functional antibody response between serotypes 6A and 6B.

Concomitant Vaccine Antibody Response (DTaP Antigens)

The GMCs for diphtheria toxoid, tetanus toxoid, PT, and FHA measured 1 month after the infant series are presented in Table 42 for the evaluable infant immunogenicity population. All subjects in the 13vPnC+DTaP, 7vPnC+DTaP, and the DTaP groups had the prespecified antibody level after the infant series for tetanus in the evaluable infant immunogenicity population. All subjects in the 3 groups also had the prespecified antibody level for tetanus before the infant series, so there was no change in immune response to be detected. The majority of subjects achieved the prespecified level after the infant series for diphtheria toxoid, PT, and FHA in the 13vPnC+DTaP (99.4% in each antigen), 7vPnC+DTaP (96.6% in each antigen), and the DTaP (100% in each antigen) groups in the evaluable infant immunogenicity population. In all 3 groups there was a marked increase in the proportions of subjects with a prespecified antibody level for diphtheria toxoid, PT, and FHA after the infant series compared with the corresponding proportions before the infant series.

**Table 42. Concomitant DTaP GMCs After Infant Series – Evaluable Infant Immunogenicity Population**

| | Vaccine Group (as Randomized) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | DTaP (Catch-up 7vPnC) (Group 3) | | | Ratio Group 1 / Group 3 | |
| DTaP Antigen | n[a] | GMC[b] | (95% CI[c]) | n[a] | GMC[b] | (95% CI[c]) | n[a] | GMC[b] | (95% CI[c]) | Ratio[d] | (95% CI[e]) |
| Diphtheria | 177 | 1.03 | (0.94, 1.12) | 176 | 1.10 | (0.97, 1.25) | 175 | 0.93 | (0.86, 1.02) | 1.10 | (0.97, 1.24) |
| FHA | 177 | 62.30 | (56.59, 68.59) | 176 | 53.86 | (47.27, 61.37) | 175 | 67.48 | (61.64, 73.86) | 0.92 | (0.81, 1.05) |
| PT | 177 | 66.12 | (60.45, 72.32) | 176 | 57.26 | (49.23, 66.60) | 175 | 67.64 | (62.87, 72.78) | 0.98 | (0.87, 1.10) |
| Tetanus | 177 | 1.50 | (1.31, 1.70) | 176 | 1.37 | (1.17, 1.60) | 175 | 1.66 | (1.50, 1.83) | 0.90 | (0.77, 1.06) |

Abbreviations: PT = pertussis; FHA = filamentous hemagglutinin.

a. n = Number of subjects with a determinate DTaP antibody concentration for the specified serotype.

b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.

c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

d. Ratio of GMCs; Group 1 (13vPnC+DTaP) to Group 3 (DTaP [Catch-up 7vPnC)).]).

e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 (13vPnC+DTaP) – Group 3 (DTaP [Catch-up 7vPnC))).])).

The GMCs for diphtheria toxoid, tetanus toxoid, PT, and FHA measured 1 month after the toddler dose are presented in Table 44 for the evaluable toddler immunogenicity population. All subjects (100%) in the 13vPnC+DTaP, 7vPnC+DTaP, and the DTaP groups achieved the prespecified antibody level after the toddler dose for diphtheria toxoid, tetanus toxoid, PT, and FHA in the evaluable toddler immunogenicity population.

**Table 44. Concomitant DTaP GMCs After Toddler Dose – Evaluable Toddler Immunogenicity Population**

| | Vaccine Group (as Randomized) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | DTaP (Catch-up 7vPnC) (Group 3) | | | Ratio Group 1 / Group 3 | |
| DTaP Antigen | n[a] | GMC[b] | (95% CI[c]) | n[a] | GMC[b] | (95% CI[c]) | n[a] | GMC[b] | (95% CI[c]) | Ratio[d] | (95% CI[e]) |
| Diphtheria | 157 | 2.65 | (2.43, 2.90) | 154 | 3.18 | (2.94, 3.45) | 163 | 2.63 | (2.39, 2.91) | 1.01 | (0.88, 1.15) |
| FHA | 157 | 143.68 | (130.94, 157.66) | 154 | 141.19 | (129.20, 154.30) | 163 | 180.31 | (163.12, 199.32) | 0.80 | (0.70, 0.91) |
| PT | 157 | 144.46 | (130.68, 159.68) | 154 | 135.65 | (124.16, 148.21) | 163 | 150.21 | (136.20, 165.65) | 0.96 | (0.84, 1.11) |
| Tetanus | 157 | 2.90 | (2.56, 3.28) | 154 | 2.60 | (2.29, 2.95) | 163 | 2.89 | (2.58, 3.25) | 1.00 | (0.85, 1.19) |

Abbreviations: PT = pertussis; FHA = filamentous hemagglutinin.

a. n = Number of subjects with a determinate DTaP antibody concentration for the specified serotype.

b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.

c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

d. Ratio of GMCs; Group 1 (13vPnC+DTaP) to Group 3 (DTaP [Catch-up 7vPnC)).]).

e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 (13vPnC+DTaP) – Group 3 (DTaP [Catch-up 7vPnC))).])).

*Assessor's comments: The overall immunogenicity results from this study are generally in agreement with what has been reported from previous studies. No concerns regarding immunogenicity are raised by these results.*

- Safety results

Local reactions, infant series: The number and percentage of subjects with local reactions within 7 days after doses 1 in the infant series are presented in Table 53. The frequencies following the second dose were generally slightly higher compared to the first dose, but the frequencies for local reactions following the third dose were similar to those after the first dose (data not shown in this AR). Most local reactions reported within 7 days of vaccine administration were mild or moderate in severity.

**Table 53. Subjects Reporting Local Reactions Within 7 Days – Dose 1 Infant Series Safety Population**

| | Vaccine Group (as Administered) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | DTaP (Catch-up 7vPnC) (Group 3) | | | Difference Group 1 – Group 3 | |
| Injection Site[a] Local Reaction | N[b] | n[c] | % | N[b] | n[c] | % | N[b] | n[c] | % | Difference[d] | (95% CI[e]) |
| Redness[f] | | | | | | | | | | | |
| Any | 171 | 100 | 58.5 | 172 | 96 | 55.8 | 165 | 17 | 10.3 | 48.2 | (39.0, 56.7) |
| Mild | 170 | 82 | 48.2 | 172 | 88 | 51.2 | 165 | 17 | 10.3 | 37.9 | (28.9, 46.7) |
| Moderate | 164 | 31 | 18.9 | 166 | 30 | 18.1 | 162 | 0 | 0.0 | 18.9 | (13.2, 25.7) |
| Severe | 161 | 0 | 0.0 | 162 | 1 | 0.6 | 162 | 0 | 0.0 | 0.0 | (-2.3, 2.3) |
| Swelling[f] | | | | | | | | | | | |
| Any | 168 | 69 | 41.1 | 168 | 60 | 35.7 | 164 | 8 | 4.9 | 36.2 | (27.9, 44.4) |
| Mild | 168 | 64 | 38.1 | 168 | 53 | 31.5 | 164 | 8 | 4.9 | 33.2 | (25.1, 41.5) |
| Moderate | 162 | 20 | 12.3 | 165 | 21 | 12.7 | 162 | 0 | 0.0 | 12.3 | (7.7, 18.4) |
| Severe | 161 | 0 | 0.0 | 162 | 1 | 0.6 | 162 | 0 | 0.0 | 0.0 | (-2.3, 2.3) |
| Tenderness[g] | | | | | | | | | | | |
| Any | 163 | 22 | 13.5 | 164 | 10 | 6.1 | 162 | 2 | 1.2 | 12.3 | (6.7, 18.5) |
| Significant | 161 | 0 | 0.0 | 162 | 0 | 0.0 | 162 | 0 | 0.0 | 0.0 | (-2.3, 2.3) |
| Any local reaction[h] | 175 | 119 | 68.0 | 174 | 106 | 60.9 | 165 | 20 | 12.1 | 55.9 | (46.8, 64.2) |

a. Injection site to evaluate local reactions.
b. N = number of subjects reporting yes for at least 1 day or no for all days.
c. n = Number of subjects reporting the event.
d. Difference in proportions, Group 1 – Group 3, expressed as a percentage.
e. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions, Group 1 – Group 3, expressed as a percentage.
f. Mild, 0.5-2.0 cm; moderate, 2.5-7.0 cm; and severe, >7.0 cm.
g. Significant = present and interfered with limb movement.
h. Any local reaction = any redness, any swelling, any tenderness.

Local reactions toddler dose: The number and percentage of subjects with local reactions reported within 7 days after the toddler dose are presented in Table 59. Most local reactions reported within 7 days of vaccine administration were mild or moderate in severity and only 1 subject in the 13vPnC+DTaP group experienced significant tenderness.

**Table 59. Subjects Reporting Local Reactions Within 7 Days – Toddler Dose Safety Population**

| Injection Site[a] Local Reaction | Vaccine Group (as Administered) 13vPnC+DTaP (Group 1) N[b] | n[c] | % | 7vPnC+DTaP (Group 2) N[b] | n[c] | % | DTaP (Catch-up 7vPnC) (Group 3) N[b] | n[c] | % | Difference Group 1 – Group 3 Difference[d] | (95% CI[e]) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Redness[f] | | | | | | | | | | | |
| Any | 148 | 92 | 62.2 | 152 | 87 | 57.2 | 149 | 52 | 34.9 | 27.3 | (15.8, 38.1) |
| Mild | 148 | 74 | 50.0 | 151 | 72 | 47.7 | 148 | 42 | 28.4 | 21.6 | (10.5, 32.4) |
| Moderate | 141 | 39 | 27.7 | 139 | 38 | 27.3 | 145 | 19 | 13.1 | 14.6 | (5.0, 24.0) |
| Severe | 140 | 0 | 0.0 | 136 | 0 | 0.0 | 141 | 0 | 0.0 | 0.0 | (-2.6, 2.6) |
| Swelling[f] | | | | | | | | | | | |
| Any | 149 | 73 | 49.0 | 144 | 66 | 45.8 | 148 | 39 | 26.4 | 22.6 | (11.6, 33.2) |
| Mild | 147 | 63 | 42.9 | 143 | 60 | 42.0 | 146 | 33 | 22.6 | 20.3 | (9.5, 30.8) |
| Moderate | 143 | 24 | 16.8 | 138 | 26 | 18.8 | 146 | 19 | 13.0 | 3.8 | (-4.6, 12.2) |
| Severe | 140 | 0 | 0.0 | 136 | 0 | 0.0 | 141 | 0 | 0.0 | 0.0 | (-2.6, 2.6) |
| Tenderness[g] | | | | | | | | | | | |
| Any | 142 | 20 | 14.1 | 140 | 14 | 10.0 | 142 | 8 | 5.6 | 8.5 | (1.2, 15.8) |
| Significant | 140 | 1 | 0.7 | 136 | 0 | 0.0 | 141 | 0 | 0.0 | 0.7 | (-2.0, 3.9) |
| Any local reaction[h] | 153 | 105 | 68.6 | 152 | 94 | 61.8 | 151 | 56 | 37.1 | 31.5 | (20.3, 42.0) |

a. Injection site to evaluate local reactions.
b. N = number of subjects reporting yes for at least 1 day or no for all days.
c. n = Number of subjects reporting the event.
d. Difference in proportions, Group 1 – Group 3, expressed as a percentage.
e. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions, Group 1 – Group 3, expressed as a percentage.
f. Mild, 0.5-2.0 cm; moderate, 2.5-7.0 cm; and severe, >7.0 cm.
g. Significant = present and interfered with limb movement.
h. Any local reaction = any redness, any swelling, any tenderness.

Systemic reactions, infant series: The number and percentage of subjects reporting systemic events, including the use of antipyretic medications, within 7 days after doses 1, 2, and 3 of the infant series are presented in Table 61. After each dose of the infant series, the percentages of subjects who reported any systemic events in the 13vPnC+DTaP group were higher than those in the DTaP group but were similar to those in the 7vPnC+DTaP group. The frequencies of systemic reactions were similar following the second and third compared to the first dose.

**Table 61. Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days – Dose 1 Infant Series Safety Population**

| | Vaccine Group (as Administered) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | DTaP (Catch-up 7vPnC) (Group 3) | | | Difference Group 1 – Group 3 | |
| Systemic Event | N[a] | n[b] | % | N[a] | n[b] | % | N[a] | n[b] | % | Difference[c] | (95% CI[d]) |
| Fever ≥37.5°C but ≤39°C | 168 | 61 | 36.3 | 168 | 57 | 33.9 | 165 | 36 | 21.8 | 14.5 | (4.7, 24.3) |
| Fever >39°C but ≤40°C | 161 | 1 | 0.6 | 163 | 2 | 1.2 | 162 | 1 | 0.6 | 0.0 | (-2.8, 2.8) |
| Fever >40°C | 161 | 0 | 0.0 | 162 | 0 | 0.0 | 162 | 0 | 0.0 | 0.0 | (-2.3, 2.3) |
| Decreased appetite | 163 | 21 | 12.9 | 163 | 15 | 9.2 | 165 | 12 | 7.3 | 5.6 | (-1.0, 12.5) |
| Irritability | 165 | 31 | 18.8 | 164 | 27 | 16.5 | 164 | 20 | 12.2 | 6.6 | (-1.3, 14.6) |
| Increased sleep | 170 | 49 | 28.8 | 165 | 44 | 26.7 | 165 | 36 | 21.8 | 7.0 | (-2.4, 16.4) |
| Decreased sleep | 164 | 30 | 18.3 | 169 | 36 | 21.3 | 167 | 23 | 13.8 | 4.5 | (-3.5, 12.6) |
| Hives (urticaria) | 161 | 5 | 3.1 | 162 | 2 | 1.2 | 162 | 0 | 0.0 | 3.1 | (0.6, 7.1) |
| Use of antipyretic medication to treat symptoms | 161 | 6 | 3.7 | 162 | 4 | 2.5 | 162 | 1 | 0.6 | 3.1 | (-0.2, 7.3) |
| Any systemic event[e] | 177 | 108 | 61.0 | 174 | 104 | 59.8 | 172 | 74 | 43.0 | 18.0 | (7.4, 28.2) |

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Difference in proportions, Group 1 – Group 3, expressed as a percentage.
d. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions, Group 1 – Group 3, expressed as a percentage.
e. Includes fever ≥37.5°C, decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria).

Systemic events, toddler dose: The percentage of subjects reporting any systemic events in the 13vPnC+DTaP group was similar to that in the 7vPnC+DTaP group and was slightly higher than that in the DTaP group (Table 67).

**Table 67. Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days – Toddler Dose Safety Population**

| | Vaccine Group (as Administered) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13vPnC+DTaP (Group 1) | | | 7vPnC+DTaP (Group 2) | | | DTaP (Catch-up 7vPnC) (Group 3) | | | Difference Group 1 – Group 3 | |
| Systemic Event | N[a] | n[b] | % | N[a] | n[b] | % | N[a] | n[b] | % | Difference[c] | (95% CI[d]) |
| Fever ≥37.5°C but ≤39°C | 145 | 71 | 49.0 | 146 | 72 | 49.3 | 146 | 46 | 31.5 | 17.5 | (6.1, 28.5) |
| Fever >39°C but ≤40°C | 141 | 6 | 4.3 | 136 | 12 | 8.8 | 141 | 5 | 3.5 | 0.7 | (-4.4, 5.9) |
| Fever >40°C | 139 | 2 | 1.4 | 137 | 3 | 2.2 | 141 | 0 | 0.0 | 1.4 | (-1.3, 5.1) |
| Decreased appetite | 143 | 28 | 19.6 | 141 | 28 | 19.9 | 143 | 14 | 9.8 | 9.8 | (1.2, 18.3) |
| Irritability | 143 | 26 | 18.2 | 141 | 30 | 21.3 | 144 | 24 | 16.7 | 1.5 | (-7.4, 10.5) |
| Increased sleep | 145 | 27 | 18.6 | 142 | 25 | 17.6 | 143 | 23 | 16.1 | 2.5 | (-6.3, 11.5) |
| Decreased sleep | 142 | 18 | 12.7 | 137 | 13 | 9.5 | 141 | 16 | 11.3 | 1.3 | (-6.5, 9.2) |
| Hives (urticaria) | 140 | 5 | 3.6 | 136 | 3 | 2.2 | 141 | 3 | 2.1 | 1.4 | (-3.0, 6.2) |
| Use of antipyretic medication to treat symptoms | 141 | 10 | 7.1 | 138 | 13 | 9.4 | 142 | 6 | 4.2 | 2.9 | (-2.8, 8.9) |
| Any systemic event[e] | 148 | 93 | 62.8 | 152 | 97 | 63.8 | 149 | 75 | 50.3 | 12.5 | (1.1, 23.7) |

a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the event.
c. Difference in proportions, Group 1 – Group 3, expressed as a percentage.
d. Exact 2-sided confidence interval (based on Chan & Zhang) for the difference in proportions, Group 1 – Group 3, expressed as a percentage.
e. Includes fever ≥37.5°C, decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria).

Adverse events: AEs were reported by similar percentages of subjects in the 13vPnC+DTaP, 7vPnC+DTaP, and DTaP groups during the infant series and at the toddler dose. In the 3 vaccine groups, the most frequently reported types of AEs were infections and infestations. The AEs reported were generally consistent with childhood illnesses.

Serious adverse events, Infant series: Febrile convulsion was reported during the study by 22 subjects: 6 subjects in the 13vPnC+DTaP group, 9 subjects in the 7vPnC+DTaP group and 7 subjects in the DTaP group. All cases of febrile convulsion reported during the study met the criteria for an SAE, and all led to withdrawal. One (1) case of febrile convulsion that occurred after the toddler dose for a subject in the DTaP group (subject 10011016) persisted when the subject was discontinued from the study, and the event was resolved after the discontinuation. All other cases were resolved during the subject's participation to the study. The majority of febrile convulsions occurred due to fever caused by concurrent viral illness. None of the cases of febrile convulsion was considered related to the study vaccine.

Kawasaki's disease was reported as an SAE during the study by 4 subjects: 2 subjects in the DTaP group and 1 subject each in the 13vPnC+DTaP group and 7vPnC+DTaP group; all of these cases led to withdrawal. In addition, 1 subject in the 13vPnC+DTaP group was diagnosed as having Kawasaki's disease after having completed the study, though the symptom had been reported at the toddler dose; as noted in Section 12.4.2.3, this event met the criteria for an SAE although it was not recorded as such in the study database.

All cases of Kawasaki's disease persisted. However, all acute symptoms resolved and all subjects are being followed for long term follow up. None of the cases of Kawasaki's disease was considered related to the study vaccine.

Based on recent national surveillance reviews in Japan in 2007 and in 2009, the number of patients with Kawasaki's disease is increasing. In the nationwide survey of Kawasaki's disease conducted in 2007, targeting patients who were affected by this disease in 2005 and 2006, the average annual incidence rate was 184.6 per 100,000 children aged 0-4 years. In the nationwide survey of Kawasaki's disease conducted in 2009, which included patients treated for the disease in 2007 and 2008, annual incidence rates were 215.3 and 218.6 per 100,000

children aged 0-4 years in 2007 and 2008, respectively. These were the highest annual Kawasaki's disease incidence rates ever recorded in Japan.

*Assessor's comment: There was a significant difference in the proportion of recipients of 13vPnc and 7vPnC who experienced fever (≥37.5°C but ≤39°C) compared to DTaP. The serious adverse events of febrile seizures and Kawasakis disease were fairly equally distributed between all vaccine groups. The discussions/conclusions of the MAH regarding these 2 events are endorsed.*

Serious adverse events, Toddler dose: In the DTaP group, 1 severe AE of febrile convulsion occurred in the after toddler dose safety population. There were no related severe AEs.

**6096A1-1000**; A Phase 1 Open-label Study to Assess the Safety and Tolerability of a Single Dose of 13-valent Pneumococcal Conjugate Vaccine in Healthy Chinese Adults, Children and Infants

- **Description**

Study 6096A1-1000-CN (B1851046) was conducted in China and was a Phase 1, open-label, single-center study to assess the safety and tolerability of a single intramuscular dose of 13vPnC for approximately 1 month after vaccination in healthy Chinese subjects in 3 age groups:

- Group 1: Adults aged 18 through 55 years (before the fifty-sixth birthday)
- Group 2: Children aged 3 through 5 years (before the sixth birthday)
- Group 3: Infants aged approximately 2 months (42 to 98 days)

Subjects were enrolled into the 3 age groups sequentially: Group 1, followed by Group 2, and then Group 3. The safety of subjects in Groups 1 and 2 was assessed by a safety review committee prior to enrolling subjects in the subsequent age group.
All vaccinated subjects were assessed for safety for approximately 1 month after vaccination.

- **Methods**

- Objectives
  To assess the safety and tolerability of a single dose of 13vPnC in healthy Chinese subjects in 3 age groups:
  - Group 1: Adults aged 18 through 55 years (before the fifty-sixth birthday)
  - Group 2: Children aged 3 through 5 years (before the sixth birthday)
  - Group 3: Infants aged approximately 2 months (42 to 98 days)

- Study design
  This was a phase 1, open-label, single-center study to assess the safety and tolerability of a single dose of 13vPnC for approximately 1 month after vaccination in healthy Chinese subjects in 3 age groups: adults, children 3-5 years and infants 2 months of age. Subjects were enrolled into the 3 age groups sequentially: group 1, followed by group 2, and then group 3. The safety of subjects in groups 1 and 2 was assessed by a safety review committee (SRC) prior to enrolling subjects in the subsequent age group.

  All vaccinated subjects were assessed for safety for approximately 1 month after vaccination. At the end of the study, parents/legal guardians of infants in group 3 were offered 3 additional doses of Prevenar for their children in order to complete the infant pneumococcal vaccination schedule recommended in China.

- Study population /Sample size
  Main Criteria for Inclusion: Healthy Chinese male or female adults, children and infants with a signed and dated informed consent document with no previous vaccination with licensed or investigational pneumococcal vaccine. At the time of enrollment subjects in group 1 were to be aged 18 through 55 years, subjects in group 2 were to be aged 3 through 5 years, and subjects in group 3 were to be aged 42 to 98 days. Subjects were to be healthy as determined by medical history, physical examination, and judgment of the investigator.

Subjects and/or parent/legal guardian had to be willing and able to comply with scheduled visits, and study procedures. All male and female subjects (in group 1) who were biologically capable of having children were to agree and commit to the use of a reliable method of birth control from the signing of the ICF until the end of the study. Female subjects (in group 1) who were biologically capable of having children were to have negative urine pregnancy tests.
Subjects were ineligible to participate if they were previously vaccinated with a licensed or investigational pneumococcal vaccine, had a previous anaphylactic reaction to any vaccine or vaccine-related component, or if there was any contraindication to vaccination with pneumococcal vaccine. Subjects with previous conditions such as bleeding diathesis or prolonged bleeding, known or suspected immune deficiency or suppression, major known congenital malformation or serious chronic disorder, significant neurological disorder or history of seizure, severe acute or chronic medical or psychiatric condition or laboratory abnormality were also ineligible to participate. Women who were breastfeeding or pregnant (known or suspected), and subjects who received any investigational products or medical devices within 28 days before investigational product administration or during the study were excluded from participation. Subjects who were related to site staff or Pfizer employees also were not eligible to participate.

Determination of Sample Size: Approximately 72 subjects participated in this study at 1 site. A sample size of 20 adults aged 18 through 55 years, 20 children aged 3 through 5 years, and 20 infants aged 42 to 98 days was required for this study based on regulatory requirements in China. An additional 4 subjects were to be enrolled in each age group for a total of 24 subjects per age group to allow for drop-outs.

- Treatments
  13-valent Pneumococcal Conjugate Vaccine (13vPnC) is the investigational product used in this study. 13vPnC was supplied as a 0.5 mL suspension in a prefilled syringe. A single dose (0.5 mL) of 13vPnC was administered intramuscularly into the deltoid muscle of the arm or anterolateral muscle of the thigh, as appropriate.

- Outcomes/endpoints
  Safety Evaluations: Any subject who received at least 1 dose of investigational product was included in the evaluation for safety. Subjects were observed for any acute reactions for at least 30 minutes after vaccination. Each day for 7 days after vaccination (days 1 to 7, where day 1 is the day of vaccination), the subject or the subject's parent/legal guardian/caregiver monitored and recorded the following in an e-diary:
  Local reactions
    - Group 1: pain, redness, and swelling at the injection site
    - Groups 2 and 3: tenderness, redness, and swelling at the injection site

  Systemic events
    - Group 1: fever, vomiting, diarrhea, headache, fatigue, muscle pain, and joint pain
    - Groups 2 and 3: fever, decreased appetite, irritability, increased sleep, and decreased sleep

  Use of antipyretic medication to treat or prevent symptoms

  These prospectively collected local reactions and systemic events were considered solicited AEs. All other AEs (including SAEs) were collected and recorded in the CRF from the signing of the ICF until the end of the study (approximately 1 month after vaccination). A Safety Review Committee (SRC) reviewed safety data (SAEs, solicited local reactions and systemic events) during day 1 through day 7 and determined whether the study should proceed to enroll subjects in the subsequent age group, i.e. in progressively more vulnerable populations, Groups 1 to 3.

- Statistical Methods
  The proportion of subjects reporting solicited local reactions, systemic events, and use of antipyretic medications on any day within the 7-day period (days 1 to 7) after investigational product administration was summarized for each group.
  Other AEs reported within approximately 1 month after vaccination were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and were summarized by group.

All summaries showed, by group, the number and percentage of subjects reporting at least 1 event and the number of events.
Safety data was summarized periodically during the study to ensure the safety of subjects or as needed for safety review by the SRC.

➢ **Results**

- Recruitment/ Number analysed
  All (100%) of the subjects who were enrolled in the study, received vaccination, and completed the study.

- Baseline data
  Table 5 presents demographic summary for all enrolled subjects. All (100%) of the subjects were of Asian origin, of which 58.3% were males and 41.7% were females. The mean age in groups 1, 2 and 3 was 43.3 years, 4.5 years and 79.6 days, respectively.

**Table 5 Demographic Characteristics – All Subjects**

| | Vaccine Group (as Enrolled) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13vPnC Group 1 N[a]=24 | | 13vPnC Group 2 N[a]=24 | | 13vPnC Group 3 N[a]=24 | | Total N[a]=72 | |
| | n | % | n | % | n | % | n | % |
| Sex | | | | | | | | |
| Male | 13 | 54.2 | 13 | 54.2 | 16 | 66.7 | 42 | 58.3 |
| Female | 11 | 45.8 | 11 | 45.8 | 8 | 33.3 | 30 | 41.7 |
| Race | | | | | | | | |
| Asian | 24 | 100.0 | 24 | 100.0 | 24 | 100.0 | 72 | 100.0 |
| Age at vaccination[b] | | | | | | | | |
| 18 years - 55 years | 24 | 100.0 | 0 | 0.0 | 0 | 0.0 | 24 | 33.3 |
| 3 years - 5 years | 0 | 0.0 | 24 | 100.0 | 0 | 0.0 | 24 | 33.3 |
| 42 days - 98 days | 0 | 0.0 | 0 | 0.0 | 24 | 100.0 | 24 | 33.3 |
| Unit | Years | | Years | | Days | | | |
| Mean (SD) | 43.3 (9.1) | | 4.5 (0.7) | | 79.6 (15.2) | | | |
| Median | 43.4 | | 4.5 | | 78.5 | | | |
| Min, max | 19.3, 55.1 | | 3.2, 5.6 | | 52, 98 | | | |

a. These values are used as the denominators for percentages.
b. For subjects assigned the vaccine, but not vaccinated, the enrollment date was used instead of vaccination date. For screened only subjects, the visit/assessment date on the demographic page in case report form (CRF) was used. For group 1 and 2, the age at time of vaccination is calculated by (vaccination date – date of birth +1)/365.25. For group 3, the age at time of vaccination is calculated by (vaccination date – date of birth +1).

- Efficacy results
  Not applicable.

- Safety results
  <u>Local Reactions</u>

Table 8 presents the subjects reporting local reactions within 7 days (safety population). In group 1, the most frequently reported local reaction was pain at the injection site, reported by 23 subjects (95.8%). The pain at the injection site was mostly mild to moderate in intensity. Table 8 also shows that 1 subject in group 1 had an emergency room (ER) visit due to pain. This was actually a data entry error in e-diary (the data entry error details have been recorded on site source documents, which have been verified by the site manager during the onsite monitoring visit). The subject visited the ER because of a fever of 38.5°C rather than pain at injection site.

In group 2, the most frequently reported local reaction was tenderness, reported by 18 subjects (75%), but in no case did it interfere with limb movement.

In group 3, the most frequently reported local reaction was swelling, reported by 6 subjects (25%), which was mild or moderate in intensity.

**Table 8 Subjects Reporting Local Reactions Within 7 Days – Safety Population**

| | Vaccine Group (as Administered) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 13vPnC Group 1 | | | | 13vPnC Group 2 | | | | 13vPnC Group 3 | | | |
| Local Reaction | N[a] | n[b] | % | (95% CI[c]) | N[a] | n[b] | % | (95% CI[c]) | N[a] | n[b] | % | (95% CI[c]) |
| Redness[d] | | | | | | | | | | | | |
| Any | 24 | 4 | 16.7 | (4.7, 37.4) | 24 | 4 | 16.7 | (4.7, 37.4) | 24 | 3 | 12.5 | (2.7, 32.4) |
| Mild | 24 | 3 | 12.5 | (2.7, 32.4) | 24 | 2 | 8.3 | (1.0, 27.0) | 24 | 3 | 12.5 | (2.7, 32.4) |
| Moderate | 24 | 3 | 12.5 | (2.7, 32.4) | 24 | 2 | 8.3 | (1.0, 27.0) | 24 | 0 | 0.0 | (0.0, 14.2) |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| Necrosis or exfoliative dermatitis | 24 | 0 | 0.0 | (0.0, 14.2) | NA | | | | NA | | | |
| Swelling[d] | | | | | | | | | | | | |
| Any | 24 | 4 | 16.7 | (4.7, 37.4) | 24 | 7 | 29.2 | (12.6, 51.1) | 24 | 6 | 25.0 | (9.8, 46.7) |
| Mild | 24 | 3 | 12.5 | (2.7, 32.4) | 24 | 5 | 20.8 | (7.1, 42.2) | 24 | 4 | 16.7 | (4.7, 37.4) |
| Moderate | 24 | 3 | 12.5 | (2.7, 32.4) | 24 | 5 | 20.8 | (7.1, 42.2) | 24 | 2 | 8.3 | (1.0, 27.0) |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| Necrosis or exfoliative dermatitis | 24 | 0 | 0.0 | (0.0, 14.2) | NA | | | | NA | | | |
| Pain at injection site[e] | | | | | | | | | | | | |
| Any | 24 | 23 | 95.8 | (78.9, 99.9) | NA | | | | NA | | | |
| Mild | 24 | 23 | 95.8 | (78.9, 99.9) | NA | | | | NA | | | |
| Moderate | 24 | 3 | 12.5 | (2.7, 32.4) | NA | | | | NA | | | |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) | NA | | | | NA | | | |
| ER or Hospitalized[f] | 24 | 1 | 4.2 | (0.1, 21.1) | NA | | | | NA | | | |
| Tenderness[g] | | | | | | | | | | | | |
| Any | NA | | | | 24 | 18 | 75.0 | (53.3, 90.2) | 24 | 3 | 12.5 | (2.7, 32.4) |
| Present | NA | | | | 24 | 18 | 75.0 | (53.3, 90.2) | 24 | 3 | 12.5 | (2.7, 32.4) |
| Interferes with limb movement | NA | | | | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| Any local reaction[h] | 24 | 23 | 95.8 | (78.9, 99.9) | 24 | 18 | 75.0 | (53.3, 90.2) | 24 | 9 | 37.5 | (18.8, 59.4) |

Abbreviation: NA = Not applicable; CRF = Case report form.

a. N = number of subjects reporting yes for at least 1 day or no for all days.

b. n = Number of subjects reporting the specific characteristic.

c. Exact 2-sided confidence interval (CI) based on the observed proportion of subjects.
d. For Group 1, mild is 2.5 to 5.0 cm, moderate is >5.0 to 10.0 cm, severe is >10.0 cm, and necrosis or exfoliative dermatitis, if any of them is recorded on the adverse event CRF to be evident. For Group 2 or Group 3, mild is 0.5 to 2.0 cm, moderate is >2.0 to 7.0 cm, and severe is >7.0 cm.
e. For Group 1 only. Mild = does not interfere with activity, moderate = interferes with activity, severe =prevents daily activity, and ER or Hospitalized = requires an emergency room (ER) visit or hospitalization.
f. Data entry error in e-dairy for subject 10011024's ER visit due to pain at injection site. Subject visited the ER due to fever rather than pain.
g. For Group 2 or Group 3 only.
h. Any local reaction = any redness, any swelling, or any pain at injection site for Group 1; any redness, any swelling, or any tenderness for Group 2 or Group 3.

Table 11 presents the subjects reporting systemic events and antipyretic use within 7 days, in **group 1.** According to the SFDA grading for fever, 1 subject in group 1 had fever ≥37.7°C which was considered mild and was ≥37.7°C but ≤38.5°C.

Table 12 presents the subjects reporting systemic events and the antipyretic medication use within 7 days in **group 2 and 3** (safety population).
In group 2, only 1 subject reported a systemic event of increased sleep. In group 3, 3 subjects each reported irritability and increased sleep, while 4 subjects reported decreased sleep. No subjects in either group 2 or 3 reported fever ≥38.0°C. No subjects in either group 2 or 3 used antipyretic medication within 7 days of vaccination.

**Table 11 Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days – Group 1 – Safety Population**

| Systemic Events | Vaccine Group (as Administered) 13vPnC Group 1 N[a] | n[b] | % | (95% CI[c]) |
|---|---|---|---|---|
| Fever | | | | |
| ≥38.0°C | 24 | 1 | 4.2 | (0.1, 21.1) |
| ≥38°C but ≤38.4°C | 24 | 0 | 0.0 | (0.0, 14.2) |
| >38.4°C but ≤38.9°C | 24 | 1 | 4.2 | (0.1, 21.1) |
| >38.9°C but ≤40.0°C | 24 | 0 | 0.0 | (0.0, 14.2) |
| >40.0°C | 24 | 0 | 0.0 | (0.0, 14.2) |
| Fever Grades by SFDA[d] | | | | |
| ≥37.7°C | 24 | 1 | 4.2 | (0.1, 21.1) |
| ≥37.7°C but ≤38.5°C | 24 | 1 | 4.2 | (0.1, 21.1) |
| ≥38.6°C but ≤39.5°C | 24 | 0 | 0.0 | (0.0, 14.2) |
| ≥39.6°C but ≤40.5°C | 24 | 0 | 0.0 | (0.0, 14.2) |
| >40°C | 24 | 0 | 0.0 | (0.0, 14.2) |
| Vomiting[e] | | | | |
| Any | 24 | 0 | 0.0 | (0.0, 14.2) |
| Mild | 24 | 0 | 0.0 | (0.0, 14.2) |
| Moderate | 24 | 0 | 0.0 | (0.0, 14.2) |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) |
| ER or hospitalized[f] | 24 | 0 | 0.0 | (0.0, 14.2) |
| Diarrhea[g] | | | | |
| Any | 24 | 0 | 0.0 | (0.0, 14.2) |
| Mild | 24 | 0 | 0.0 | (0.0, 14.2) |
| Moderate | 24 | 0 | 0.0 | (0.0, 14.2) |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) |
| ER or hospitalized[f] | 24 | 0 | 0.0 | (0.0, 14.2) |
| Headache[h] | | | | |
| Any | 24 | 1 | 4.2 | (0.1, 21.1) |
| Mild | 24 | 1 | 4.2 | (0.1, 21.1) |
| Moderate | 24 | 0 | 0.0 | (0.0, 14.2) |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) |
| ER or hospitalized[f] | 24 | 0 | 0.0 | (0.0, 14.2) |
| Fatigue[h] | | | | |
| Any | 24 | 3 | 12.5 | (2.7, 32.4) |
| Mild | 24 | 3 | 12.5 | (2.7, 32.4) |
| Moderate | 24 | 0 | 0.0 | (0.0, 14.2) |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) |
| ER or hospitalized[f] | 24 | 0 | 0.0 | (0.0, 14.2) |
| Muscle pain[h] | | | | |

| | | | | |
|---|---|---|---|---|
| Any | 24 | 5 | 20.8 | (7.1, 42.2) |
| Mild | 24 | 5 | 20.8 | (7.1, 42.2) |
| Moderate | 24 | 2 | 8.3 | (1.0, 27.0) |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) |
| ER or hospitalized[f] | 24 | 0 | 0.0 | (0.0, 14.2) |
| Joint pain[h] | | | | |
| Any | 24 | 1 | 4.2 | (0.1, 21.1) |
| Mild | 24 | 1 | 4.2 | (0.1, 21.1) |
| Moderate | 24 | 0 | 0.0 | (0.0, 14.2) |
| Severe | 24 | 0 | 0.0 | (0.0, 14.2) |
| ER or hospitalized[f] | 24 | 0 | 0.0 | (0.0, 14.2) |
| Use of antipyretic medications[i] | 24 | 2 | 8.3 | (1.0, 27.0) |
| Any systemic event[j] | 24 | 6 | 25.0 | (9.8, 46.7) |

Note: Oral temperature collected for Group 1.
Abbreviation: SFDA = State Food and Drug Administration; e-diary = electronic diary
a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the specific characteristic.
c. Exact 2-sided confidence interval (CI) based on the observed proportion of subjects.
d. Oral temperatures classified following the guidelines published by China SFDA.
e. Mild, 1 to 2 times in 24 hours; moderate, >2 times in 24 hours; severe, requires intravenous (IV) hydration.
f. ER or hospitalized = requires an emergency room (ER) visit or hospitalization.
g. Mild, 2 to 3 loose stools in 24 hours; moderate, 4 to 5 loose stools in 24 hours; severe, 6 or more loose stools in 24 hours.
h. Mild = does not interfere with activity, moderate = some interference with activity, severe = significant; prevents daily routine activity.
i. Data collection error in e-dairy. The investigational site confirmed that use of antipyretic medications for 2 subjects, 10011001 and 10011007, was reported in error.
j. Any systemic event = any fever ≥38.0°C, any vomiting, any diarrhea, any headache, any fatigue, any muscle pain, or any joint pain.

**Table 12 Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days – Group 2 and Group 3 – Safety Population**

| | Vaccine Group (as Administered) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13vPnC Group 2 | | | | 13vPnC Group 3 | | | |
| Systemic Events | N[a] | n[b] | % | (95% CI[c]) | N[a] | n[b] | % | (95% CI[c]) |
| Fever | | | | | | | | |
| ≥38.0°C | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| ≥38.0°C but ≤39.0°C | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| >39.0°C but ≤40.0°C | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| >40.0°C | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| Decreased appetite | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| Irritability | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 3 | 12.5 | (2.7, 32.4) |
| Increased sleep | 24 | 1 | 4.2 | (0.1, 21.1) | 24 | 3 | 12.5 | (2.7, 32.4) |
| Decreased sleep | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 4 | 16.7 | (4.7, 37.4) |
| Use of antipyretic medications | 24 | 0 | 0.0 | (0.0, 14.2) | 24 | 0 | 0.0 | (0.0, 14.2) |
| Any systemic event[d] | 24 | 1 | 4.2 | (0.1, 21.1) | 24 | 7 | 29.2 | (12.6, 51.1) |

Note: Axillary temperature collected for Group 2 and Group 3.
a. N = number of subjects reporting yes for at least 1 day or no for all days.
b. n = Number of subjects reporting the specific characteristic.
c. Exact 2-sided confidence interval (CI) based on the observed proportion of subjects.
d. Any systemic event = any fever ≥38.0°C, any decreased appetite, any irritability, any increased or decreased sleep.

Summary of Adverse Events
Only 1 AE (bronchopneumonia) was reported in this study, which occurred in group 3 and was also serious and severe. This AE was determined by the investigator to be not related to the vaccination. No non-serious AEs were reported during the study.

| Assessor's comment: The Chinese study was very small, and the safety data obtained are not considered to add much to the already substantial safety data base of Prevenar 13. |
|---|

**3. Discussion on clinical aspects**
The Japanese study generally confirmed the immunogenicity and safety results obtained in other studies with Prevenar13. The Chinese study only had a safety objective, and considering the limited size of the study it is not considered to contribute to the overall safety information for Prevenar 13.

## III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submitted studies are not considered to change the overall benefit risk balance of Prevenar 13, and no further regulatory action is required.

- **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

## IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable.