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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 035

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

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I. INTRODUCTION

On December 22, 2009, 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

Information on the pharmaceutical formulation used in the study(ies)

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin cross-reactive material 197 (CRM_{197}). The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B per 0.5-mL dose. The final formulation contains 5 mM succinate buffer, 0.02% polysorbate 80, with 0.125 mg of aluminum as aluminum phosphate per 0.5-mL dose.

Clinical aspects

1. Introduction

Wyeth has developed Prevenar 13, a 13-valent pneumococcal conjugate vaccine (13vPnC), as a successor to the currently registered vaccine, Prevenar, for use in infants and young children to prevent pneumococcal disease (invasive pneumococcal disease [IPD], nonbacteremic pneumonia, and acute otitis media [AOM]) caused by the 13 pneumococcal serotypes contained in the vaccine. Prevenar is a 7-valent pneumococcal conjugate vaccine (7vPnC) that contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. In addition to these serotypes, 13vPnC contains serotypes 1, 3, 5, 6A, 7F, and 19A.

The MAH submitted final reports for:

Study 6096A1-006: Final 6-Month Follow-up Addendum to Final Toddler Report: (Pivotal EU study)
A Phase 3, Randomized, Active-Controlled, Double-Blind Trial of the Safety, Tolerability, and Immunologic Non-inferiority of a 13-valent Pneumococcal Conjugate Vaccine Compared to a 7-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given in a 2-, 3-, 4-, and 11- to 12-Month Schedule With Routine Pediatric Vaccinations.

Study 6096A1-500: Final 6-Month Follow-up Addendum to Final Infant and Toddler Report:
A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Italy.

Study 6096A1-501: Final 6-Month Follow-up Addendum to Final Infant and Toddler Report:
A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Spain.

Study 6096A1-3005: Final Toddler Report: A Phase 3, Randomized, Active-Controlled, Double-Blind Trial Evaluating The Safety, Tolerability, and Immunogenicity of 3 lots of 13- Valent Pneumococcal Conjugate Vaccine In Healthy Infants given with Routine Pediatric Vaccinations in The United States.

For one study (6096A1-3005) immunogenicity and safety data from the toddler dose are presented and it should be noted that the infant series data were already submitted as part of the MAA. This CSR also includes the additional non-inferiority comparison of the anti-polysaccharide IgG responses after the infant series that were submitted in response to questions during review of the MAA.

Safety data collected after the infant series, ie, the period from after the dose 3 blood draw to the toddler dose vaccination is also included. A review of these additional data is also presented in this Module 2.5 addendum. For the other 3 studies (6096A1-006, 6096A1-500, and 6096A1-501) safety data from the 6-month follow-up period are presented, and once again it should be noted that both the infant series and toddler dose were submitted with the MAA.

2. Clinical studies

Study 6096A1-006: Final 6-Month Follow-up Addendum to Final Toddler Report (Pivotal EU study):
A Phase 3, Randomized, Active-Controlled, Double-Blind Trial of the Safety, Tolerability, and Immunologic Non-inferiority of a 13-valent Pneumococcal Conjugate Vaccine Compared to a 7-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given in a 2-, 3-, 4-, and 11- to 12-Month Schedule With Routine Pediatric Vaccinations.

Description
Only a brief description of the study will be included as it has already been assessed during the original MAA procedure.

- **Methods**

  - Objective(s)

Demonstrate that the PnC serotype-specific IgG responses induced by 13vPnC are non-inferior to those induced by 7vPnC or 7vPnC reference measured 1 month after the infant series.
Assess the non-inferiority of antigen-specific response (Dip, HBV, Hib) 1 month after dose 3 of PnC and concomitant vaccine in the 13vPnC group relative to the 7vPnC group

  - 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 compared with 7vPnC in healthy infants. The trial was conducted at 56 sites in Germany.

  - Study population /Sample size

Approximately 600 subjects (300 subjects per group) were to be enrolled in this study in order to achieve 270 evaluable subjects per group.

  - Treatments

Subjects were to be randomly assigned (in a 1:1 ratio prospectively) to receive either 13vPnC and Infanrix hexa or 7vPnC and Infanrix hexa given in a 2-, 3-, 4- (infant series) and 11- to 12- (toddler dose) month schedule.

  - Outcomes/endpoints

AEs were to be recorded on the eCRF based on ancillary information on the e-diary, clinical evaluation during a study visit, and verbal questioning of the parent about the child's health since the last visit. AEs were recorded from the signing of the ICF to visit 4 and from visit 5 to visit 6.
At visit 5, any newly diagnosed chronic medical conditions since visit 4 were recorded. All serious adverse events (SAEs) were recorded from the signing of the ICF to 6 months after the last study vaccination.
A telephone contact was to be made 6 months after the last study vaccination to record any newly diagnosed chronic medical conditions, hospitalizations, SAEs, and other reportable information (ORI) that occurred since the last study visit.

  - Statistical Methods

The data are descriptive.

- **Results**

  - Recruitment/ Number analysed

The actual number of vaccinated subjects was 603, ie, 300 subjects in the 13vPnC group and 303 subjects in the 7vPnC group. The actual number of subjects who completed the toddler dose of study vaccine was 574, ie, 289 subjects in the 13vPnC group and 285 subjects in the 7vPnC group (including

blood draw). A total of 578 subjects completed the 6-month follow-up, 288 in the 13vPnC group and 290 subjects in the 7vPnC group.
The safety population for this report totaled 578 subjects.
Of these, 4 subjects received an incorrect vaccination and are not included in the summary tables (none of them had AEs). Subjects were analyzed according to the vaccine actually administered; thus, the summary table shows 574 subjects, 287 subjects in each of the vaccine groups.

- Efficacy results
  N.a.

- Safety results

AEs were reported for 20 (7.0%) subjects in the 13vPnC group and 22 (7.7%) subjects in the 7vPnC group. These AEs reflected common childhood illnesses and accidents. The AEs categorized as infections and infestations were reported most frequently in both vaccine groups. The individual AE with the highest incidence was gastroenteritis, which occurred in 6 subjects overall (3 subjects, 1.0%, in each of the 2 vaccine groups). When data for all AEs were analyzed, no significant differences between vaccine groups were noted. Moreover, none of the AEs were considered related to study vaccine.

A total of 18 severe AEs were reported for 11 subjects overall, including 6 (2.1%) subjects in the 13vPnC group and 5 (1.7%) subjects in the 7vPnC group. The most frequently reported severe AE was gastroenteritis, which occurred in 2 (0.7%) subjects in each of the vaccine groups.

SAEs were reported for 11 (3.8%) subjects in the 13vPnC group and 14 (4.9%) subjects in the 7vPnC group. SAEs categorized as infections and infestations were reported most frequently in both vaccine groups. Of the individual SAEs, the highest incidence was for gastroenteritis, which was reported in 6 subjects overall (3 subjects, 1.0%, in each of the 2 vaccine groups). There were no significant differences between vaccine groups for SAEs, and none were considered related to study vaccine. None of the SAEs were life-threatening.

There were no deaths reported during the 6-month follow-up period.

Assessor's comment: The definition of severe AEs was not included in the study protocol, other than that all adverse events were defined as mild moderate severe or life threatening. The standard definition of Serious Adverse events (SAEs) was used. However, considering that none of the adverse events were considered related to the vaccine, this issue is of less importance.

Study 6096A1-500: Final 6-Month Follow-up Addendum to Final Infant and Toddler Report:
A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Italy

➢ **Description**

Only a brief description of the study will be included as it has already been assessed during the original MAA procedure.

➢ **Methods**

- Objective(s)

Demonstrate that the immune response after Infanrix hexa (antigen assessed:
HBV) and 13vPnC is non-inferior to the response after Infanrix hexa and 7vPnC measured 1 month after the toddler dose.
Assess the immune response to 13vPnC measured 1 month after the infant series and just before the toddler dose.
Assess the immune responses induced by 13vPnC relative to 7vPnC measured 1 month after the toddler dose.

- Study design

This was a phase 3, parallel-group, randomized, active-controlled, double-blind, multicenter trial to evaluate the safety, tolerability, and immunogenicity of 13vPnC given with routine pediatric vaccinations in healthy infants.

- Study population /Sample size

Approximately 600 subjects were to participate in this study at approximately 10 to 30 sites. Enrolled subjects were randomly assigned at a ratio of 1:1 into 1 of the 2 vaccine groups to receive either 13vPnC + Infanrix hexa or 7vPnC + Infanrix hexa. Three hundred (300) subjects were to be enrolled in each vaccine group to obtain a final number of 225 evaluable subjects per group at the toddler dose.

- Treatments

Each subject was to receive 1 dose (0.5 mL) of either 13vPnC or 7vPnC together with a concomitant dose (0.5 mL) of Infanrix hexa at each of the 3 vaccination visits.

- Outcomes/endpoints

Each subject's parent(s)/legal guardian(s) was contacted by telephone approximately 6 months after the last study vaccination and asked to report any hospitalizations, serious adverse events (SAEs), or newly diagnosed chronic medical conditions that occurred since the last study visit.

- Statistical Methods

The data are descriptive.

➢ **Results**

- Recruitment/ Number analysed

604 subjects received the first infant series dose, 589 received the second dose, and 569 received the toddler dose. Of those who received the toddler dose, 285 and 281 subjects completed the toddler dose period in the 13vPnC and 7vPnC groups, respectively. After the toddler dose interval, 2 subjects in the 7vPnC group were withdrawn from the study, so that 285 and 279 subjects completed the study. Because a telephone contact was to be attempted on all subjects 6 months after their last vaccination (regardless of the number of vaccinations), the numbers of subjects for the 6-month follow-up period were greater than the numbers of subjects completing the study. In the 13vPnC group, 290 subjects entered and all completed the 6-month follow-up. In the 7vPnC group, 288 subjects entered and 286 subjects completed the 6-month follow-up.

- Efficacy results

N.a.

- Safety results

AEs were reported for 21 subjects during the relevant period, 10 (3.3%) in the 13vPnC group and 11 (3.6%) in the 7vPnC group. The AEs categorized as infections and infestations were reported most frequently in both vaccine groups. Of the individual AEs, the highest incidence was for gastroenteritis (4 [1.3%] subjects in the 7vPnC group) and febrile convulsion (2 [0.7%] subjects for 13vPnC and 1 [0.3%] subject for 7vPnC). When data for all AEs were analyzed, no significant differences between vaccine groups were noted for any AE. None of the AEs reported were considered to be related to study vaccine.

Four (4) severe AEs were reported for 3 subjects in the 7vPnC group and none were reported for the 13vPnC group. The severe AEs included atrioventricular block, bronchitis, and pneumonia. No life-threatening AEs were reported. There were no deaths reported during the 6-month follow-up period.

SAEs were reported during the 6 month follow-up period for 20 subjects, 9 (3.0%) in the 13vPnC group and 11 (3.6%) in the 7vPnC group. SAEs categorized as infections and infestations were reported most frequently in both vaccine groups. Of the individual SAEs, the highest incidence was for gastroenteritis (4 [1.3%] subjects in the 7vPnC group) and febrile convulsion (2 [0.7%] subjects for 13vPnC and 1 [0.3%] subject for 7vPnC). As with the AEs, there were no significant differences between vaccine groups for SAEs and none of the SAEs were considered to be related to study vaccine.

Study 6096A1-501: Final 6-Month Follow-up Addendum to Final Infant and Toddler Report:

A Phase 3, Randomized, Active-Controlled, Double-blind Trial Evaluating the Safety, Tolerability, and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants Given With Routine Pediatric Vaccinations in Spain.

- **Description**

Only a brief description of the study will be included as it has already been assessed during the original MAA procedure.

- **Methods**

- Objective(s)

Demonstrate that the immune response after Meningitec (antigen assessed: MnC by SBA) and 13vPnC is non-inferior to response after Meningitec and 7vPnC measured 1 month after a 2-dose Meningitec infant series.
Assess the non-inferiority of antigen-specific response to PT, FHA, PRN, Dip, Tet, and polio types 1, 2, 3 after Infanrix hexa and 13vPnC relative to Infanrix hexa and 7vPnC.
Assess the immune responses to 13vPnC measured 1 month after dose 2 and 1 month after dose 3 of the infant series and 1 month after the toddler dose.

- Study design

This was a phase 3, parallel-group, randomized, active-controlled, double-blind, multicenter trial to evaluate the safety, tolerability, and immunogenicity of 13vPnC in healthy infants.

- Study population /Sample size

Approximately 600 subjects (300 subjects per group) were to be enrolled in this study in order to achieve 270 evaluable subjects per group across 35 sites.

- Treatments

Each subject was to receive 1 dose (0.5 mL) of either 13vPnC or 7vPnC together with 1 dose (0.5 mL) of each of the following concomitant vaccines: Infanrix hexa/Infanrix-IPV+Hib, Meningitec, and MMR II.

- Outcomes/endpoints

Each subject's parent(s)/legal guardian(s) was contacted by telephone approximately 6 months after the last study vaccination; this included both subjects who completed the study and those who discontinued prematurely. They were asked to report any newly diagnosed chronic medical conditions, hospitalizations, serious adverse events (SAEs), and other reportable information that had occurred since the last study visit.

- Statistical Methods

The data are descriptive.

- **Results**

- Recruitment/ Number analysed

619 subjects were randomly assigned to study vaccine; 616 subjects received the first infant series dose, 605 received the second dose, 597 received the third dose, and 582 received the toddler dose. Five hundred seventy-nine (579) subjects completed the toddler dose and the study. Because a telephone contact was to be attempted for all subjects 6 months after their last vaccination (regardless of the number of vaccinations), the numbers of subjects for the 6-month follow-up period were greater than the numbers of subjects completing the study. In the 13vPnC group, 299 subjects entered and all completed the 6-month follow-up. In the 7vPnC group, 292 subjects entered and 289 subjects completed the 6-month follow-up.

- Efficacy results

N.a.

- Safety results

AEs were reported for 13 subjects during the relevant period, 6 (1.9%) in the 13vPnC group and 7 (2.3%) in the 7vPnC group. The AEs categorized as infections and infestations were reported most frequently in both vaccine groups. When data for all AEs were analyzed, no significant differences

between vaccine groups were noted for any AE. None of the AEs reported were considered related to study vaccine. Most of the AEs reported were the types of conditions and symptoms expected in infants of this age. Four (4) severe AEs were reported for 1 subject (501-015-000813) in the 7vPnC group and none were reported for the 13vPnC group.
There were no deaths reported during the 6-month follow-up period.
SAEs were reported during this period for 9 subjects, 3 (1.0%) in the 13vPnC group and 6 (2.0%) in the 7vPnC group. SAEs categorized as infections and infestations were reported most frequently in both vaccine groups. Of the individual SAEs, the highest incidence in the 13vPnC group was for gastroenteritis (2 subjects, 0.6%) and in the 7vPnC group was for febrile convulsion (2 subjects, 0.7%). As with the AEs, there were no significant differences between vaccine groups for SAEs and none of the SAEs were considered related to study vaccine.

Study 6096A1-3005: Final Toddler Report: A Phase 3, Randomized, Active-Controlled, Double-Blind Trial Evaluating The Safety, Tolerability, and Immunogenicity of 3 lots of 13- Valent Pneumococcal Conjugate Vaccine In Healthy Infants given with Routine Pediatric Vaccinations in The United States.

- **Description**

Only a brief description of the study will be included as it has already been assessed during the original MAA procedure. The immunogenicity and safety data from the toddler dose from Study 6096A1-3005 are presented in the CSR submitted at this time, however it should be noted that the infant series data were already submitted as part of the MAA. This present CSR also includes the additional non-inferiority comparison of the anti-polysaccharide IgG responses after the infant series that were submitted in response to questions during review of the MAA. The safety data collected after the infant series (ie, the period from after the dose 3 blood draw to the toddler dose vaccination) are also described.

- **Methods**

- Objective(s)

Demonstrate that the immune responses induced by 3 lots of 13vPnC are equivalent at 1 month after the infant series.
Demonstrate the non-inferiority of immune response induced by Pediarix given with 13vPnC relative to Pediarix given with 7vPnC 1 month after the infant series (antigens assessed: Tet; polio types 1, 2, 3; HBV). (The results relating to this objective were assessed previously)
The secondary objective of this study was to demonstrate that the immune responses induced by the 3 lots of 13vPnC are equivalent when measured by serum IgG levels 1 month after the toddler dose.

- Study design

This was a parallel-group, randomized, active-controlled, double-blind, multicenter trial conducted to evaluate the safety, tolerability, and immunogenicity of 3 lots of 13vPnC in healthy infants when coadministered with routine pediatric vaccinations.

- Study population /Sample size

Approximately 1645 subjects (470 subjects in the 13vPnC pilot scale lot 1 group, 470 subjects in the 13vPnC pilot scale lot 2 group, 470 subjects in the 13vPnC manufacturing scale lot group, and 235 subjects in the 7vPnC group) were to participate in this study at approximately 85 sites, to achieve 1400 evaluable subjects (400 subjects in the 13vPnC pilot scale lot 1 group, 400 subjects in the 13vPnC pilot scale lot 2 group, 400 subjects in the 13vPnC manufacturing scale lot group, and 200 subjects in the 7vPnC group).

- Treatments

All subjects were to receive 1 dose (0.5 mL) of either 13vPnC or 7vPnC at each of the 4 vaccination visits along with a concomitant dose of Pediarix and Hib vaccine at the 2-, 4-, and 6-month visits, and with MMR, varicella, and hepatitis A vaccines at the 12-month visit according to their randomization.

- Outcomes/endpoints

Blood samples (approximately 5 mL) were to be collected at visit 4 (28 to 42 days after the infant series) and at visit 6 (28 to 42 days after the toddler dose), with a total volume of approximately 10 mL of blood for the duration of the study.

For subjects in the 7vPnC and 13vPnC groups, 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) were determined for each blood sample and expressed as micrograms per milliliter (µg/mL).
For each of the concomitant vaccine antigen responses described below, the assays were performed for all subjects in the 7vPnC group, and for an equal number of subjects from the 13vPnC groups:

- Serum levels of IgG antibodies to tetanus toxoid were measured using an antitetanus toxoid ELISA performed on blood samples collected 1 month after the infant series. Results were reported as international units per milliliter (IU/mL).
- Serum levels of antibody to poliovirus (strains 1, 2, and 3) were measured using a polio in vitro plaque neutralization assay performed on blood samples collected 1 month after the infant series. Results were reported as antibody titers.
- Serum levels of antibody to HBsAg were measured using an FDA-approved in vitro diagnostic kit and performed on blood samples collected 1 month after the infant series. Results were reported as milli-international units per milliliter (mIU/mL).

- Statistical Methods

The pneumococcal IgG serotype antibody concentrations were logarithmically transformed for analysis. Within each lot and for each antibody concentration separately, geometric means of the antibody concentration at each of the visits were calculated and rank ordered from lowest (1) to highest (3). Two (2)-sided, 95% CIs were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. In addition, the ratio of the GMCs and corresponding 2-sided, 95% CIs were computed to aid in interpretation of results. For the geometric mean ratio, the CIs were computed using the Student t distribution for the mean difference of the measures on the log scale (lowest relative to middle, lowest relative to highest and middle relative to highest). To evaluate equivalency among the 3 lots, the equivalence test of Wiens and Iglewicz was used.
For each of the pneumococcal serotypes, the proportion of subjects achieving a serum IgG ≥0.35 µg/mL and the proportion of subjects achieving a serum IgG ≥1.00 µg/mL 1 month after the infant series and 1 month after the toddler dose were computed. In addition, the proportions of subjects achieving antibody concentration ≥0.15 µg/mL 1 month after the infant series and 1 month after the toddler dose were computed. Exact, unconditional, 2-sided, 95% CIs on the pairwise difference in proportions were calculated to aid in interpretation of results. The CIs were computed using the non-inferiority procedure of Chan and Zhang, using the standardized test statistics and gamma=0.000001. To evaluate the consistency among the 3 lots, the equivalence test of Wiens and Iglewicz was used. The 3 lots of 13vPnC were to be considered equivalent if, for all 13 serotypes, the maximum difference between any 2 lots is less than 0.693 and greater than –0.693 using the equivalence testing procedure for 3 vaccine groups given by Wiens and Iglewicz. Similar descriptive procedures were used for other time points.

- **Results**

- Recruitment/ Number analysed

A total of 1712 subjects were randomly assigned in a 2:2:2:1 ratio to receive 13vPnC pilot scale lot 1, 13vPnC pilot scale lot 2, 13vPnC manufacturing scale lot, or 7vPnC, together with concomitant Pediarix and Hib vaccine at 2, 4, and 6 months of age for the infant series. However, of the 1712 randomly assigned subjects, 3 subjects (2 randomly assigned subjects to 13vPnC pilot scale lot 2 and 1 subject assigned to 13vPnC manufacturing scale lot) had not given consent to be in the study, and thus were withdrawn from the study prior to receiving study vaccine. A total of 1508 subjects were previously reported as completing the infant series (see section 8.1 in infant CSR-74251), however, the data for 1 subject randomly assigned to 13vPnC manufacturing scale lot changed after the analysis of the infant series. Therefore, 1507 subjects (88.0%) completed the infant series.
A total of 76 subjects (4.4%) were withdrawn after the infant series (after the blood draw following dose 3 of the infant series up to administration of the toddler dose); a similar percentage of subjects were withdrawn after the infant series from each 13vPnC group (4.1% in the pilot scale lot 1 group, 5.9% in the pilot scale lot 2 group, and 3.7% in the manufacturing scale lot group) and the 7vPnC group (3.7%). An additional 3 subjects (0.1%) with an unknown completion status also withdrew after the infant series, but the study conclusion form was completed at a subsequent visit. The remaining 1428 subjects (1220 in the 13vPnC groups and 208 in the 7vPnC group) were vaccinated with the toddler dose and made up the safety population. A total of 25 subjects (1.5%) were withdrawn during the toddler dose period before the blood sample was obtained (17 in the 13vPnC groups and 8 subjects in the 7vPnC group). Thus, 1403 subjects (82.0%) completed the toddler dose portion of the study. A telephone contact was to be attempted for all subjects 6 months after their last vaccination (including

subjects who did not complete the study because of early discontinuation). Of the 1464 subjects who agreed to be contacted, 1430 subjects 85.3%, 83.2%, and 83.0% in the 13vPnC groups, and 81.7% in the 7vPnC group) completed the 6-month follow-up telephone contact. A total of 1376 subjects (80.4%) completed the study; a similar percentage of subjects completed the study from each 13vPnC group (82.4%, 78.7%, and 80.4% in the 13vPnC groups) and the 7vPnC group (79.7%). Twenty-seven (27) subjects were withdrawn after the toddler dose. One (1) subject (13vPnC pilot scale lot 1) was withdrawn because of an SAE; the remaining 26 subjects were lost to follow-up.

- Efficacy results

This assessment report presents the planned assessments of pneumococcal immune responses in 13vPnC lots measured 1 month after the toddler dose (visit 6), a secondary objective of the study. In addition, this report presents the additional assessments of pneumococcal immune responses measured 1 month after the toddler dose in the 7vPnC group, and varicella and mumps immune responses measured 1 month after the toddler dose.

Immune Response to Pneumococcal Conjugate Vaccines

The three 13vPnC lots were determined to be equivalent across all serotypes as confidence intervals for the differences between each 2-way comparison of vaccine lots, expressed as the natural log-transformed geometric mean concentration (GMC) values, was less than the absolute value of 0.693 (2-fold criterion). The differences between vaccine lots in log-transformed geometric means were small for all serotypes (table 9-2). Across the common serotypes, the largest differences were 0.18 for lot 1 to lot 2 (serotype 6B), -0.37 for lot 1 to the manufacturing scale lot (serotype 19F), and -0.33 for lot 2 to the manufacturing scale lot (serotype 19F). Across the additional serotypes, the largest differences were 0.17 for lot 1 to lot 2 (serotype 5), 0.10 for lot 1 to the manufacturing scale lot (serotypes 5 and 6A), and -0.13 for lot 2 to the manufacturing scale lot (serotype 3). Similar results were seen for the all-available population.

Table 9-2: Pneumococcal IgG GMCs Equivalency Assessment (µg/mL) After the Toddler Dose- Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)											
	13vPnC Pilot Lot 1			13vPnC Pilot Lot 2			13vPnC Manufacturing Lot			Difference (95% CI) in Log-Transformed Geometric Means		
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	13vPnC Pilot Lot 1 - Pilot Lot 2	13vPnC Pilot Lot 1 - Manufacturing Lot	13vPnC Pilot Lot 2 - Manufacturing Lot
7vPnC												
4	364	2.29	(2.11, 2.48)	342	2.25	(2.07, 2.44)	355	3.06	(2.79, 3.35)	0.02 (-0.10, 0.13)	-0.29 (-0.41, -0.17)	-0.31 (-0.43, -0.19)
6B	368	11.14	(10.24, 12.11)	341	9.33	(8.55, 10.19)	357	9.92	(9.15, 10.75)	0.18 (0.06, 0.30)	0.12 (-0.00, 0.23)	-0.06 (-0.18, 0.06)
9V	368	1.91	(1.76, 2.06)	342	1.95	(1.80, 2.10)	357	1.99	(1.84, 2.15)	-0.02 (-0.13, 0.09)	-0.04 (-0.15, 0.07)	-0.02 (-0.13, 0.09)
14	366	6.61	(6.06, 7.22)	344	7.05	(6.42, 7.74)	358	6.91	(6.32, 7.56)	-0.06 (-0.19, 0.06)	-0.04 (-0.17, 0.08)	0.02 (-0.11, 0.15)
18C	362	1.95	(1.78, 2.12)	341	2.20	(2.01, 2.41)	354	2.48	(2.27, 2.71)	-0.12 (-0.25, 0.00)	-0.24 (-0.37, -0.12)	-0.12 (-0.25, 0.01)
19F	362	4.51	(4.05, 5.03)	342	4.67	(4.23, 5.14)	353	6.51	(5.91, 7.18)	-0.03 (-0.18, 0.11)	-0.37 (-0.51, -0.22)	-0.33 (-0.47, -0.20)
23F	362	3.35	(3.02, 3.71)	340	3.46	(3.14, 3.82)	353	3.10	(2.81, 3.43)	-0.03 (-0.17, 0.11)	0.08 (-0.07, 0.22)	0.11 (-0.03, 0.25)
Additional												
1	367	2.75	(2.53, 2.99)	344	2.95	(2.68, 3.24)	357	3.01	(2.75, 3.30)	-0.07 (-0.20, 0.06)	-0.09 (-0.21, 0.03)	-0.02 (-0.15, 0.11)
3	366	0.75	(0.69, 0.81)	343	0.71	(0.65, 0.77)	356	0.80	(0.74, 0.87)	0.06 (-0.06, 0.18)	-0.07 (-0.18, 0.04)	-0.13 (-0.25, -0.01)
5	368	3.11	(2.87, 3.37)	343	2.63	(2.42, 2.87)	357	2.80	(2.60, 3.02)	0.17 (0.05, 0.28)	0.10 (-0.00, 0.21)	-0.06 (-0.17, 0.05)
6A	366	7.52	(6.93, 8.17)	342	6.97	(6.41, 7.59)	355	6.83	(6.30, 7.41)	0.08 (-0.04, 0.19)	0.10 (-0.02, 0.21)	0.02 (-0.10, 0.14)
7F	366	4.35	(4.01, 4.72)	343	4.24	(3.86, 4.66)	358	4.58	(4.21, 4.98)	0.03 (-0.10, 0.15)	-0.05 (-0.17, 0.07)	-0.08 (-0.20, 0.05)
19A	362	8.41	(7.73, 9.14)	341	8.32	(7.66, 9.04)	353	8.60	(7.91, 9.36)	0.01 (-0.11, 0.13)	-0.02 (-0.14, 0.10)	-0.03 (-0.15, 0.08)

a. n = Number of subjects with a determinate immunoglobulin G (IgG) antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transforms of confidence levels based on the Student t distribution for the mean logarithm of the concentrations.
Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_GMC_13V_EQUIV.SAS. Runtime ID: 07MAY2009 16:53
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/Immuno_6MAY09.zip/imm_pnc_elisa_gmc_equiv_13v_eval_tp.htm

The percentage of responders in the evaluable pneumococcal toddler immunogenicity population with antibody concentrations ≥0.35 µg/mL for the 7 common serotypes was at least 98.3% for the 3 lots. For the 6 additional serotypes, the percentage of responders was at least 99.1% for all serotypes except serotype 3, where the percentage of responders was 83.6% for the pilot lot 1 group, 80.8% for the pilot lot 2 group, and 88.5% for the manufacturing lot group. Similar results were seen in the all-available toddler immunogenicity population for all 13 serotypes.

The percentage of responders in the evaluable pneumococcal toddler immunogenicity population with antibody concentrations ≥1.00 µg/mL for the 7 common serotypes of the three 13vPnC lots was at least 79.6% (Table 9-4). For the 6 additional serotypes, the percentage of responders was at least 91.0% for all serotypes except serotype 3, where the percentage of responders with antibody concentrations ≥1.00 µg/mL was 32.0%, 30.3%, and 36.8% for the 3 lots of 13vPnC. Similar results were seen in the all-available toddler immunogenicity population for all 13 serotypes.

Table 9-3: Comparison of Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL for Each 13vPnC Group After the Toddler Dose - Evaluable Pneumococcal Toddler Immunogenicity Population

	Vaccine Group (as Randomized)													
	13vPnC Pilot Lot 1				13vPnC Pilot Lot 2				13vPnC Manufacturing Lot				Difference (95% CI) in Percentage			
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	13vPnC Pilot Lot 1 - Pilot Lot 2	13vPnC Pilot Lot 1 - Manufacturing Lot	13vPnC Pilot Lot 2 - Manufacturing Lot
7vPnC															
4	364	361	99.2	(97.6, 99.8)	342	339	99.1	(97.5, 99.8)	355	355	100.0	(99.0, 100.0)	0.1 (-1.61, 1.81)	-0.8 (-2.39, 0.23)	-0.9 (-2.54, 0.20)
6B	368	368	100.0	(99.0, 100.0)	341	341	100.0	(98.9, 100.0)	357	357	100.0	(99.0, 100.0)	0.0 (-1.02, 1.11)	0.0 (-1.03, 1.04)	0.0 (-1.13, 1.06)
9V	368	367	99.7	(98.5, 100.0)	342	341	99.7	(98.4, 100.0)	357	354	99.2	(97.6, 99.8)	0.0 (-1.25, 1.37)	0.6 (-0.76, 2.18)	0.5 (-0.87, 2.18)
14	366	366	100.0	(99.0, 100.0)	344	343	99.7	(98.4, 100.0)	358	358	100.0	(99.0, 100.0)	0.3 (-0.74, 1.62)	0.0 (-1.03, 1.04)	-0.3 (-1.61, 0.76)
18C	362	358	98.9	(97.2, 99.7)	341	336	98.5	(96.6, 99.5)	354	352	99.4	(98.0, 99.9)	0.4 (-1.52, 2.39)	-0.5 (-2.30, 1.04)	-0.9 (-2.87, 0.74)
19F	362	356	98.3	(96.4, 99.4)	342	338	98.8	(97.0, 99.7)	353	351	99.4	(98.0, 99.9)	-0.5 (-2.55, 1.50)	-1.1 (-3.06, 0.57)	-0.6 (-2.44, 1.00)
23F	362	360	99.4	(98.0, 99.9)	340	337	99.1	(97.4, 99.8)	353	347	98.3	(96.3, 99.4)	0.3 (-1.21, 2.05)	1.1 (-0.52, 3.16)	0.8 (-1.05, 2.87)
Additional															
1	367	367	100.0	(99.0, 100.0)	344	341	99.1	(97.5, 99.8)	357	354	99.2	(97.6, 99.8)	0.9 (-0.17, 2.53)	0.8 (-0.20, 2.44)	-0.0 (-1.79, 1.66)
3	366	306	83.6	(79.4, 87.3)	343	277	80.8	(76.2, 84.8)	356	315	88.5	(84.7, 91.6)	2.8 (-2.85, 8.55)	-4.9 (-9.99, 0.21)	-7.7 (-13.14, -2.37)
5	368	367	99.7	(98.5, 100.0)	343	341	99.4	(97.9, 99.9)	357	356	99.7	(98.4, 100.0)	0.3 (-1.00, 1.84)	0.0 (-1.27, 1.30)	-0.3 (-1.84, 1.02)
6A	366	366	100.0	(99.0, 100.0)	342	342	100.0	(98.9, 100.0)	355	354	99.7	(98.4, 100.0)	0.0 (-1.04, 1.08)	0.3 (-0.76, 1.56)	0.3 (-0.83, 1.56)
7F	366	366	100.0	(99.0, 100.0)	343	341	99.4	(97.9, 99.9)	358	356	99.4	(98.0, 99.9)	0.6 (-0.47, 2.09)	0.6 (-0.48, 2.00)	-0.0 (-1.59, 1.49)
19A	362	362	100.0	(99.0, 100.0)	341	341	100.0	(98.9, 100.0)	353	353	100.0	(99.0, 100.0)	0.0 (-1.04, 1.09)	0.0 (-1.05, 1.04)	0.0 (-1.09, 1.07)

a. N = number of subjects with a determinate immunoglobulin G (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.
Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_COMP_13V_POP.SAS. Runtime ID: 07MAY2009 08:54
Source: EDMS Cabinets/CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Toddler Reports, Tables, Figures/Immunogenicity/Immuno_6MAY09.zip/imm_pnc_elisa_compare_13v_pt35_eval_tp.htm

A non-inferiority comparison of the anti-polysaccharide IgG responses after the infant series and after the toddler dose was performed during the procedure and submitted in response to questions. These analyses showed that the responses to the 7 common serotypes in 13vPnC were non-inferior to the 7vPnC responses. Additional analyses comparing the responses to the 6 additional serotypes to the lowest responder to the 7 common serotypes in 7vPnC recipients are presented in the CSR. These data showed that responses to the 6 additional serotypes were non-inferior for all serotypes, except for serotype 3. At the additional comparison level of ≥0.15 µg/mL, non-inferiority criterion was met for all 13 serotypes, including serotype 3. And, when compared to the actual responses in 7vPnC recipients, the responses to the 6 additional serotypes, including serotype 3, were superior in 13vPnC recipients. These data are similar to what was seen in the US pivotal trial, study 004. The inability of the serotype 3 response to meet the non-inferiority criteria in these 2 studies performed in a US infant population is very different from the responses to serotype 3 in all other phase 3 clinical trials which were higher. These studies were performed in various European countries using several infant vaccination schedules. The differences in responses cannot be attributed to differences in vaccine or monovalent conjugated serotype 3 bulk substance, because common vaccine and drug substance lots were used across studies. The reason for the relatively lower responses seen in the US trials is unknown.

Responses to concomitant vaccine antigens
Varivax was to be administered concomitantly with 13vPnC or 7vPnC at the 12-month visit. Responses to the varicella antigen in Varivax were evaluated at 2 prespecified antibody levels associated with seroconversion (≥1.25 gpELISA units/mL) and long-term protection (≥5.00 gpELISA units/mL). The proportion of responders in the 13vPnC and 7vPnC groups were similar. All (100%) Varivax recipients in both the 13vPnC and 7vPnC groups achieved antibody levels ≥1.25 gpELISA units/mL; 98.8% and 97.7% in the 13vPnC and 7vPnC groups, respectively, achieved antibody levels ≥5.00 gpELISA units/mL.
Geometric mean values were 15.38 gpELISA units/mL in the 13vPnC combined group and 16.04 gpELISA units/mL in the 7vPnC group. The geometric mean ratio (13vPnC/ 7vPnC) was 0.96 and the ratio at the lower limit of the 95% CI was 0.85.

The proportion of subjects in the evaluable concomitant vaccine toddler immunogenicity population achieving a mumps serum antibody titer ≥10.0 antibody (Ab) units/mL was 95.7% in the 13vPnC combined group and 97.6% in the 7vPnC group. The difference (13vPnC combined – 7vPnC) in the proportion of responders between vaccine groups was -1.9, and the difference at the lower limit of the 95% CI was -6.5.
The geometric mean levels of mumps antibodies after the toddler dose were 58.55 Ab units/mL for the 13vPnC combined group and 66.91 Ab units/mL for the 7vPnC group in the evaluable concomitant vaccine toddler immunogenicity population. The ratio (13vPnC/ 7vPnC) was 0.88 and the ratio at the lower limit of the 95% CI was 0.71.

- Safety results

Safety results after the toddler dose
The endpoints for the safety analysis were the incidence of local reactions, systemic events, and AEs. Parent(s)/legal guardian(s) were required to monitor the occurrence of local reactions and systemic events that occurred within 7 days after the toddler dose and enter these into an e-diary.
Local reactions included tenderness, induration, and erythema at the site of the pneumococcal conjugate injection. The systemic events specified in the protocol were fever (core [rectal] temperature of equal to or greater than 100.4°F [38.0°C]) and use of antipyretic medications to treat and to prevent symptoms, as well as decreased appetite, irritability, hives (urticaria), increased sleep, and decreased sleep. The severity of local reactions was also assessed and reported in the e-diary.
Adverse events were to be collected from the signing of the informed consent until the infant series blood draw at 1 month after dose 3 and between visit 5 and visit 6. All SAEs were to be recorded from the signing of the informed consent to 6 months after the last study vaccination when a telephone contact was to be made to record any newly diagnosed chronic medical conditions, hospitalizations, SAEs, and other reportable information that occurred since the last study visit. Presented in this section are the safety results from the toddler dose and the 6-month follow-up telephone contact.
Safety data from the infant series visits were presented and assessed previously.

Reactogenicity
A summary of local reaction reported wihthi 7 days of the toddler dose is presented in Table 10-1. The frequency of subjects with at least 1 local reaction was similar in the 13vPnC combined group (69.0%) and the 7vPnC group (75.2%; Table 10-1). Most local reactions were mild in severity.

Table 10-1: Subjects Reporting Local Reactions Within 7 Days - Toddler Dose

	Vaccine Group (as Administered)						
	13vPnC Combined			7vPnC			
Local Reaction	N[a]	n[b]	%	N[a]	n[b]	%	p-Value[c]
Tenderness							
Any	826	473	57.3	131	83	63.4	0.215
Significant[d]	630	42	6.7	97	4	4.1	0.500
Induration							
Any	698	220	31.5	110	48	43.6	0.016
Mild[e]	689	199	28.9	107	44	41.1	0.013
Moderate[e]	627	53	8.5	101	18	17.8	0.006
Severe[e]	603	0	0.0	93	0	0.0	N/A
Erythema							
Any	749	319	42.6	121	64	52.9	0.038
Mild[e]	735	288	39.2	116	58	50.0	0.032
Moderate[e]	631	67	10.6	104	22	21.2	0.005
Severe[e]	603	0	0.0	93	0	0.0	N/A
Any of the above	889	613	69.0	141	106	75.2	0.140

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

The number and percentage of subjects with systemic events within 7 days after the toddler dose are summarized in Table 10-3. Overall, the percentage of subjects having 1 or more systemic events, excluding the use of antipyretic medications, was 90.5% in the 13vPnC combined group and 88.9% in the 7vPnC group. There were no significant differences between the vaccine groups in the incidence of individual systemic events or for any systemic event.

Table 10-3: Subjects Reporting Systemic Events and Antipyretic Medication Use Within 7 Days - Toddler Dose

	Vaccine Group (as Administered)						
	13vPnC Combined			7vPnC			
Systemic Event	N[a]	n[b]	%	N[a]	n[b]	%	p-Value[c]
Fever ≥38°C but ≤39°C	667	192	28.8	107	32	29.9	0.819
Fever >39°C but ≤40°C	592	26	4.4	95	5	5.3	0.603
Fever >40°C	586	6	1.0	93	0	0.0	>.99
Decreased appetite	790	410	51.9	115	58	50.4	0.842
Irritability	943	771	81.8	160	128	80.0	0.583
Increased sleep	779	372	47.8	126	60	47.6	>.99
Decreased sleep	770	361	46.9	117	50	42.7	0.427
Hives (urticaria)	607	13	2.1	96	5	5.2	0.085
Use of medication to treat symptoms	845	532	63.0	127	82	64.6	0.768
Use of medication to prevent symptoms	889	637	71.7	150	108	72.0	>.99
Any systemic event[d]	1001	906	90.5	171	152	88.9	0.487

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

Other adverse events

During the toddler dose, ie, the period from the toddler dose to the blood draw after the toddler dose, 438 subjects (36.2%) in the 13vPnC combined group had 728 AEs and 76 subjects (36.5%) in the 7vPnC group had 138 AEs. The AEs categorized under infections and infestations were reported most frequently in both vaccine groups, with otitis media and upper respiratory tract infection being the most common infections. Otitis media was reported in 70 recipients (5.8%) of 13vPnC and 20 recipients (9.6%) of 7vPnC, and upper respiratory tract infection was reported in 62 recipients (5.1%) of 13vPnC and 11 recipients (5.3%) of 7vPnC. No statistically significant differences between vaccine groups in the incidence of AEs were observed for any system organ class; however, a significantly (p=0.045) higher percentage of subjects in the 7vPnC group had otitis media than in the 13vPnC combined group and a significantly (p=0.044) higher percentage of subjects in the 7vPnC group had constipation than in the 13vPnC combined group.

During the toddler dose 7 subjects (0.6%) in the 13vPnC combined group had 8 severe or life-threatening AEs and 2 subjects (1.0%) in the 7vPnC group had 3 events. A single life-threatening AE, near drowning, was reported in a 13vPnC recipient. No event considered severe occurred in multiple subjects. No statistically significant differences between vaccine groups were noted for individual AEs, however, in the system organ class of gastrointestinal disorders, a significantly (p=0.021) higher percentage of 7vPnC recipients than 13vPnC recipients reported severe AEs. This included severe diarrhea in 1 subject and severe constipation in 1 subject; both subjects were recipients of 7vPnC.

During the toddler dose 21 recipients (1.7%) of 13vPnC had 24 related AEs and 1 recipient (0.5%) of 7vPnC had a related AE. The most frequent related AEs were in the category of general disorders and administration site conditions. The majority of these events occurred at concomitant vaccine injection sites, and the others described reactions that were not captured in the e-diary (bruising or "knot" at injection site). The most frequent related AEs were pyrexia and rash. Pyrexia assessed as related occurred in 3 recipients (0.2%) of 13vPnC and 1 recipient (0.5%) of 7vPnC. All 4 cases of rash assessed as related were reported in 4 recipients (0.3%) of 13vPnC. No statistically significant differences between vaccine groups were noted for any related AE.

During the toddler dose, 9 recipients (0.7%) of 13vPnC had a total of 11 SAEs and 1 recipient (0.5%) of 7vPnC had 3 SAEs. The most common SAEs were in the category of infections and infestations, which were in 0.3% of subjects in the 13vPnC combined group and 0.5% of subjects in the 7vPnC group. No statistically significant differences between vaccine groups were noted in the incidence of SAEs.

One (1) SAE was assessed as related to study vaccine. Subject 3005-040-003830 received the 13vPnC manufacturing lot at the toddler dose and concomitant MMR, varicella, and HAV. Four (4) days later the subject had bronchial hyperreactivity, which was considered to be of moderate severity. Approximately 8 months preceding this event, 2 days after receiving dose 2 of the infant series, the subject also had an SAE of bronchiolitis, which was considered to be of moderate severity and not related to the study vaccine.

No subjects were withdrawn because of AEs during the toddler dose.

No deaths were reported after the toddler dose.

6 months follow-up after the infant dose

Summaries of the AEs to be reported after the infant series, up until the toddler dose are provided below. After the infant series, 111 subjects (7.7%) in the 13vPnC combined group had 140 AEs and 14 subjects (5.7%) in the 7vPnC group had 15 AEs. In addition, an AE was reported for 1 subject who received a vaccination other than the randomly assigned vaccine during the infant series.

The AEs reported most frequently after the infant series were categorized as infections and infestations, including 38 events in 32 recipients of 13vPnC (2.2%) and 2 events in 2 recipients of 7vPnC (0.8%); and as respiratory, thoracic and mediastinal disorders, including 29 events in 25 recipients of 13vPnC (1.7%) and 6 events in 5 recipients of 7vPnC (2.0%). The incidence of individual AEs did not exceed 1.0% of recipients of either study vaccine; rhinitis allergic, bronchial hyperreactivity, and eczema had the highest incidences and were reported by no more than 0.8% of

recipients of either study vaccine. Any differences between the 13vPnC combined and 7vPnC groups were not statistically significant.
After the infant series, 25 severe or life threatening AEs were reported in 17 subjects (1.2%) in the 13vPnC combined group and 2 events in 2 subjects (0.8%) in the 7vPnC group. None of the severe or life threatening AEs after the infant series were related to study vaccination.
One (1) of the AEs was life threatening. Subject 3005-038-003637 was hospitalized for respiratory arrest. This AE resolved on the day of onset.
No significant differences were observed between the 13vPnC combined group and the 7vPnC group.
Thirty-seven (37) SAEs were reported in 25 recipients of 13vPnC (1.7%) and 3 SAEs were reported in 3 recipients of 7vPnC (1.2%) after the infant series. In addition, 1 SAE (respiratory syncytial virus bronchiolitis) was reported in a subject who received a vaccination other than the randomly assigned vaccine. None of the SAEs were considered related to the vaccine. The most common SAEs were those categorized as infections and infestations. Serious infections occurred in 17 recipients of 13vPnC (1.2%), which includes the 1 subject who received a vaccination other than the randomly assigned vaccine. Cellulitis was the most common event in this category and occurred in 3 recipients of 13vPnC (0.2%); no recipients of 7vPnC reported cellulitis. Among the recipients of 7vPnC, 1 subject (0.4%) had a serious infection of pneumonia. No statistically significant differences between vaccine groups were noted in the incidence of SAEs.

3. Discussion on clinical aspects

MAH overall conclusions:
Additional pneumococcal immunogenicity data from study 3005 show that the responses elicited by 13vPnC in its final formulation are comparable and non-inferior to those elicited by 7vPnC following a 2, 4, 6-month infant series and following the toddler dose. The results from study 3005 also indicate that coadministration of 13vPnC does not interfere with responses to mumps or varicella antigens in comparison with results following coadminstration of 7vPnC.
The toddler dose safety data from study 3005 demonstrated similar rates of local reactions and systemic events among 13vPnC and 7vPnC recipients. There were no differences in the rates and nature of SAEs and other AEs associated with 13vPnC compared with 7vPnC in the additional safety data from studies 006, 500, 501, and 3005. The safety profile of 13vPnC was shown to be comparable with 7vPnC and the frequency of adverse drug reactions (ADRs) has not changed compared with the frequency reported in the MAA.
The data presented in this Article 46 submission package does not alter the benefit-risk assessment of 13vPnC.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Immunogenicity: The results of study 3005 confirm what was reported during the MAA procedure. The responses to serotype 3 were considerably lower than to the other serotypes, which was also seen in the previously reported clinical trials. Many of the data presented in the clinical study report were already discussed during the procedure, and will not be addressed again here.
Safety: The results presented confirm the previous safety profile of Prevenar 13. No new safety signals were detected.

- **Overall conclusion**
- **Recommendation**

X Fulfilled –

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

None.