22 May 2014
EMA/CHMP/495981/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prevenar 13

International non-proprietary name: pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure No. EMEA/H/C/001104/II/0098

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 29 November 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Prevenar 13	pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2, 4.4, 4.8 and 5.1 to add information on the use of Prevenar 13 in populations associated with high risk of pneumococcal infection. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Kristina Dunder

1.2. Steps taken for the assessment

Submission date:	29 November 2013
Start of procedure:	22 December 2013
Rapporteur's preliminary assessment report circulated on:	22 January 2014
Rapporteur's updated assessment report circulated on:	13 February 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 February 2014
MAH's responses submitted to the CHMP on:	21 March 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	8 April 2014
CHMP opinion:	22 May 2014

2. Scientific discussion

2.1. Introduction

Prevenar 13 is a 13-valent pneumococcal conjugate vaccine (13vPnC), containing 13 pneumococcal capsular polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), conjugated to cross-reactive material 197 (CRM197) carrier protein.

Prevenar 13 was first approved in the European Union (EU), on 09 December 2009 for active immunisation for the prevention of invasive disease, pneumonia, and acute otitis media caused by Streptococcus pneumoniae in infants and children from 6 weeks to 5 years of age. Since that time the indication has been extended to include adults aged 50 years and older, children and adolescents aged 6 to 17 years, and adults aged 18 to 49 years.

In December 2012, the MAH submitted a Type II variation (EMEA/H/C/1104/II/76) to add information to the SmPC from 3 clinical studies on the use of 13vPnC in populations with specific conditions associated with increased risk of pneumococcal disease. These included study 6096A1-3014 in children and adolescents with sickle cell disease (SCD, primary analysis submitted) and study 6115A1-3017 in adults with human immunodeficiency virus (HIV) infection (final analysis submitted), each study in subjects who previously had received 23-valent pneumococcal polysaccharide vaccine (23vPS). The variation also included results from study 6096A1-4001 in infants born prematurely (primary analysis submitted). The CHMP adopted a positive Opinion on this procedure on 19 September 2013.

The final results from 2 additional studies in high-risk populations (6115A1-3002 and 6115A1-3003), and the 6-month follow-up safety and 1-year antibody persistence and safety data from study 6096A1-3014 (i.e., no study vaccine administered at 1 year) are now available. The variation currently being submitted includes final study reports for these 3 studies:

- 6115A1-3002 (B1851021): HIV-infected individuals aged ≥ 6 years, not previously immunized with a pneumococcal vaccine; final study report.
- 6115A1-3003 (B1851022): recipients of allogeneic hematopoietic stem cell transplant (HSCT) aged ≥ 2 years, who have not received a pneumococcal vaccine since HSCT; final study report.
- 6096A1-3014 (B1851013): children and adolescents aged ≥ 6 to <18 years with SCD, previously immunized with 23vPS; 6-month safety addendum and 1-year final study report).

These studies are submitted in accordance with Article 46 of the Pediatric Regulation (EC) No 1901/2006. Additionally, study 6115A1-3002 is a post-authorisation commitment to the European Union Marketing Authorisation (MEA 013).

2.2. Clinical Efficacy aspects

The three study reports will be described and assessed together in the following sections.

2.2.1. Methods – analysis of data submitted

Study 6115A1-3002 (B1851021) in HIV-Infected Subjects

Study Design:

This was a Phase 3, open-label, single arm, multicenter trial to evaluate the safety, tolerability, and immunogenicity of 1, 2 and 3 doses of 13vPnC in human immunodeficiency virus (HIV)-infected subjects aged 6 years and older who had not been previously immunized with pneumococcal vaccine. The study was conducted in South Africa and Romania.

Approximately 300 subjects (150 pediatric subjects aged 6 to <18 years and 150 adults aged ≥ 18 years) were to participate in this study at approximately 30 sites. Subjects received 3 doses of 13vPnC followed by 1 dose of 23vPS, with each dose administered at monthly intervals.

The CHMP noted that the current study included subjects who had not been previously vaccinated with 23vPS in contrast to the previously assessed study 6115A1-3017 (see variation II/76) in HIV infected subjects.

Objectives

Primary Objective:

- To evaluate the immune responses 1 month after 3 doses of 13-valent pneumococcal conjugate vaccine (13vPnC) compared with the immune responses 1 month after 2 doses of 13vPnC as measured by serotype-specific immunoglobulin G (IgG) geometric mean fold rises (GMFRs) in subjects ≥ 6 years of age.

Primary Safety Objective:

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

Secondary Objectives:

- To evaluate the immune responses 1 month after 3 doses of 13vPnC compared with the immune responses 1 month after 2 doses of 13vPnC as measured by serotype-specific IgG geometric mean concentrations (GMCs) in subjects ≥ 6 years of age.
- To evaluate the immune responses 1 month after 3 doses of 13vPnC compared with the immune responses 1 month after 2 doses of 13vPnC as measured by serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) and fold rise OPA GMTs in subjects ≥ 6 years of age.
- To evaluate the immune responses 1 month after 3 doses of 13vPnC compared with the immune responses 1 month after 2 doses of 13vPnC as measured by serotype-specific IgG GMCs, IgG GMFRs, OPA GMTs, and OPA GMFRs in the pediatric subgroup (6 to <18 years of age), and in the adult subgroup (≥ 18 years of age).

Exploratory Objectives:

- To evaluate the immune responses 1 month after dose 1 of 13vPnC, as measured by serotype-specific IgG GMCs, IgG GMFRs, OPA GMTs, and OPA GMFRs in subjects ≥ 6 years of age, in the pediatric subgroup (6 to <18 years of age), and in the adult subgroup (≥ 18 years of age).
- To evaluate the immune responses to the 12 common serotypes and 6A, 1 month after 23-valent pneumococcal polysaccharide vaccine (23vPS), as measured by serotypespecific IgG GMCs, IgG GMFRs, OPA GMTs, and OPA GMFRs in subjects ≥ 6 years of age, in the pediatric subgroup (6 to <18 years of age), and in the adult subgroup (≥ 18 years of age).

Main Criteria for Inclusion:

Subjects eligible for the study were HIV-infected male or female subjects aged 6 years or older with a viral load of <50,000 copies/mL and CD4+ T-cell count ≥ 200 cells/μL within 6 months before the investigational product administration. Subjects received stable dose of highly active antiretroviral therapy (HAART) for at least 6 weeks prior to the investigational product administration, or were not receiving antiretroviral therapy. Subjects were naive to any licensed or experimental pneumococcal vaccine. Subjects with preexisting stable disease (as specified in the protocol) were eligible. Subjects or subjects' parents/legal guardians, as appropriate, had to be able to complete an electronic diary (e-diary) and complete all relevant study procedures during study participation, and were expected to be available for the duration of the trial (approximately 8 months). Subjects biologically capable of having children agreed to abstinence or committed to the use of a reliable method of birth control from the signing of the informed consent form (ICF) until 3 months after the last dose of investigational product.

Subjects were excluded if they had an active acquired immune deficiency syndrome (AIDS)-related illness, including opportunistic infections or malignancy, had a history of culture proven invasive disease caused by Streptococcus pneumoniae infection within the last year, or had any other disorder that in the investigator's opinion precluded them from participating in the study, or had any of the other exclusion criteria specified in the protocol.

Vaccines Administered:

13-valent Pneumococcal Conjugate Vaccine: Commercial formulation

23-valent Pneumococcal Polysaccharide Vaccine: commercial formulation. 23vPS is a commercially available pneumococcal polysaccharide vaccine supplied as a 0.5-mL solution. Each 0.5-mL dose consisted of a mixture of purified capsular polysaccharides from 23 types of S pneumoniae: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F, and was formulated to contain 25 µg of each of the 23 purified capsular pneumococcal polysaccharide serotypes.

Each subject received 3 doses (0.5 mL each) of 13vPnC followed by 1 dose (0.5 mL) of 23vPS, with each dose given at approximately 1 month intervals. Each dose of vaccine was administered intramuscularly.

Immunogenicity Evaluations:

Blood samples for immunogenicity assessments were collected from all subjects immediately before and approximately 1 month (28 to 42 days) after each investigational product administration.

Serum concentrations of anticapsular IgG were determined for each of the 13 pneumococcal serotypes contained in 13vPnC using an enzyme-linked immunosorbent assay (ELISA) for each blood sample. IgG concentrations were determined for blood samples collected before and 1 month after vaccination. Serum OPA titers for the 13 pneumococcal serotypes were determined for all blood samples collected before and 1 month after vaccination.

Safety Evaluations:

On Days 1 to 14 after each dose of 13vPnC, subjects reported reactogenicity (local reactions and systemic events) in e-diaries. Local reactions included pain, redness, and swelling at the injection site. Systemic events included fever, vomiting, diarrhea, headache, fatigue, muscle pain, joint pain, and use of antipyretic and pain medications for treatment of symptoms associated with 13vPnC administration.

AEs were recorded in the AE case report form (CRF) from the signing of the ICF through to Visit 5 (approximately 1 month after the last vaccination with 23vPS). Ongoing AEs were recorded. At Visit 6 (Final Telephone Contact), the parent/legal guardian or subject was contacted by telephone to inquire about serious adverse events (SAEs) including hospitalizations, and newly diagnosed major illnesses or chronic medical conditions that occurred since Visit 5. SAEs were recorded in the AE CRF and reported to the sponsor on an SAE form from the signing of the ICF through to the end of the study at the Visit 6 follow-up phone call. In addition, at Visit 6, any emergency room visits that met the criteria of an SAE that occurred since Visit 5 were recorded and reported. AEs were categorized according to the Medical Dictionary for Regulatory Activities. 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.

Statistical Methods

No formal statistical comparisons were made in this open-label study. The number and percentage of subjects enrolled and included in each immunogenicity population were tabulated for each age group and the total sample.

Immunogenicity:

Serotype-specific IgG concentrations and OPA titers were logarithmically transformed for analysis. For each of the 13 serotypes contained in 13vPnC, IgG GMCs and OPA GMTs were computed at each visit (before Vaccination 1 and 1 month after each vaccination); 2-sided, 95% confidence intervals (CIs) on the GMCs and GMTs were constructed at each visit by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. The ratio of IgG concentrations 1 month after 3 doses of 13vPnC relative to that after 2 doses of 13vPnC was assessed for each subject based on logarithmically transformed assay results, and the IgG GMCs and corresponding 2-sided 95% CIs were computed for comparison of 3 doses of 13vPnC relative to 2 doses of 13vPnC. Similarly, the ratio of OPA titers after 3 doses of 13vPnC relative to that after 2 doses of 13vPnC was computed for comparison of 3 doses of 13vPnC relative to 2 doses of 13vPnC with corresponding 95% CIs.

The protocol and SAP did not pre specify an analysis to demonstrate a statistically significant immune response for the comparisons of IgG GMCs and GMFRs and OPA GMTs and GMFRs after vaccine doses. However, the criterion of a lower limit of the 2-sided 95% CI for the GMFRs > 1 was used for a statistically significant increased immune response and the criterion of an upper limit of the 2-sided 95% CI for the GMFRs < 1 was used for a statistically significant decreased immune response. Additionally, the ratios of IgG GMFRs and the ratios of OPA GMFRs were computed for comparison of 1 dose versus 2 doses as well as the comparison of 3 doses versus 2 doses.

Reverse cumulative distribution curves for IgG concentrations and OPA titers are presented after 3 doses of 13vPnC and after 2 doses of 13vPnC for each of the 13 serotypes contained in 13vPnC. Serotype-specific kinetic curves were presented graphically for IgG concentrations and OPA titers assessed at each time point.

The revised lower limit of quantitation (LLOQ) thresholds on the microcolony OPA (mcOPA) assay was documented and additional analysis was performed on the OPA endpoints in other 13vPnC adult studies. Additional immunogenicity analyses were performed. However, to quantify functional antibodies in the OPA assays with appropriate precision and accuracy, the LLOQ was determined for each serotype-specific OPA assay during assay validation. In addition, alternative analyses were conducted where OPA titers below LLOQ were set to 0.5*LLOQ.

Safety:

The local reactions and systemic events, including fever and use of antipyretics and pain medications, were summarized by 2 types of tables and 1 plot for each vaccination, age group, and overall population separately. The AEs and SAEs were summarized by age group and overall population separately for each dose (Dose 1, 2, and 3). In addition, tables for related events, and events characterized as severe or life threatening were tabulated by age group and total sample for those events occurring during the study. The AEs collected from the signing of the ICF to first dose of 13vPnC were listed.

All summaries showed the number and percentage of subjects who experienced at least 1 event of each preferred term, arranged by system organ class, and the number of occurrences of the event.

Study 6115A1-3003 (B1851022): recipients of allogeneic hematopoietic stem cell transplant (HSCT) aged ≥2 years, who have not received a pneumococcal vaccine since HSCT; final study report.

Study Design:

This was a Phase 3, open-label trial to evaluate the safety, tolerability, and immunogenicity of 4 doses of 13vPnC followed by 1 dose of 23vPS in recipients of allogeneic hematopoietic stem cell transplantation

(HSCT) aged 2 years and older. The study was conducted in Belgium, Canada, the Czech Republic, France, Germany, the Netherlands, Poland, Spain, Sweden, and the United States.

Approximately 300 subjects participated in this study at up to 100 sites. It was anticipated that at least 150 adults (≥ 18 years) would be enrolled, though the total number of subjects enrolled and the ratio of pediatric subjects (≥ 2 to <18 years) to adults (≥ 18 years) was dependent on the sites ability to recruit into each strata. In this study, approximately 3 to 6 months (91 to 203 days) after HSCT, all subjects were to receive 4 doses of 13vPnC followed by 1 dose of 23vPS. Doses 1 to 3 of 13vPnC were to be administered at approximately 1-month intervals, Dose 4 at approximately 6 months after Dose 3 of 13vPnC, and 23vPS was to be administered at approximately 1 month after Dose 4 of 13vPnC.

The CHMP noted that the study did not include a healthy control group, and therefore comparisons to healthy subjects are not possible.

Objectives

Primary Objective:

- To evaluate the immune responses 1 month after 3 doses of 13-valent pneumococcal onjugate vaccine (13vPnC) as measured by fold rises of serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) in subjects ≥ 2 years of age.

Secondary Objectives:

- To evaluate the immune responses 1 month after 3 doses of 13vPnC as measured by serotype-specific IgG GMCs in subjects ≥ 2 years of age.
- To evaluate the immune responses 1 month after 4 doses of 13vPnC as measured by serotype-specific IgG GMCs and fold rises of IgG GMCs in subjects ≥ 2 years of age.
- To evaluate the immune responses 1 month after 3 doses and 1 month after 4 doses of 13vPnC as measured by IgG GMCs and fold rise IgG GMCs in the pediatric subgroup (≥ 2 to <18 years) and by serotype-specific IgG GMCs and fold rise IgG GMCs in the adult subgroup (≥ 18 years).

Exploratory Objectives:

- To evaluate the immune responses measured by serotype-specific IgG GMCs and fold rise IgG GMCs in subjects ≥ 2 years of age, in the pediatric subgroup (≥ 2 to <18 years) and in the adult subgroup (≥ 18 years).
    - 1 month after Dose 1 and 1 month after Dose 2 of 13vPnC.
        - Fold rise IgG GMCs: 1 month after Dose 1 and 1 month after Dose 2 relative to before Dose 1.
    - Before and 1 month after Dose 4 of 13vPnC.
        - Fold rise IgG GMCs: 1 month after Dose 4 relative to before Dose 4.
    - 1 month after Dose 4 of 13vPnC compared with 1 month after Dose 3 of 13vPnC.
        - Fold rise IgG GMCs: 1 month after Dose 4 relative to 1 month after Dose 3.
    - 1 month after 23-valent pneumococcal polysaccharide vaccine (23vPS) for the 12 common serotypes and 6A.
        - Fold rise IgG GMCs: 1 month after 23vPS relative to before 23vPS, 1 month after 23vPS relative to before Dose 1 of 13vPnC.

- To evaluate the immune response 1 month after 3 doses of 13vPnC and 1 month after 4 doses of 13vPnC as measured by proportion of subjects achieving a serotype-specific IgG concentration ≥ 0.35 μg/mL in subjects ≥ 2 years of age, in the pediatric subgroup (≥ 2 to <18 years) and in the adult subgroup (≥ 18 years).

Primary Safety Objective:

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

Inclusion/Exclusion Criteria:

Subjects eligible for the study were male or female recipients of allogeneic HSCT aged ≥2 years of age. Subjects underwent allogeneic HSCT approximately 3 to 6 months (91 to 203 days) before enrollment for hematologic disorder. Subjects also underwent allogeneic HSCT with full myeloablative conditioning or reduced intensity conditioning and had stable engraftment (absolute neutrophil count [ANC] >1000/μL; platelet count >50,000/μL). Subjects with complete hematologic remission of underlying disease with very good partial remission (VGPR) acceptable in the case of lymphoma and myeloma were eligible. Subjects biologically capable of having children agreed to abstinence or were committed to the use of a reliable method of birth control from signing of the informed consent form (ICF) until 3 months after the last vaccination. Subjects who had a hematological recovery as defined by ANC >1000/μL; platelet count >50,000/μL were eligible. Subjects or a parent/legal guardian had to be able to complete an electronic diary (e-diary) and complete all relevant study procedures during study participation.

Subjects were excluded if they had an autologous HSCT, had an uncontrolled graft-versus-host disease (GVHD), had a Lansky/Karnofsky score of ≤60%, or had previously been vaccinated with any licensed or experimental pneumococcal vaccine since HSCT. Subjects with receipt of donor lymphocyte infusions during the 28 days preceding enrollment; plasma products or immunoglobulins during the 60 days preceding enrollment; rituximab and chemotherapy for relapse of underlying malignant disease since HSCT; and advanced therapy medicinal products (ATMP) including gene therapy products, somatic cell therapy products, and tissue engineered products at any time before enrollment were also excluded.

Vaccines Administered:

- 13-valent Pneumococcal Conjugate Vaccine: Commercial formulation
- 23-valent Pneumococcal Polysaccharide Vaccine: Commercial formulation

Subjects received 1 dose (0.5 mL) of 13vPnC at each of the 13vPnC visits (Visits 1, 2, 3, and 5), and a single 23vPS dose (0.5 mL) at Visit 6. Each dose of vaccine was administered intramuscularly.

Immunogenicity Evaluations:

Seven (7) blood samples (total volume of approximately 70 mL of blood [10 mL at Visits 1 to 7]) for immunogenicity assessments were collected for the duration of the study from all subjects.

Serotype-specific IgG concentrations to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) were determined by enzyme-linked immunosorbent assay (ELISA). The immunogenicity variables collected for this study were the results of IgG ELISAs performed on the blood samples collected.

The CHMP noted that OPA responses were not studied at all.

Safety Evaluations

On days 1 to 14 after the 13vPnC administration, subjects reported reactogenicity (local reactions and systemic events) in e-diaries. Local reactions included pain, redness, and swelling at the injection site.

Systemic events included fever, vomiting, diarrhea, headache, fatigue, muscle pain, joint pain, and use of antipyretic and pain medications for treatment of symptoms.

AEs were recorded on the case report form (CRF) from the time the subject had taken at least 1 dose of study treatment through last subject visit. For nonserious AEs, all AEs were reported from the time that the subject provided informed consent through Visit 4 and from Visit 5 to Visit 7. At Visit 5 and Visit 8, only newly diagnosed chronic medical conditions (including autoimmune or neuroinflammatory diseases) that occurred since the last visit were recorded (in addition to all serious adverse events [SAEs] reported during these intervals). Stop dates were collected for all AEs that resolved from Visit 1 through Visit 8. The SAEs collected from the signing of the ICF to the first dose of 13vPnC were listed. The information collected for SAEs was more detailed than that captured on the AE CRF. AEs were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). The relationship between AEs and the investigational product was characterized as related or not related as described in the protocol. The severity of AEs was characterized as mild, moderate, severe, or life-threatening.

Statistical Methods

The number and percentage of subjects consenting, assigned vaccine, completing, and withdrawing from the study were tabulated for each age group and the total sample.

Immunogenicity

For the 13 serotypes contained in 13vPnC, the serotype-specific IgG concentrations were logarithmically transformed for analysis. IgG GMCs were computed at each visit (before Vaccination 1, before Vaccination 4 and 1 month after each vaccination). Two (2)-sided, 95% confidence intervals were constructed at each visit by back transformation of the confidence intervals for the mean of the logarithmically transformed ssay results computed using the Student t distribution.

Fold rises in IgG concentrations were summarized by geometric means and confidence intervals using methodology similar to that used for GMCs. IgG GMCs and IgG geometric mean fold rises (GMFRs) were computed for subjects aged $\geq$ 2 years, $\geq$ 2 to <18 years, and $\geq$ 18 years.

The proportion of subjects with serotype-specific IgG concentrations $\geq$ 0.35 μg/mL was assessed after each vaccination and the corresponding exact 95% confidence intervals using the F distribution were generated. The difference in proportion of subjects with IgG $\geq$ 0.35 μg/mL and corresponding 95% confidence intervals for the difference in dependent proportions using an adjusted Wald interval were computed for the comparison of immune response 1 month after 4 doses of 13vPnC versus 1 month after 3 doses of 13vPnC. Differences were considered statistically higher when lower limit of 95%CI were greater than 0.

Reverse cumulative distribution curves (RCDCs) for IgG concentrations were presented after 4 doses of 13vPnC and after 3 doses of 13vPnC for each of the 13 serotypes contained in 13vPnC. RCDC were based on the evaluable immunogenicity population for subjects aged $\geq$ 2 years, $\geq$ 2 to <18 years, and $\geq$ 18 years and were plotted on the same graph repeated by age group for each serotype.

Serotype-specific antibody response curves were presented graphically for IgG concentrations assessed at each time point. Antibody response curves were based on the evaluable immunogenicity population for subjects aged $\geq$ 2 years, $\geq$ 2 to <18 years, and $\geq$ 18 years.

Safety

The local reactions and systemic events, including fever and use of antipyretic medications and pain medication, were summarized by 2 types of tables and 1 plot by vaccine dose, age group, and overall population. For local reactions and systemic events, including fever, the duration of the event was summarized for each vaccine dose, age group, and total sample, using descriptive statistics. AEs and

severe AEs were summarized for each age group separately for each dose. In addition, a listing of SAEs, subjects hospitalized, and deaths was generated. Nonstudy vaccines received from the time of HSCT to before Dose 1 and any nonstudy vaccines received after vaccination at Dose 1 were categorized using only preferred terms according to the World Health Organization (WHO) Drug dictionary. The number and percentage of subjects receiving each vaccine was tabulated for each age group.

Study 6096A1-3014 (B1851013): children and adolescents aged ≥6 to <18 years with SCD, previously immunized with 23vPS; 6-month safety addendum and 1-year final study report).

Study Design

This was a Phase 3, multicenter, open-label, single-arm study in children ≥ 6 to <18 years of age previously immunized with 23vPS who received 2 doses of 13vPnC, given approximately 6 months apart. Originally, 200 subjects were planned to be enrolled at up to 20 sites; however, due to difficulty identifying adequate numbers of subjects meeting the inclusion criteria, this was amended to 150 subjects at up to 25 sites. The study was conducted in the USA, the United Kingdom (UK), Italy, Lebanon, Egypt, France, and Saudi Arabia.

The CHMP noted that the first phase of this study was assessed in variation II/76, i.e. up to 1 month after the second dose.

Objectives

Primary Objectives:

- To evaluate the immune response 1 month after 2 doses of 13-valent pneumococcal conjugate vaccine (13vPnC) given 6 months apart compared to 1 month after 1 dose of 13vPnC as measured by fold rise in serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) in children with sickle cell disease (SCD) who had previously been vaccinated with at least 1 dose of 23-valent pneumococcal polysaccharide vaccine (23vPS).

Primary safety objective:

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

Secondary Objectives:

- To evaluate the immune response 1 month after 2 doses of 13vPnC given 6 months apart compared to 1 month after 1 dose of 13vPnC as measured by serotype-specific IgG GMCs in children with SCD who had previously been vaccinated with at least 1 dose of 23vPS.
- To describe the immune response 1 year after 2 doses of 13vPnC given 6 months apart as measured by the serotype-specific IgG GMCs in children with SCD who had previously been vaccinated with at least 1 dose of 23vPS.

Exploratory Objectives:

- To evaluate the immune response 6 months after Dose 1 of 13vPnC as measured by serotype-specific IgG GMCs, and fold rise IgG GMCs (1 month after Dose 2 relative to before Dose 2) in children with SCD who have previously been vaccinated with at least 1 dose of 23vPS.
- To evaluate the immune response 1 month after 2 doses of 13vPnC given 6 months apart compared to 1 month after 1 dose of 13vPnC, as measured by the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs), and the fold rise in OPA GMTs in children with SCD who had previously been vaccinated with at least 1 dose of 23vPS.

- To describe the immune response 1 year after 2 doses of 13vPnC given 6 months apart as measured by the serotype-specific OPA GMTs in children with SCD who had previously been vaccinated with at least 1 dose of 23vPS.

Inclusion Criteria

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

1. Male or female subject aged ≥ 6 and <18 years.

2. Diagnosis of SCD by hemoglobin (Hb) electrophoresis or polymerase chain reaction (PCR); (HbSS, HbSC, HbSD, HbSE, and HbSβ-thal).

3. Documentation to show 23vPS vaccination at least 6 months prior to enrollment.

4. Available for entire study period and whose parent/legal guardian could be reached by telephone.

5. Subject and/or parent/legal guardian were able to complete all relevant study procedures during study participation.

6. Negative urine pregnancy test for female subjects who were postmenarche.

7. All female and male subjects who were biologically capable of having children must have agreed to abstinence or commit to the use of a reliable method of birth control for the duration of the study and for 3 months after the last vaccination.

Exclusion Criteria:

Subjects were ineligible to participate in this study if they met any of the following exclusion criteria:

1. History of culture-proven invasive disease caused by *Streptococcus pneumoniae* within the last year.

2. Subject had/has a major illness or condition that, in the investigator's judgment, substantially increased the risk associated with the subject's participation in, and completion of the study.

3. Subject had a major illness or condition that, in the investigator's judgment, precluded the evaluation of the subject's response to vaccination.

4. History of hematopoietic stem cell transplantation.

5. Previous vaccination with pneumococcal conjugate vaccine.

6. Had a dose of 23vPS recommended between enrollment and the blood draw at Visit 6.

7. Previous anaphylactic reaction to any vaccine or vaccine-related component.

8. Contraindication to vaccination with pneumococcal conjugate vaccine.

9. Bleeding diathesis or condition associated with prolonged bleeding time that would have contraindicated intramuscular injection.

10. Receipt of immunoglobulin infusion or injection during the 42 days preceding enrollment.

11. Known or suspected immune deficiency or suppression.

12. Pregnant or breastfeeding female.

13. Participation in another investigational trial from 28 days before enrollment until the end of the study. (Note: participation in purely observational studies was acceptable).

14. Subject was a direct descendant (child or grandchild) of a member of site study personnel or was study personnel.

15. Active hepatitis C infection requiring interferon or ribavirin treatment.

Immunogenicity Evaluations

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) in 13vPnC were determined for all subjects for each blood sample by enzyme-linked immunosorbent assay (ELISA) and expressed as micrograms per milliliter (µg/mL).

Serum OPA assays to the 13 pneumococcal serotypes were performed on all blood samples collected, and the results were reported as antibody titers.

Safety Evaluations

Local reactions and systemic events were not collected during the study period covered in this report. All information related to collection of local reactions and systemic events can be found in the primary analysis CSR and in the final protocol and protocol amendments.

All observed or volunteered AEs, defined as any untoward medical occurrence regardless of suspected causal relationship to the investigational product, were reported. For all AEs or SAEs, sufficient information was to be obtained by the investigator to determine the causality of the AE. AEs were recorded in the CRF from the time the subject or subject's parent/legal guardian provided informed consent through Visit 2 and from Visit 3 to Visit 4. For SAEs, the active reporting period began from the time that the subject provided informed consent through Visit 6. SAEs occurring to a subject after the active reporting period had ended was reported to the sponsor if the investigator became aware of them; at a minimum all SAEs that investigator believed had at least a reasonable possibility of being related to the study were reported to the sponsor. Follow-up by the investigator was required until the event or its squeals resolved or stabilized at a level acceptable to the investigator, and the MAH concurred with that assessment.

Statistical Methods

The primary data analysis was the summarization of data following 2 doses of 13vPnC. The IgG geometric mean fold rises (GMFRs) following Dose 2 relative to after dose 1 for each serotype was the primary analysis endpoint. This was summarized for subjects having data following both doses using 95% confidence intervals (CIs). IgG GMCs and OPA GMTs at each blood sampling visit, the GMFRs at each dose, the GMFRs in OPA following Dose 2 relative to Dose 1 for each serotype and the difference in GMFRs between doses were similarly summarized. The primary immunogenicity population was the evaluable immunogenicity population, which consisted of subjects eligible for the study, received all the assigned vaccinations, had blood drawn within required time frames, had sufficient valid and determinate assay result for the proposed analysis, received no prohibited vaccines or medications, did not receive immunoglobulins or chronic systemic corticosteroids during the study, and had no major protocol violations. The all-available immunogenicity population consisted of subjects who had at least 1 valid and determinate pneumococcal assay result related to a proposed analysis.

All subjects who received 2 doses of 13vPnC and continued in the study after the 6-month follow-up telephone contact (Visit 5) were included in the safety population. All of the safety and immunogenicity data up to Visit 4 were included in the primary analysis report. The analyses of immunogenicity and safety data for the 1-year follow-up visit are presented in this report. Immunogenicity data were also presented kinetically in this report by including the data collected during the vaccination phase (Visit 1-4).

2.2.2. Results

Study 6115A1-3002 (B1851021) in HIV-Infected Subjects

Subject Disposition and Demography:

Of the 303 subjects assigned to receive study vaccine, 301 subjects (99.3%) received Dose 1 of 13vPnC (150 pediatric [99.3%] and 151 adult [99.3%] subjects), 290 subjects (95.7%) received Dose 2 of 13vPnC (145 pediatric [96.0%] and 145 adult [95.4%] subjects), 286 subjects (94.4%) received Dose 3 of 13vPnC (144 pediatric [95.4%] and 142 adult [93.4%] subjects), and 282 subjects (93.1%) received 23vPS (143 pediatric [94.7%] and 139 adult [91.4%] subjects). The majority of subjects assigned to the study completed the blood draw after the 23vPS dose (280 subjects, 92.4%). Of the 280 subjects to complete the blood draw after the 23vPS dose, 141 (93.4%) were from the 6- to <18-year age group and 139 (91.4%) were from the ≥ 18-year age group. A total of 279 subjects (92.1%) completed the study, with 141 (93.4%) from the 6- to <18-year age group and 138 (90.8%) from the ≥ 18-year age group. Completion of the study meant completing the 6-month follow up.

Two (2) subjects who were assigned to the study did not receive vaccine and were withdrawn from the study. Of the 23 subjects (7.6%) withdrawn before the blood draw visit after 23vPS, 10 (6.6%) were from the paediatric population and 13 (8.6) were from the ≥ 18-year age group.

The majority of the subjects in the overall safety population (≥ 6-year age group) were female (54.5%) and black or African American (84.7%), with a mean age at vaccination of 25.8±16.72 years. The 6- to <18-year age group had a slightly higher proportion of male subject than the ≥ 18-year age group (49.3% and 41.7%, respectively). The mean age of the 6- to <18-year age group was 10.3 years, while the mean age of the ≥ 18-year age group was 41.2 years.

The majority of the safety population was receiving HAART at baseline (97.3%), and that was similar between the 2 age groups. The mean CD4+ cell count at the first and second baseline assessments were 717.0 cells/µL and 718.1 cells/µL, respectively; the mean CD4+ cell count was higher in the 6- to <18-year age group compared with the ≥ 18-year age group at both baseline assessments. The mean viral load at the first and second baseline assessments was 2090.0 copies/mL and 1592.2 copies/mL, respectively; the mean viral load was lower in the 6- to <18-year age group at first assessment and higher at second assessment compared with the ≥ 18-year age group. The subjects in the 2 subgroups (age 6 to <18 years) and (age ≥ 18 years) were similar with respect to demographic characteristics.

IgG Results

IgG GMCs and GMFRs Before and After Doses:

IgG GMCs were statistically significantly higher after Dose 1 than before Dose 1 for all serotypes; ie, the lower limit of the 95% CI for the GMFR (postdose 1/predose 1) was >1. GMFRs for Dose 1 ranged from 1.38 to 10.38 in the overall evaluable population (GMFR data not shown in this AR). Generally, results for the 6 to <18 year age group and the ≥ 18-year age group were comparable to each other and to the overall evaluable immunogenicity population; GMFRs (postdose 1/predose 1) were higher for serotypes 4 and 14 in the 6 to <18 years age group compared with the ≥ 18 years age group.

IgG GMCs at all sampling time points (before and 1 month after Dose 1 and 1 month after each succeeding vaccination) were presented by the MAH. In each group, the IgG GMCs after Dose 2 and Dose 3 and after the 23vPS dose were generally similar to, or somewhat higher than, those after Dose 1 for

most serotypes. Overall, IgG GMCs in subjects 6 to <18 years of age and in those ≥ 18 years of age were similar.

Comparison of IgG Response Between Doses:

Dose 2 vs Dose 1: IgG GMCs after Dose 2 were similar to or higher than those after Dose 1 in the overall population and in the 2 age subgroups. The GMFRs of IgG GMCs (postdose 2/postdose 1) ranged from 0.99 to 1.24 in subjects ≥ 6 years of age and were statistically significantly higher after Dose 2 (the lower limit of the 2-sided, 95% CI for the GMFRs >1) for 7 of the 13 serotypes (1, 3, 4, 6B, 7F, 19F, and 23F).

Dose 3 vs Dose 2: IgG GMCs after Dose 3 were similar to or higher than those after Dose 2 in the overall population and in the 2 age subgroups. In subjects aged ≥ 6 years The GMFRs of IgG GMCs (postdose 3/postdose 2) ranged from 0.99 to 1.10; IgG GMCs after Dose 3 were statistically significantly higher for 6 of the 13 serotypes (4, 6B, 7F, 9V, 19F, and 23F).

Dose 3 vs Dose 1: IgG GMCs were similar or higher after Dose 3 than after Dose 1 in the overall group and in the paediatric and adult subgroups. The GMFRs of IgG GMCs (postdose 3/postdose 1) ranged from 0.97 to 1.31 in the subjects aged ≥ 6 years; IgG GMCs after Dose 3 were statistically significantly higher (i.e., lower limit of 95% CI of GMFR >1) than GMCs after Dose 1 for 9 of the 13 serotypes (all but serotypes 5, 14, 18C, and 19A).

23vPS dose vs Dose 3: The GMFRs of IgG GMCs ranged from 0.92 to 1.09 for subjects in the overall population (≥ 6-year age group). GMCs were statistically significantly higher after 23vPS for 3 of 13 serotypes (5, 9V, and 19F), were statistically significantly lower (the upper limit of the 2-sided, 95% CI for the GMFRs <1) for 3 serotypes (6B, 18C, and 23F), and were similar to those after 13vPnC Dose 3 for the other 7 serotypes. Results in subjects 6 to <18 years of age and in those ≥ 18 years of age were not notably different than those in the overall population.

Comparison of IgG GMFRs Between Doses:

GMFRs (postdose/predose) were compared between doses, based on the ratio of GMFRs (eg, GMFR Dose 2/GMFR Dose 1), to assess the rise in antibody response from prevaccination levels after successive doses. The comparison of GMFRs (postdose/predose) between Dose 1 and Dose 2 (GMFR Dose 2/GMFR Dose 1) showed that GMFRs (postdose/predose) for Dose 1 were higher than GMFRs (postdose/predose) for Dose 2, while GMFRs (postdose/predose) for Dose 2 and Dose 3 were similar in the overall study population and in each age subgroup.

OPA Results

OPA GMTs and GMFRs Before and After Doses:

OPA GMTs were statistically significantly higher after Dose 1 than before Dose 1 for all serotypes; ie, the lower limit of the 95% CI for the GMFR (postdose 1/predose 1) was >1. GMFRs for Dose 1 ranged from 4.5 to 66.8 in the overall evaluable population. In general, GMFRs for the 2 age groups were comparable, with a few exceptions; GMFRs for serotypes 4, 18C, 19F, and 23F were higher in the 6 to <18-year age group while the GMFR for 7F was lower in the 6 to <18-year age group.

OPA GMTs at all sampling time points (before and 1 month after Dose 1 and 1 month after each succeeding vaccination) were presented by the MAH. OPA GMTs after Dose 1, Dose 2, and Dose 3 and after the 23vPS dose remained higher than baseline levels (before Dose 1) for all serotypes in each age subgroup and in the entire study population. For most serotypes, the GMTs after Dose 2 and Dose 3 and after the 23vPS dose were somewhat higher than those after Dose 1 in the overall population and in each age subgroup. OPA GMTs after each dose were generally higher in the paediatric subgroup than in the

adult subgroup. To illustrate the kinetic patterns OPA response curves are shown for some serotypes below.

Comparison of OPA Response Between Doses: (GMFR data not shown in this AR)

Dose 2 vs Dose 1: In the overall population, GMFRs (postdose 2/postdose 1) of OPA GMTs ranged from 1.0 to 2.8 (Table 9). OPA GMTs after Dose 2 were statistically significantly higher (the lower limit of the 2-sided, 95% CI for the GMFRs >1) than after Dose 1 for 10 of 13 serotypes (all but 1, 7F, and 14) in the overall population. Results were similar in the 2 age subgroups.

Dose 3 vs Dose 2: The GMFRs (postdose 3/postdose 2) ranged from 1.1 to 1.7 in subjects aged ≥ 6 years. OPA GMTs after Dose 3 were statistically significantly higher than after Dose 2 for 12 of 13 serotypes (all but serotype 14) in the overall population (Table 10). Similar results were observed in the 2 age subgroups.

Dose 3 vs Dose 1: GMFRs (postdose 3/postdose 1) of OPA GMTs ranged from 1.1 to 4.6 in the overall population. OPA GMTs after Dose 3 were statistically significantly higher (i.e., lower limit of 95% CI of GMFR >1) than those after Dose 1 for all 13 serotypes in the overall evaluable population. Results were not notably different in the 2 age subgroups.

23vPS dose vs Dose 3: GMFRs ranged from 0.9 to 1.4 for subjects in the ≥ 6 year age group. OPA GMTs after the 23vPS dose were similar to or higher than those after Dose 3 for most serotypes. OPA GMTs were statistically significantly higher after 23vPS than after Dose 3 of 13vPnC for 8 of the 13 serotypes (all but 4, 6A, 6B, and 23F); OPA GMTs were statistically significantly lower after 23vPS for serotypes 6A (not in 23vPS) and 6B; ie, the upper limit of the 95% CI of the GMFR was <1. Results were not notably different in the 2 age subgroups.

The CHMP noted that the OPA GMTs were consistently numerically higher in children compared to adults. Otherwise the pattern seen in IgG responses, i.e. GMC and GMT rises after the first dose, which were modestly increased after dose 2 and 3. There were also modest increases after the 23vPS vaccine. When comparing with the previously submitted study in subjects with earlier 23vPS vaccination, the GMCs and GMTs in the current study were higher, but there were differences also between baseline levels, so this should be interpreted with caution.

Study 6115A1-3003 (B1851022): recipients of allogeneic hematopoietic stem cell transplant (HSCT) aged ≥2 years, who have not received a pneumococcal vaccine since HSCT; final study report.

Subject Disposition and Demography

Of the 251 subjects assigned to receive study vaccine, 247 subjects (98.4%) received Dose 1 of 13vPnC (59 pediatric [96.7%] and 188 adult [98.9%] subjects), 231 subjects (92.0%) received Dose 2 of 13vPnC (55 pediatric [90.2%] and 176 adult [92.6%] subjects), 221 subjects (88.0%) received Dose 3 of 13vPnC (54 pediatric [88.5%] and 167 adult [87.9%] subjects), 192 subjects (76.5%) received Dose 4 of 13vPnC (46 pediatric [75.4%] and 146 adult [76.8%] subjects), and 185 subjects (73.7%) received 23vPS (45 pediatric [73.8%] and 140 adult [73.7%] subjects). The majority of subjects assigned to the study completed the blood draw 1 month after Dose 3 of 13vPnC (217 subjects [86.5%]; 53 pediatric [86.9%] and 164 adult [86.3%]). A total of 185 subjects (73.7%) completed the blood draw 1 month after the 23vPS dose. Of the 185 subjects to complete the blood draw 1 month after the 23vPS dose, 45 subjects (73.8%) were from the 2- to <18-year age group and 140 subjects (73.7%) were from the ≥ 18-year age group. A total of 184 subjects (73.3%) completed the study, with 45 subjects (73.8%) from the 2- to

<18-year age group and 139 subjects (73.2%) from the ≥ 18-year age group. Completing the study was defined as completing the 6-month follow up.

The sex of the majority of subjects in the overall safety population (age ≥ 2 years) was male (59.5%), and the ethnicity of the majority of subjects in the overall age group (age ≥ 2 years) was white (76.5%). The overall age group (age ≥ 2 years) had a mean age at vaccination of 38.4±19.26 years. The mean age of the 2- to <18-year age group was 10.3±4.41 years, while the mean age of the ≥ 18-year age group was 47.3±12.39 years. Other demographic characteristics were similar between the age groups.

IgG Results

To address the primary objective of the study, GMFRs in serotype specific IgG GMCs from baseline (before Dose 1) to 1 month after 3 doses of 13vPnC were assessed in subjects ≥ 2 years of age and in the subgroups 2 to <18 years of age and ≥ 18 years of age. IgG GMCs were statistically significantly higher (lower limit of 95% CI for the GMFR >1) after Dose 3 than before Dose 1 for all serotypes in the evaluable immunogenicity population as a whole and in the 2 age subgroups.

Overall, GMFRs from baseline (before Dose 1) to after Dose 1, Dose 2, or Dose 3 (doses spaced 1 month apart) increased with each succeeding dose in the group ≥ 2 years of age; GMFRs for each dose were as follows: Dose 1 (range: 1.64 to 6.01), Dose 2 (range: 1.93 to 11.02) and Dose 3 (range: 2.99 to 23.85). Results were similar in the pediatric and adult subgroups.

For all age groups, the GMFRs from baseline to after Dose 4, given 6 months after Dose 3, were notably higher than the GMFRs for the first 3 doses of 13vPnC, each given a month apart; i.e., in the overall population, GMFRs after Dose 4 ranged from 6.28 to 55.02 across serotypes.

The GMFRs from baseline (before Dose 1) to after a single dose of 23vPS, given 1 month after Dose 4 of 13vPnC, were generally similar or lower than those for Dose 4 of 13vPnC in all age groups.

IgG GMCs at each time point and in each age group were presented by the MAH. Overall, GMCs increased after each 13vPnC dose for all serotypes. Although IgG GMCs declined over the 6 months between Dose 3 and Dose 4, antibody levels before Dose 4 remained higher than those after Dose 1 for all serotypes and after Dose 2 for 8 of 13 serotypes (all but serotypes 1, 3, 4, 5, 7F, which remained above baseline) in the overall population. In the 2 age subgroups, IgG GMCs before Dose 4 remained higher than those after Dose 1 for most serotypes. With few exceptions, IgG GMCs were higher in the 2 to <18 year group than in the >18 year age group.

In all age groups, a notable increase was observed in IgG GMCs after Dose 4 relative to antibody concentrations before Dose 4 (Table 13). In the overall population the GMFRs (postdose 4/predose 4) ranged from 3.00 to 6.97 across serotypes. For each serotype the rise in IgG GMCs after Dose 4 was statistically significant (lower limit of 95% CI for GMFR >1) for subjects in the overall study population and in the 2 age subgroups.

When postvaccination IgG GMCs were compared between doses, antibody concentrations were significantly increased after each succeeding 13vPnC dose in subjects ≥ 2 years old for most serotypes. The GMFRs in IgG GMCs from Dose 1 to Dose 2 (postdose 2/postdose 1) ranged from 1.07 to 1.83. IgG GMCs were statistically significantly higher after Dose 2 than after Dose 1, for all serotypes, except for serotype 14, in subjects aged ≥ 2 years; a similar pattern of response was observed in the 2 age subgroups (aged 2 to <18 years and ≥ 18 years). To illustrate the kinetic patterns IgG response curves are shown for some serotypes below.

In subjects aged ≥ 2 years, GMFRs from Dose 2 to Dose 3 (postdose 3/postdose 2) ranged from 1.28 to 2.09. For all serotypes, IgG GMCs were statistically significantly higher after Dose 3 than after Dose 2; ie,

the lower limit of the 95% CI for the GMFR was >1. Similarly, IgG GMCs in each subgroup were statistically significantly higher after Dose 3 than after Dose 2 for all serotypes.

After the 6-month interval between Dose 3 and Dose 4, the GMFRs (postdose 4/postdose 3) ranged from 1.20 to 3.61 across serotypes. IgG GMCs were statistically significantly higher (lower limit of 95% CI for the GMFR >1) after Dose 4 than after Dose 3 for all serotypes in the overall population. A similar pattern of response was observed in each of the 2 age subgroups, except for serotype 3 in the 2 to <18-year-old group (GMFR lower limit of 95% CI <1 for serotype 3).

Serotype-specific IgG GMCs did not increase from after Dose 4 to after the 23vPS dose for most serotypes (lower limit of the 95% CI for GMFR <1 for 12 of 13 serotypes, exception 9V in the overall group and adult subgroup) in subjects aged ≥ 2 years and in the pediatric and adult subgroups; however immune responses were generally maintained after the 23vPS dose.

The CHMP noted that the study did not include healthy immunocompetent subjects as a control group, and OPA responses were not measured. The IgG responses increased with each subsequent dose, and although a decrease was seen between dose 3 and 4, the response to the fourth dose was higher than the the third dose, which could be interpreted as an indication of immunological memory. In conclusion the results are reassuring regarding the benefit of vaccinating HSCT recipients. The benefit of the 23vPS vaccine in increasing the immune responses to the serotypes present in Prevenar 13 is not demonstrated, but it is possible that immune responses to the remaining serotypes increased, although these were not measured.

Study 6096A1-3014 (B1851013): children and adolescents aged ≥6 to <18 years with SCD, previously immunized with 23vPS; 6-month safety addendum and 1-year final study report).

Subject Disposition and Demography

A total of 147 subjects completed the 6-month follow-up visit including the 1 subject who did not receive Dose 2, but did complete the 6-month follow-up visit. Of the 146 subjects who might have been eligible for the 1-year follow-up visit, 57 subjects had either already completed the study before Protocol Amendment 2 , which introduced the 1-year follow-up visit, or they decided not to continue while they were given the opportunity to reconsent for the 1-year follow-up visit. Of the 89 subjects who were eligible for the 1-year follow-up visit and decided to continue for the 1-year follow-up, 87 subjects completed the follow-up visit and 2 subjects withdrew before the visit.

Of the 89 (56.3%) subjects who continued after the 6-month follow-up visit, 82 (51.9%) subjects had blood drawn within the specified time frame at the 1-year follow-up visit, 5 (3.2%) subjects had blood drawn outside the window at >469 days, and 2 (1.3%) subjects did not have blood sample drawn.

Permitted nonstudy vaccines were given to 18 (20.7%) subjects between the 6-month follow-up and 1-year follow-up visits. The majority (14 [16.1%]) of subjects received an influenza vaccine. No subject received a prohibited vaccine. Between the 6-month follow-up and the 1-year follow-up visits, 9 (10.3%) subjects received blood transfusions. Of the 158 enrolled subjects, 81 (51.3%) were included in the evaluable immunogenicity population at the 1-year follow-up visit. The reasons for exclusion from the evaluable immunogenicity population at 1-year follow-up were: excluded from the all available immunogenicity population at 1-year follow-up (71 subjects, 44.9%), blood draw >469 days after Vaccination 2 (5 subjects, 3.2%), and received prohibited vaccines or medications during the study (1 subject, 0.6%).

IgG Results

Overall, the IgG GMCs increased after each dose. The IgG GMCs at 1 year after Dose 2 were higher than the IgG GMCs before Dose 1 for all serotypes, with the exception of serotype 3. For serotype 3 the IgG GMC was 1.02 µg/mL before Dose 1 and 1.01 µg/mL at 1 year after Dose 2. For all serotypes, IgG GMCs at 1 year after Dose 2 were lower than IgG GMCs 1 month after Dose 1, before Dose 2, and 1 month after Dose 2.

The CHMP noted that the immune responses 1 month after the second dose were assessed in variation II76, and will not be further discussed here. The GMCs at 1 year after dose 2 were generally higher compared to the prevaccination levels, but for serotypes 1, 3 and 5 the 95% CI were overlapping.

OPA Results

Overall, the OPA GMTs increased after each dose. The OPA GMTs at 1 year after Dose 2 were higher than the OPA GMTs before Dose 1 for all serotypes, including serotype 3.

The OPA GMTs at 1 year after Dose 2 were higher than those before Dose 2 for 6 serotypes (1, 5, 7F, 9V, 19F and 23F). For all serotypes, the OPA GMTs at 1 year after Dose 2 were lower than the OPA GMTs 1 month after Dose 1 and 1 month after Dose 2.

The CHMP noted that the OPA responses were elevated at one year after dose 2 compared to prevaccination values, with non-overlapping 95% CIs.

2.2.3. Discussion

The current variation includes additional data for risk groups, which are considered very important by the CHMP. In a previous variation (II/76), data from the study on subjects with sickle cell disease and another study in HIV infected individuals were assessed, as well as a study in preterm infants.

In general, the immune response in the current studies was in agreement with previously submitted data. The resulting SmPC changes (see section 2.5 below) are mostly endorsed as they adequately describe the data.

In HIV infected subjects, the GMCs and GMTs increased substantially after the first dose, and were modestly increased after dose 2 and 3. There was also minor increase after the 23vPS vaccine. The OPA GMTs were consistently numerically higher in children compared to adults. When comparing with the previously submitted study in subjects with earlier 23vPS vaccination, the GMCs and GMTs in the current study were higher, but there were differences also between baseline levels, so this should be interpreted with caution.

In HSCT recipients, the study in HSCT recipients was uncontrolled and immune responses were only assessed using IgG ELISA, not OPA. The IgG responses increased with each subsequent dose, and although a decrease was seen between dose 3 and 4, the response to the fourth dose was higher than the response to the third dose, which could be interpreted as an indication of immunological memory. In conclusion the results are reassuring regarding the benefit of vaccinating HSCT recipients. The benefit of the 23vPS vaccine in increasing the immune responses to the serotypes present in Prevenar 13 is not demonstrated, but it is possible that immune responses to the remaining serotypes increased, although these were not measured. The proposed dosing, 3 doses at 1 month intervals with a fourth dose 6 months after the third dose, is considered justified by the presented immunogenicity data. Considering that the study in HSCT recipients was uncontrolled, it is not considered appropriate to include a statement in the SPC comparing the results of 4 doses in HSCT recipients to healthy subjects of the same age.

In Sickle cell disease subjects, the immune responses 1 month after the second dose were assessed in variation II/76. With the present submission, the GMCs at 1 year after dose 2 were generally higher compared to the pre-vaccination levels, but for serotypes 1, 3 and 5 the 95% CI were overlapping. The OPA responses were in agreement with the IgG responses, but the 95% CIs were not overlapping for any serotypes. The final data from the study in sickle cell disease patients confirm the preliminary data submitted with variation II/76.

2.3. Clinical Safety aspects

2.3.1. Methods – analysis of data submitted

Study 6115A1-3002 (B1851021) in HIV-Infected Subjects

Local Reactions

In the overall safety population (ages 6 years of age and older) at least one local reaction was reported in 62.4% to 71.5% of subjects across the three 13vPnC doses (Table 1). The percentages of subjects with local reactions in the 2 age subgroups were not notably different than in the overall safety population. In the younger age subgroup (6 to <18 years) the percentage of subjects with local reactions decreased over the 3 doses whereas, this pattern was not present in the older subgroup (≥18 years). The majority of local reactions were mild or moderate and duration of local reactions did not exceed 3 days in the safety population overall or in the 2 age subgroups.

Pain was the local reaction reported most frequently in subjects aged ≥6 years of age. In the 2 age subgroups, the percentage of subjects reporting pain was comparable to that observed in the safety population overall. However, severe pain was somewhat more frequently reported in the group aged 6 to <18 years (≤8.1%) than in the group aged ≥18-years (≤5.5%) or in the overall safety population (≤5.1%).

In the 2 subgroups, the percentages of subjects reporting redness and swelling were higher in subjects aged 6 to <18 years (redness ≤20.7%; swelling ≤29.9%) than in subjects aged ≥18 years (redness ≤2.3%; swelling ≤9.6%) and in the safety population overall (redness ≤19.9%; swelling ≤0.6%).

Table 1 Subjects Reporting Local Reactions Within 14 Days of Each 13vPnC Dose - Safety Population, Age Group: ≥ 6 Years

	Vaccine Sequence (as Administered)											
	13vPnC/13vPnC/13vPnC//23vPS											
	Dose 1				Dose 2				Dose 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	180	21	11.7	(7.4, 17.3)	187	16	8.6	(5.0, 13.5)	154	7	4.5	(1.8, 9.1)
Mild	179	20	11.2	(7.0, 16.7)	186	12	6.5	(3.4, 11.0)	153	6	3.9	(1.5, 8.3)
Moderate	173	2	1.2	(0.1, 4.1)	180	4	2.2	(0.6, 5.6)	152	2	1.3	(0.2, 4.7)
Severe	172	0	0.0	(0.0, 2.1)	178	1	0.6	(0.0, 3.1)	150	0	0.0	(0.0, 2.4)
Swelling[d]												
Any	191	38	19.9	(14.5, 26.3)	191	33	17.3	(12.2, 23.4)	160	19	11.9	(7.3, 17.9)
Mild	184	24	13.0	(8.5, 18.8)	190	26	13.7	(9.1, 19.4)	157	12	7.6	(4.0, 13.0)
Moderate	181	16	8.8	(5.1, 14.0)	184	12	6.5	(3.4, 11.1)	154	8	5.2	(2.3, 10.0)
Severe[g]	172	1	0.6	(0.0, 3.2)	178	0	0.0	(0.0, 2.1)	150	0	0.0	(0.0, 2.4)
Pain at injection												

	Vaccine Sequence (as Administered)											
	13vPnC/13vPnC/13vPnC//23vPS											
	Dose 1				Dose 2				Dose 3			
Local Reaction	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
site[e]												
Any	238	156	65.5	(59.1, 71.6)	236	166	70.3	(64.1, 76.1)	213	131	61.5	(54.6, 68.1)
Mild	228	127	55.7	(49.0, 62.3)	227	139	61.2	(54.6, 67.6)	201	107	53.2	(46.1, 60.3)
Moderate	188	44	23.4	(17.6, 30.1)	199	51	25.6	(19.7, 32.3)	167	36	21.6	(15.6, 28.6)
Severe	175	9	5.1	(2.4, 9.5)	179	8	4.5	(1.9, 8.6)	156	8	5.1	(2.2, 9.9)
Any local reaction[f]	243	164	67.5	(61.2, 73.3)	239	171	71.5	(65.4, 77.2)	213	133	62.4	(55.6, 69.0)

a. N = number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
d. For ages 6-<12 years, mild = 0.5 to 2.0 cm, moderate = 2.5 to 7.0 cm, and severe is >7.0 cm. For ages ≥12 years, mild = 2.5 to 5.0 cm, moderate = 5.1 to 10.0 cm, severe >10.0 cm.
e. Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.
f. Any local reaction = any pain at injection site, any swelling, or any redness.
g. Severe swelling was reported in 1 subject, was queried, and was a data entry error as confirmed by the investigator.

Systemic Events

In the overall safety population systemic events were reported at a decreasing frequency after each succeeding dose (Dose 1, 81.2%; Dose 2, 68.7%; and Dose 3, 62.6%, Table 2). This same pattern was observed in the 2 age subgroups, with a higher percentage of systemic events reported in adults aged ≥18 years than in the subgroup aged 6 to <18 years.

In the overall safety population, the most frequently reported systemic events were: (percentages from Dose 1 to Dose 3) muscle pain (55.8% to 42.4%), fatigue (53.5% to 36.1%) and headache (50.5% to 32.2%); the frequency of these individual events declined with each dose. Muscle pain, fatigue, and headache were also reported most frequently in the 2 age subgroups, with the same pattern of declining percentages with each dose. These 3 events accounted for most of the severe systemic events in the overall population and in each age subgroup; severe muscle pain, severe fatigue, and severe headache were each reported in fewer than 10% of subjects. Overall, most systemic events were mild or moderate and lasted less than 7 days.

The incidence of fever (≥38°C) was ≤18.5% after each dose of 13vPnC, and most reports of fever were mild (<38.5°C). Similar results were observed for both age groups (6 to <18-year and ≥18-year age groups).

Fever >40oC was reported in 14 subjects at Dose 1, 2 subjects at Dose 2, and 4 subjects at Dose 3. All have been confirmed by the investigators as data entry errors, except for 1 subject in the pediatric group with fever >40oC after Dose 3.

Table 2. Subjects Reporting Systemic Events Within 14 Days of Each 13vPnC Dose – Safety Population, Age Group: ≥6 Years

	Vaccine Sequence (as Administered)											
	13vPnC/13vPnC/13vPnC/23vPS											
	Dose 1				Dose 2				Dose 3			
Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Fever												
≥38°C	189	35	18.	(13.3, 24.8)	190	27	14.2	(9.6, 20.0)	158	17	10.	(6.4, 16.7)

Table 2. Subjects Reporting Systemic Events Within 14 Days of Each 13vPnC Dose – Safety Population, Age Group: ≥6 Years

	Vaccine Sequence (as Administered)											
	13vPnC/13vPnC/13vPnC/23vPS											
	Dose 1				Dose 2				Dose 3			
Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
			5								8	
≥38°C but <38.5°C	179	15	8.4	(4.8, 13.4)	183	15	8.2	(4.7, 13.2)	155	9	5.8	(2.7, 10.7)
≥38.5°C but <39°C	174	5	2.9	(0.9, 6.6)	183	7	3.8	(1.6, 7.7)	153	6	3.9	(1.5, 8.3)
≥39°C but ≤40.0°C	174	6	3.4	(1.3, 7.4)	184	10	5.4	(2.6, 9.8)	152	4	2.6	(0.7, 6.6)
>40.0°C[d]	181	14	7.7	(4.3, 12.6)	180	2	1.1	(0.1, 4.0)	153	4	2.6	(0.7, 6.6)
Fatigue[e]												
Any	230	123	53.5	(46.8, 60.1)	211	86	40.8	(34.1, 47.7)	183	66	36.1	(29.1, 43.5)
Mild	218	93	42.7	(36.0, 49.5)	207	69	33.3	(27.0, 40.2)	177	53	29.9	(23.3, 37.3)
Moderate	195	53	27.2	(21.1, 34.0)	184	29	15.8	(10.8, 21.8)	163	25	15.3	(10.2, 21.8)
Severe	178	16	9.0	(5.2, 14.2)	183	12	6.6	(3.4, 11.2)	156	10	6.4	(3.1, 11.5)
Headache[e]												
Any	220	111	50.5	(43.7, 57.2)	207	81	39.1	(32.4, 46.1)	177	57	32.2	(25.4, 39.6)
Mild	209	96	45.9	(39.0, 52.9)	199	59	29.6	(23.4, 36.5)	171	45	26.3	(19.9, 33.6)
Moderate	191	39	20.4	(14.9, 26.8)	190	39	20.5	(15.0, 27.0)	160	22	13.8	(8.8, 20.1)
Severe	176	14	8.0	(4.4, 13.0)	182	5	2.7	(0.9, 6.3)	154	8	5.2	(2.3, 10.0)
Vomiting[f]												
Any	180	23	12.8	(8.3, 18.6)	185	19	10.3	(6.3, 15.6)	159	14	8.8	(4.9, 14.3)
Mild	180	20	11.1	(6.9, 16.6)	183	14	7.7	(4.2, 12.5)	156	10	6.4	(3.1, 11.5)
Moderate	172	2	1.2	(0.1, 4.1)	179	4	2.2	(0.6, 5.6)	155	6	3.9	(1.4, 8.2)
Severe[g]	173	2	1.2	(0.1, 4.1)	179	3	1.7	(0.3, 4.8)	153	3	2.0	(0.4, 5.6)
Diarrhea[h]												
Any	199	60	30.2	(23.9, 37.0)	190	35	18.4	(13.2, 24.7)	162	27	16.7	(11.3, 23.3)
Mild	196	49	25.0	(19.1, 31.7)	187	30	16.0	(11.1, 22.1)	160	24	15.0	(9.9, 21.5)
Moderate	177	14	7.9	(4.4, 12.9)	180	10	5.6	(2.7, 10.0)	153	6	3.9	(1.5, 8.3)
Severe	173	2	1.2	(0.1, 4.1)	179	5	2.8	(0.9, 6.4)	154	4	2.6	(0.7, 6.5)
Muscle pain[e]												
Any	226	126	55.8	(49.0, 62.3)	216	97	44.9	(38.2, 51.8)	191	81	42.4	(35.3, 49.8)
Mild	213	100	46.9	(40.1, 53.9)	208	75	36.1	(29.5, 43.0)	182	57	31.3	(24.7, 38.6)
Moderate	187	36	19.3	(13.9, 25.6)	191	34	17.8	(12.7, 24.0)	163	30	18.4	(12.8, 25.2)
Severe	177	10	5.6	(2.7, 10.1)	180	7	3.9	(1.6, 7.8)	156	11	7.1	(3.6, 12.3)
Joint pain[e]												
Any	205	79	38.5	(31.8, 45.6)	201	61	30.3	(24.1, 37.2)	174	49	28.2	(21.6, 35.5)
Mild	199	63	31.7	(25.3, 38.6)	193	43	22.3	(16.6, 28.8)	170	37	21.8	(15.8, 28.7)
Moderate	184	28	15.2	(10.4, 21.2)	188	22	11.7	(7.5, 17.2)	159	18	11.3	(6.8, 17.3)
Severe	175	8	4.6	(2.0, 8.8)	179	6	3.4	(1.2, 7.2)	152	4	2.6	(0.7, 6.6)
Use of medication to treat pain	197	57	28.9	(22.7, 35.8)	191	36	18.8	(13.6, 25.1)	169	33	19.5	(13.8, 26.3)
Use of medication to	219	92	42.	(35.4, 48.8)	198	54	27.3	(21.2,	164	33	20.	(14.3,

Table 2. Subjects Reporting Systemic Events Within 14 Days of Each 13vPnC Dose – Safety Population, Age Group: ≥6 Years

	Vaccine Sequence (as Administered) 13vPnC/13vPnC/13vPnC/23vPS											
	Dose 1				Dose 2				Dose 3			
Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
treat fever			0					34.0)			1	27.1)
Any systemic event[i]	266	216	81.2	(76.0, 85.7)	243	167	68.7	(62.5, 74.5)	219	137	62.6	(55.8, 69.0)

a. N = number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval based upon the Clopper-Pearson method.
d. Fever >40°C (>104.0°F) reported in 18 subjects was queried; however, 17 were data entry errors as confirmed by the investigator.
e. Mild = does not interfere with activity, moderate = some interference with activity, severe = prevents routine daily activity.
f. Mild = 1 to 2 times in 24 hours, moderate = more than 2 times in 24 hours, severe = requires intravenous hydration.
g. Vomiting requiring intravenous hydration reported in 8 subjects was queried; however, all were data entry errors as confirmed by the investigator.
h. 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.
i. Any systemic event = any fever ≥38°C, any fatigue, any headache, any vomiting, any diarrhea, any muscle pain, or any joint pain.
Source: Program ID: Study 3002/CP SAF_SE_DAY14_DOSE.SAS. Runtime ID: 04JUN2013 22:22

Adverse Events

The percentage of subjects reporting any AEs after any dose of 13vPnC (does not include AEs reported after the 23vPS dose) was 26.2% in the overall safety population (≥6-year age group, Table 9); the percentage of subjects reporting any AE was higher in the 6- to <18-year age group (34.0%) compared with the ≥18-year age group (18.5%).

In the overall safety population (≥6-year age group), the most frequently occurring type (system organ class) of AEs after any dose of 13vPnC were infections and infestations, which were reported in 15.9% of subjects (18.0% of subjects in 6- to <18-year age group, 13.9% in the ≥18-year age group).

AEs reported after any dose of 13vPnC showed similar trends as those observed after any dose of investigational vaccines (13vPnC and 23vPS, not including follow-up AEs). The percentage of general disorders and administration site conditions reported after any dose of investigational vaccine (13vPnC and 23vPS) was higher than that reported after any dose of 13vPnC in the overall safety population (7% vs 3%, respectively); this percentage includes local reactions reported after 23vPS, which were reported as AEs since there was no e-diary data collection of such events after 23vPS.

The AEs reported in study 3002 were consistent with events expected in HIV-infected children and adults. Infections and infestations were the most frequently occurring types of AEs after any dose (13vPnC and 23vPS). The frequency of AEs was somewhat higher for subjects in the pediatric subgroup compared with the adult subgroup.

Table 3. Adverse Events Reported After Any Dose of 13vPnC – Safety Population

	Vaccine Sequence (as Administered) 13vPnC/13vPnC/13vPnC/23vPS								
	Age 6-<18 Years N=150			Age ≥18 Years N=151			Age ≥6 Years N=301		
System Organ Class\ Preferred Term	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]

Table 3. Adverse Events Reported After Any Dose of 13vPnC – Safety Population

	Vaccine Sequence (as Administered) 13vPnC/13vPnC/13vPnC/23vPS								
	Age 6-<18 Years N=150			Age ≥18 Years N=151			Age ≥6 Years N=301		
System Organ Class\ Preferred Term	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Any event	51	34.0	79	28	18.5	40	79	26.2	119
Eye disorders	1	0.7	1	0	0.0	0	1	0.3	1
Conjunctivitis	1	0.7	1	0	0.0	0	1	0.3	1
Gastrointestinal disorders	3	2.0	3	4	2.6	4	7	2.3	7
Abdominal pain	0	0.0	0	1	0.7	1	1	0.3	1
Gastritis	0	0.0	0	1	0.7	1	1	0.3	1
Haemorrhoids	0	0.0	0	1	0.7	1	1	0.3	1
Nausea	0	0.0	0	1	0.7	1	1	0.3	1
Salivary gland enlargement	1	0.7	1	0	0.0	0	1	0.3	1
Stomatitis	1	0.7	1	0	0.0	0	1	0.3	1
Vomiting	1	0.7	1	0	0.0	0	1	0.3	1
General disorders and administration site conditions	9	6.0	10	0	0.0	0	9	3.0	10
Pyrexia	4	2.7	5	0	0.0	0	4	1.3	5
Fatigue	3	2.0	3	0	0.0	0	3	1.0	3
Influenza like illness	1	0.7	1	0	0.0	0	1	0.3	1
Injection site pain	1	0.7	1	0	0.0	0	1	0.3	1
Infections and infestations	27	18.0	38	21	13.9	24	48	15.9	62
Influenza	5	3.3	5	9	6.0	9	14	4.7	14
Upper respiratory tract infection	6	4.0	6	2	1.3	2	8	2.7	8
Rhinitis	3	2.0	4	3	2.0	3	6	2.0	7
Sinusitis	1	0.7	1	2	1.3	3	3	1.0	4
Tonsillitis	3	2.0	3	1	0.7	1	4	1.3	4
Gastroenteritis	1	0.7	1	2	1.3	2	3	1.0	3
Pharyngitis bacterial	1	0.7	3	0	0.0	0	1	0.3	3
Oral herpes	2	1.3	2	0	0.0	0	2	0.7	2
Otitis media	1	0.7	2	0	0.0	0	1	0.3	2
Pharyngitis	1	0.7	1	1	0.7	1	2	0.7	2
Respiratory tract infection	2	1.3	2	0	0.0	0	2	0.7	2
Body tinea	1	0.7	1	0	0.0	0	1	0.3	1
Cystitis	0	0.0	0	1	0.7	1	1	0.3	1
Herpes virus infection	1	0.7	1	0	0.0	0	1	0.3	1
Lobar pneumonia	1	0.7	1	0	0.0	0	1	0.3	1
Lower respiratory tract infection	1	0.7	1	0	0.0	0	1	0.3	1
Subcutaneous abscess	1	0.7	1	0	0.0	0	1	0.3	1
Tinea capitis	1	0.7	1	0	0.0	0	1	0.3	1
Tooth abscess	0	0.0	0	1	0.7	1	1	0.3	1
Tooth infection	0	0.0	0	1	0.7	1	1	0.3	1
Varicella	1	0.7	1	0	0.0	0	1	0.3	1
Viraemia	1	0.7	1	0	0.0	0	1	0.3	1
Injury, poisoning and procedural complications	2	1.3	2	2	1.3	2	4	1.3	4

Table 3. Adverse Events Reported After Any Dose of 13vPnC – Safety Population

	Vaccine Sequence (as Administered) 13vPnC/13vPnC/13vPnC/23vPS								
	Age 6-<18 Years N=150			Age ≥18 Years N=151			Age ≥6 Years N=301		
System Organ Class\ Preferred Term	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]	No. of Subjects[a]	%	No. of Events[b]
Lip injury	1	0.7	1	0	0.0	0	1	0.3	1
Procedural pain	0	0.0	0	1	0.7	1	1	0.3	1
Radius fracture	1	0.7	1	0	0.0	0	1	0.3	1
Road traffic accident	0	0.0	0	1	0.7	1	1	0.3	1
Metabolism and nutrition disorders	0	0.0	0	1	0.7	1	1	0.3	1
Hypercholesterolaemia	0	0.0	0	1	0.7	1	1	0.3	1
Musculoskeletal and connective tissue disorders	2	1.3	3	1	0.7	2	3	1.0	5
Arthralgia	2	1.3	2	1	0.7	1	3	1.0	3
Myalgia	0	0.0	0	1	0.7	1	1	0.3	1
Pain in extremity	1	0.7	1	0	0.0	0	1	0.3	1
Nervous system disorders	4	2.7	4	3	2.0	3	7	2.3	7
Headache	3	2.0	3	2	1.3	2	5	1.7	5
Convulsion	1	0.7	1	0	0.0	0	1	0.3	1
Intercostal neuralgia	0	0.0	0	1	0.7	1	1	0.3	1
Reproductive system and breast disorders	0	0.0	0	1	0.7	1	1	0.3	1
Dysmenorrhoea	0	0.0	0	1	0.7	1	1	0.3	1
Respiratory, thoracic and mediastinal disorders	13	8.7	15	1	0.7	1	14	4.7	16
Cough	8	5.3	8	0	0.0	0	8	2.7	8
Oropharyngeal pain	2	1.3	2	1	0.7	1	3	1.0	3
Rhinorrhoea	2	1.3	2	0	0.0	0	2	0.7	2
Nasal disorder	1	0.7	1	0	0.0	0	1	0.3	1
Upper-airway cough syndrome	1	0.7	1	0	0.0	0	1	0.3	1
Wheezing	1	0.7	1	0	0.0	0	1	0.3	1
Skin and subcutaneous tissue disorders	3	2.0	3	1	0.7	1	4	1.3	4
Rash	2	1.3	2	0	0.0	0	2	0.7	2
Eczema	1	0.7	1	0	0.0	0	1	0.3	1
Exfoliative rash	0	0.0	0	1	0.7	1	1	0.3	1
Vascular disorders	0	0.0	0	1	0.7	1	1	0.3	1
Hypertension	0	0.0	0	1	0.7	1	1	0.3	1

a. Number (No.) of subjects reporting at least 1 event of type specified. "Any event" represents the number of subjects reporting at least 1 event of any kind.

b. The total number of events of the type specified. Subjects can be represented more than once. "Any event" represents the total number of events.

Deaths

One (1) subject died during the study in a road traffic accident and passed away at the scene of the accident. The investigator and the sponsor considered the event of road traffic accident leading to death to be not related to 13vPnC vaccination or the protocol procedures.

Serious Adverse Events, Related SAEs, AE Withdrawals

In the overall safety population (≥6-year age group), 8 subjects reported 9 SAEs during the study. The incidence of SAEs reported in the 2 age groups was the same (2.0% each). The most common category of SAEs was infections and infestations; SAEs were reported by 1.4% or fewer subjects after each dose. None were considered to be related to study vaccine as assessed by the investigator. No subjects were withdrawn from the study for safety-related reasons.

Other Significant Adverse Events

There were 2 subjects who experienced AEs (one convulsion, one wheezing) that were considered to be of clinical importance/significant.

The CHMP considered that the overall safety results are in agreement with the previously assessed study 6115A1-3017 (II76) in HIV infected adults, although the rate of adverse events was higher in the previous study. The MAH conclusions regarding safety are endorsed.

Study 6115A1-3003 (B1851022): recipients of allogeneic hematopoietic stem cell transplant (HSCT) aged ≥2 years, who have not received a pneumococcal vaccine since HSCT; final study report.

Local Reactions

Most subjects in the overall safety population (age ≥2 years) experienced at least one local reaction after each 13vPnC dose. A higher percentage of subjects experienced local reactions after dose 4 than after the other 3 doses. The majority of local reactions after each dose were mild or moderate.

Pain was the most frequently occurring local reaction after Doses 1 to 4 of 13vPnC. Severe pain was reported after each dose: Dose 1, 5 subjects (3.0%); Dose 2, 6 subjects (4.6%); Dose 3, 5 subjects (4.3%); and Dose 4, 6 subjects (6.7%).

Redness and swelling occurred less frequently after Doses 1 to 4. Severe local redness and swelling were reported infrequently, particularly after the first three 13vPnC doses (in only 1 or 2 subjects, ≤1.7%). After Dose 4, 5 subjects (5.6%) experienced severe redness and 4 subjects (4.5%) experienced severe swelling.

Percentages of any local reaction were somewhat higher in the pediatric age subgroup than in the adult subgroup, with pain the most common local reaction in both age subgroups. Redness and swelling were consistently more common in the pediatric age group than in the adult age group.

Mean durations of local reactions were similar in both age groups and did not exceed 4.5 days after any dose.

<u>Systemic Events</u>

Most subjects in the overall safety population (age ≥2 years) experienced systemic events after each 13vPnC dose. For the majority of events a higher percentage of subjects experienced systemic events after dose 4 than after the other 3 doses.

In the overall safety population, the most frequently reported systemic events within 14 days after each dose of 13vPnC were fatigue, muscle pain, and headache, and these were reported somewhat more often after Dose 4. In the pediatric and adult subgroups fatigue, muscle pain, and headache were also reported most often. For the majority of systemic events after each dose there was no difference in frequencies between the age groups.

The percentage of subjects age ≥2 years with fever ≥38.0°C after Dose 1, Dose 2, and Dose 3 of 13vPnC was low (6.7% to 9.9%) and increased at Dose 4 of 13vPnC (17.7%). Fever ≥38.0°C was more frequent in the 2 to <18 year group (range 12.8% to 27.8% across doses) than in the ≥18 year age group (range 4.3% to 15.4% across doses).

Mean duration of systemic events were similar after each of the doses and did not exceed 7.2 days. The mean durations of systemic events were similar between subjects in the 2- to <18-year age group and subjects in the ≥18-year age group after each dose and did not exceed 9.1 days.

Table 4. Subjects Reporting Local Reactions Within 14 Days of Each Dose of 13vPnC – Safety Population Age Group: ≥2 Years

	Vaccine Sequence (as Administered)															
	13vPnC/13vPnC/13vPnC/13vPnC/23vPS															
	Dose 1				Dose 2				Dose 3				Dose 4			
Local Reaction	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Redness[d]																
Any	168	23	13.7	(8.9, 19.8)	137	30	21.9	(15.3, 29.8)	120	17	14.2	(8.5, 21.7)	100	33	33.0	(23.9, 43.1)
Mild	168	20	11.9	(7.4, 17.8)	134	26	19.4	(13.1, 27.1)	118	13	11.0	(6.0, 18.1)	97	22	22.7	(14.8, 32.3)
Moderate	165	6	3.6	(1.3, 7.7)	129	9	7.0	(3.2, 12.8)	117	6	5.1	(1.9, 10.8)	90	16	17.8	(10.5, 27.3)
Severe	165	0	0.0	(0.0, 2.2)	127	2	1.6	(0.2, 5.6)	116	2	1.7	(0.2, 6.1)	89	5	5.6	(1.8, 12.6)
Swelling[d]																
Any	170	25	14.7	(9.7, 20.9)	133	25	18.8	(12.5, 26.5)	121	18	14.9	(9.1, 22.5)	108	41	38.0	(28.8, 47.8)
Mild	169	18	10.7	(6.4, 16.3)	131	19	14.5	(9.0, 21.7)	120	15	12.5	(7.2, 19.8)	100	25	25.0	(16.9, 34.7)
Moderate	167	9	5.4	(2.5, 10.0)	128	7	5.5	(2.2, 10.9)	117	5	4.3	(1.4, 9.7)	95	17	17.9	(10.8, 27.1)
Severe	165	1	0.6	(0.0, 3.3)	126	0	0.0	(0.0, 2.9)	115	1	0.9	(0.0, 4.7)	88	4	4.5	(1.3, 11.2)
Pain[e]																
Any	222	165	74.3	(68.1, 79.9)	194	146	75.3	(68.6, 81.2)	175	127	72.6	(65.3, 79.0)	143	113	79.0	(71.4, 85.4)
Mild	217	151	69.6	(63.0, 75.6)	184	129	70.1	(62.9, 76.6)	163	109	66.9	(59.1, 74.0)	130	94	72.3	(63.8, 79.8)
Moderate	180	50	27.8	(21.4, 34.9)	148	49	33.1	(25.6, 41.3)	141	42	29.8	(22.4, 38.1)	109	42	38.5	(29.4, 48.3)
Severe	166	5	3.0	(1.0, 6.9)	131	6	4.6	(1.7, 9.7)	117	5	4.3	(1.4, 9.7)	90	6	6.7	(2.5, 13.9)
Any local reaction[f]	223	172	77.1	(71.1, 82.5)	198	154	77.8	(71.3, 83.4)	175	129	73.7	(66.5, 80.1)	151	127	84.1	(77.3, 89.5)

a. N = number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
d. For ages 2-<12 years, mild = 0.5 to 2.0 cm, moderate = 2.5 to 7.0 cm, and severe is >7.0 cm. For ages ≥12 years, mild = 2.5 to 5.0 cm, moderate = 5.5 to 10.0 cm, severe is >10.0 cm.
e. Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.
f. Any local reaction = any pain, any swelling, or any redness.

Table 5. Subjects Reporting Systemic Events Within 14 Days of Each Dose of 13vPnC – Safety Population Age Group: ≥2 Years

	Vaccine Sequence (as Administered)															
	13vPnC/13vPnC/13vPnC/13vPnC/23vPS															
	Dose 1				Dose 2				Dose 3				Dose 4			
Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])

Table 5. Subjects Reporting Systemic Events Within 14 Days of Each Dose of 13vPnC – Safety Population Age Group: ≥2 Years

	Vaccine Sequence (as Administered)															
	13vPnC/13vPnC/13vPnC/13vPnC/23vPS															
	Dose 1				Dose 2				Dose 3				Dose 4			
Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Fever																
≥38°C	169	13	7.7	(4.2, 12.8)	131	13	9.9	(5.4, 16.4)	120	8	6.7	(2.9, 12.7)	96	17	17.7	(10.7, 26.8)
≥38°C but <38.5°C	167	10	6.0	(2.9, 10.7)	131	11	8.4	(4.3, 14.5)	119	6	5.0	(1.9, 10.7)	92	12	13.0	(6.9, 21.7)
≥38.5°C but <39°C	165	2	1.2	(0.1, 4.3)	126	3	2.4	(0.5, 6.8)	117	4	3.4	(0.9, 8.5)	90	5	5.6	(1.8, 12.5)
≥39°C but ≤40.0°C	167	3	1.8	(0.4, 5.2)	126	3	2.4	(0.5, 6.8)	116	2	1.7	(0.2, 6.1)	87	2	2.3	(0.3, 8.1)
>40.0°C	165	0	0.0	(0.0, 2.2)	126	0	0.0	(0.0, 2.9)	115	0	0.0	(0.0, 3.2)	86	0	0.0	(0.0, 4.2)
Fatigue[d]																
Any	204	119	58.3	(51.2, 65.2)	171	98	57.3	(49.5, 64.8)	157	77	49.0	(41.0, 57.1)	128	86	67.2	(58.3, 75.2)
Mild	190	88	46.3	(39.1, 53.7)	156	63	40.4	(32.6, 48.5)	148	58	39.2	(31.3, 47.5)	121	68	56.2	(46.9, 65.2)
Moderate	192	69	35.9	(29.2, 43.2)	155	61	39.4	(31.6, 47.5)	137	42	30.7	(23.1, 39.1)	106	48	45.3	(35.6, 55.2)
Severe	173	20	11.6	(7.2, 17.3)	131	13	9.9	(5.4, 16.4)	120	8	6.7	(2.9, 12.7)	93	12	12.9	(6.8, 21.5)
Headache[d]																
Any	189	84	44.4	(37.2, 51.8)	152	53	34.9	(27.3, 43.0)	142	53	37.3	(29.4, 45.8)	114	53	46.5	(37.1, 56.1)
Mild	186	71	38.2	(31.2, 45.6)	147	44	29.9	(22.7, 38.0)	138	44	31.9	(24.2, 40.4)	109	44	40.4	(31.1, 50.2)
Moderate	174	31	17.8	(12.4, 24.3)	136	20	14.7	(9.2, 21.8)	122	21	17.2	(11.0, 25.1)	98	26	26.5	(18.1, 36.4)
Severe	167	4	2.4	(0.7, 6.0)	128	2	1.6	(0.2, 5.5)	119	4	3.4	(0.9, 8.4)	90	6	6.7	(2.5, 13.9)
Vomiting[e]																
Any	173	36	20.8	(15.0, 27.6)	135	20	14.8	(9.3, 21.9)	120	13	10.8	(5.9, 17.8)	89	5	5.6	(1.8, 12.6)
Mild	172	31	18.0	(12.6, 24.6)	134	16	11.9	(7.0, 18.7)	119	6	5.0	(1.9, 10.7)	89	5	5.6	(1.8, 12.6)
Moderate	166	6	3.6	(1.3, 7.7)	131	9	6.9	(3.2, 12.6)	117	8	6.8	(3.0, 13.0)	86	0	0.0	(0.0, 4.2)
Severe	165	2	1.2	(0.1, 4.3)	126	1	0.8	(0.0, 4.3)	115	0	0.0	(0.0, 3.2)	86	0	0.0	(0.0, 4.2)
Diarrhea[f]																
Any	189	66	34.9	(28.1, 42.2)	150	44	29.3	(22.2, 37.3)	130	30	23.1	(16.1, 31.3)	101	29	28.7	(20.1, 38.6)
Mild	186	62	33.3	(26.6, 40.6)	149	41	27.5	(20.5, 35.4)	128	26	20.3	(13.7, 28.3)	100	28	28.0	(19.5, 37.9)
Moderate	171	14	8.2	(4.5, 13.4)	134	13	9.7	(5.3, 16.0)	119	6	5.0	(1.9, 10.7)	87	3	3.4	(0.7, 9.7)
Severe	168	5	3.0	(1.0, 6.8)	127	2	1.6	(0.2, 5.6)	117	2	1.7	(0.2, 6.0)	87	1	1.1	(0.0, 6.2)
Muscle pain[d]																
Any	201	103	51.2	(44.1, 58.3)	160	72	45.0	(37.1, 53.1)	152	61	40.1	(32.3, 48.4)	123	74	60.2	(50.9, 68.9)
Mild	191	83	43.5	(36.3, 50.8)	150	54	36.0	(28.3, 44.2)	142	47	33.1	(25.4, 41.5)	114	57	50.0	(40.5, 59.5)

Table 5. Subjects Reporting Systemic Events Within 14 Days of Each Dose of 13vPnC – Safety Population Age Group: ≥2 Years

	Vaccine Sequence (as Administered)															
	13vPnC/13vPnC/13vPnC/13vPnC/23vPS															
	Dose 1				Dose 2				Dose 3				Dose 4			
Event	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])
Moderate	183	46	25.1	(19.0, 32.1)	143	40	28.0	(20.8, 36.1)	132	27	20.5	(13.9, 28.3)	99	31	31.3	(22.4, 41.4)
Severe	168	9	5.4	(2.5, 9.9)	131	8	6.1	(2.7, 11.7)	118	4	3.4	(0.9, 8.5)	91	7	7.7	(3.1, 15.2)
Joint pain[d]																
Any	181	48	26.5	(20.2, 33.6)	147	37	25.2	(18.4, 33.0)	132	28	21.2	(14.6, 29.2)	99	31	31.3	(22.4, 41.4)
Mild	176	34	19.3	(13.8, 25.9)	142	30	21.1	(14.7, 28.8)	128	23	18.0	(11.7, 25.7)	93	21	22.6	(14.6, 32.4)
Moderate	175	26	14.9	(9.9, 21.0)	136	20	14.7	(9.2, 21.8)	122	13	10.7	(5.8, 17.5)	91	15	16.5	(9.5, 25.7)
Severe	167	5	3.0	(1.0, 6.8)	129	3	2.3	(0.5, 6.6)	119	4	3.4	(0.9, 8.4)	90	4	4.4	(1.2, 11.0)
Use of medication to treat pain	176	28	15.9	(10.8, 22.2)	133	15	11.3	(6.5, 17.9)	125	18	14.4	(8.8, 21.8)	93	16	17.2	(10.2, 26.4)
Use of medication to treat fever	174	29	16.7	(11.5, 23.1)	134	20	14.9	(9.4, 22.1)	131	24	18.3	(12.1, 26.0)	94	16	17.0	(10.1, 26.2)
Any systemic event[g]	223	178	79.8	(73.9, 84.9)	191	146	76.4	(69.8, 82.3)	178	124	69.7	(62.3, 76.3)	148	121	81.8	(74.6, 87.6)

a. N = number of subjects with known values.
b. n = Number of subjects with the given characteristic.
c. Exact 2-sided confidence interval based upon the Clopper-Pearson method.
d. Mild = does not interfere with activity, moderate = some interference with activity, severe = prevents daily routine activity.
e. Mild = 1 to 2 times in 24 hours, moderate = more than 2 times in 24 hours, severe = requires intravenous hydration.
f. 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.
g. Any systemic event = any fever ≥38°C, any fatigue, any headache, any vomiting, any diarrhea, any muscle pain, or any joint pain.

Adverse Events

The percentage of subjects in the overall safety population (age ≥2 years) reporting any AE after Dose 1 of 13vPnC to the Dose 3 blood draw was 85.4%. Subjects in the 2- to <18-year age group and the ≥18-year age group reported similar percentages of AEs (81.4% and 86.7%, respectively).

Infections and infestations were the most frequently reported type of AE after each 13vPnC dose in the overall safety population (aged ≥2 years) and in the pediatric (aged 2 to <18 years) and adult (≥18 years) subgroups. In each age group related AEs were infrequent and were most often categorized as general disorders and administration site conditions after each 13vPnC dose and after the 23vPS dose.

The percentage of subjects in the overall safety population (age ≥2 years) reporting any AE after Dose 4 of 13vPnC to the Dose 4 blood draw was 42.2%. Subjects in the 2- to <18-year age group and the ≥18-year age group reported similar percentages of AEs (39.1% and 43.2%, respectively).

In the overall safety population (age ≥2 years), the most frequently reported categories of AEs after Dose 4 of 13vPnC to the Dose 4 blood draw were infections and infestations (18.2%), general disorders and administration site conditions (11.5%), and musculoskeletal and connective tissue disorders (5.7%). In the 2- to <18-year age group, the most frequently reported categories of AEs were infections and infestations (17.4%), general disorders and administration site conditions (15.2%), and gastrointestinal disorders (8.7%) during the same time period. In the ≥18-year age group, the most frequently reported categories of AEs after Dose 4 of 13vPnC to the Dose 4 blood draw were infections and infestations (18.5%), general disorders and administration site conditions (10.3%), and musculoskeletal and connective tissue disorders (5.5%).

In the overall safety population (age ≥2 years), the percentage of subjects reporting any AE after 23vPS to the 23vPS blood draw was 52.2%. Subjects in the 2- to <18-year age group had lower percentages of AEs than subjects in the ≥18-year age group (46.7% and 54.0%, respectively).

The most frequently reported categories of AEs after 23vPS to the 23vPS blood draw in the overall safety population (age ≥2 years) were general disorders and administration site conditions (21.7%), infections and infestations (20.1%), and respiratory, thoracic and mediastinal disorders (6.0%). In the 2- to <18-year age group, the most frequently reported categories of AEs were infections and infestations (26.7%), general disorders and administration site conditions (11.1%), and ear and labyrinth disorders (6.7%) during the same time period. In the ≥18-year age group, the most frequently reported categories of AEs after 23vPS to the 23vPS blood draw were general disorders and administration site conditions (25.2%), infections and infestations (18.0%), and musculoskeletal and connective tissue disorders (7.2%).

Deaths

There were 14 subjects who died during the study. Of the 14 subjects who died, 2 subjects were in the 2- to <18-year age group and 12 subjects were in the ≥18-year age group. No deaths were related to study vaccines but were generally due to complications of the subject's underlying disease.

Serious Adverse Events, Related SAEs, AE Withdrawals

The percentage of subjects in the overall safety population (age ≥2 years) reporting any SAE after Dose 1 of 13vPnC to the Dose 3 blood draw was 23.5%. Subjects in the 2- to <18-year age group and the ≥18-year age group reported similar percentages of SAEs (20.3% and 24.5%, respectively). The most frequently reported categories of SAEs after Dose 1 of 13vPnC to the Dose 3 blood draw were infections

and infestations and benign, malignant, or unspecified neoplasms in the overall safety population (age ≥2 years), as well as the 2- to <18-year age group and the ≥18-year age group.

The percentage of subjects in the overall safety population (age ≥2 years) reporting any SAE after Dose 4 of 13vPnC to the Dose 4 blood draw was 5.7%. Subjects in the 2- to <18-year age group and the ≥18-year age group reported similar percentages of SAEs (4.3% and 6.2%, respectively). In the 2- to <18-year age group, SAEs reported during this time included H1N1 influenza (1 subject, 2.2%), and pneumonia (1 subject, 2.2%). SAEs reported for the ≥18-year age group after Dose 4 of 13vPnC to the Dose 4 blood draw included influenza (1 subjects, 0.7%), osteonecrosis (1 subject, 0.7%), and staphylococcal sepsis (1 subject, 0.7%).

In the overall safety population (age ≥2 years), the percentage of subjects reporting any SAE after 23vPS to the 23vPS blood draw was 6.0%. Subjects in the 2- to <18-year age group (8.9%) reported a higher percentage of SAEs than the ≥18-year age group (5.0%). In the 2- to <18-year age group, SAEs reported during this time included cellulitis (1 subject, 2.2%), device-related infection (1 subject, 2.2%), and varicella (1 subject, 2.2%). SAEs reported for the ≥18-year age group after 23vPS to the 23vPS blood draw included graft-versus-host-disease in liver (2 subjects, 1.4%), Guillain-Barré syndrome (1 subject, 0.7%), and herpes zoster (1 subject, 0.7%).

SAEs considered by the investigator to have a reasonable possible relationship to a study vaccine were reported in 5 subjects after receiving 13vPnC: 1 subject in the 2- to <18-year age group (injection site erythema and pyrexia); and 4 subjects in the ≥18-year age group (bilateral pneumonia due to possible pneumococcal infection (pneumococcal urine antigen positive), autoimmune hemolytic anemia, bilateral VIIth facial nerve paralysis, and Guillain-Barré syndrome).

The SAE assessed by the investigator as possibly related to 23vPS was reported in a pediatric subject who experienced cellulitis 2 days after receiving study vaccine 23vPS. In addition, the SAE described above (Guillain-Barré syndrome) was assessed as possibly related to 13vPnC and 23vPS.

Study 6096A1-3014 (B1851013): children and adolescents aged ≥6 to <18 years with SCD, previously immunized with 23vPS; 6-month safety addendum and 1-year final study report).

Local reactions and systemic events were not collected during the study period covered in the 6-month safety addendum or the 1-year antibody persistence report. Only SAEs or newly diagnosed chronic medical conditions were collected during the time period covered by these 2 reports.

<u>6-month Safety Addendum</u>

Overall, 63 AEs were reported for 29 subjects (19.7%). The AEs reported by more than 1 subject were sickle cell anemia with crisis (17 subjects, 11.6%), acute chest syndrome (2 subjects, 1.4%), pain (2 subjects, 1.4%), pyrexia (2 subjects, 1.4%), and pneumonia (2 subjects, 1.4%).

Of the 63 AEs reported, 62 were considered SAEs and none were related to vaccination. All SAEs resolved.

The 1 non-serious AE was allergic rhinitis, a newly diagnosed chronic medical condition, reported by 1 subject.

<u>1-year Antibody Persistence Report</u>

Overall, 38 AEs were reported for 17 subjects (19.5%). The AEs reported by more than 1 subject were sickle cell anemia with crisis (11 subjects, 12.6%), pyrexia (3 subjects, 3.4%), and pneumonia (4 subjects, 4.6%).

Of the 38 AEs reported, 37 were considered SAEs and none were related to vaccination. All SAEs resolved.

The 1 non-serious AE was hiatus hernia, which was a newly diagnosed chronic medical condition reported by 1 subject. While performing the quality review procedures for this report, it was observed that 2 newly diagnosed chronic medical conditions were incorrectly recorded during the 1-year follow-up period in the Visit 1 medical history page of the CRF and were therefore not captured in the adverse event tables of the 1-year report. These events are gastritis and avascular necrosis of the right hip.

The CHMP noted that the safety data collected in the follow-up period did not give rise to further concern. No new safety signal was detected.

2.3.2. Discussion

In HIV infected subjects, the overall safety results are in agreement with the previously assessed study 6115A1-3017 (II76) in HIV infected adults, although the rate of adverse events was higher in the previous study.

In HSCT recipients, the frequencies of local and systemic reactions were generally in agreement with previously reported rates. The number of SAEs in this study is higher than in studies in healthy subjects, as can be expected, considering that it is a more fragile population. At the CHMP's request, the MAH submitted reviews of Guillain Barre syndrome, autoimmune haemolytic anemia, and bilateral VIIth facial nerve paralysis. Given the complex constellation of comorbid conditions and concomitant medications in subjects who have undergone a HSCT, the CHMP concluded any potential causal relationship between Prevenar 13 and these events was difficult to establish. Furthermore, since the cases were isolated cases or very little in number, relationship between Prevenar 13 and these events can't be established.

In Sickle cell disease, the safety data collected in the follow-up period did not give rise to further concern. No new safety signal was detected.

2.4. Risk management plan

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

The PRAC does not advise any changes to the current conditions of the Marketing Authorisation.

Data have shown that vaccination with 13vPnC vaccine presents a positive benefit-risk balance in these populations which displayed similar frequencies of adverse events, except that headaches, vomiting, diarrhoea, pyrexia, fatigue, arthralgia, and myalgia were very common. However, the sample size of these three studies was quite low, with 303, 251, and 158 subjects assigned to receive study vaccine in, respectively, studies 6115A1-3002 (children and/or adults with HIV), 6115A1-3003 (children and/or adults with HSCT), and 6096A1-3014 (sickle cell disease). Such a sample size is not appropriate to identify uncommon and rare events that may happen after vaccination with 13vPnC vaccine, e.g. convulsion, hypotonic-hyporesponsive episode, or hypersensitivity reaction. Hence, the PRAC recommended the MAH to continue to monitor adverse events in high-risk populations in a separate discussion in next PSURs.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

A summary of the important identified and potential safety concerns and safety concerns due to missing information in the 13vPnC clinical program are provided in Table 6.

Table 6 Ongoing Safety Concerns

Important identified risks	a) Drug interaction: Increased fever rates when 13vPnC is co-administered Infanrix hexa b) Anaphylaxis/hypersensitivity c) Convulsions/seizures d) Apnoea
Important potential risks	a) Drug interaction: neurological events of HHE and convulsions with co-administration of 13vPnC and Infanrix hexa. c) Lack of effect in subjects who are fully vaccinated.
Important missing information	a) Unanticipated safety signals (including the onset of rare events) not seen in clinical trials of 13vPnC (including wheezing). b) Effectiveness of 13vPnC c) Potential changes in the epidemiology of nonvaccine *S pneumoniae* serotypes that may occur. d) Safety and immunogenicity in high-risk populations.[a] i) Pneumococcal vaccine naïve HIV-infected subjects. ii) Subjects with allogeneic HSCT. e) Impact of 13vPnC on nasopharyngeal carriage (infants/children) f) Effect of antipyretics on immune response to vaccination (infants/children).[b] f) Safety of more than 1 dose of 13vPnC in adults administered >1 year apart. g) Vaccine exposure during pregnancy and lactation.

Abbreviations: HHE = hypotonic-hyporesponsive episode; HIV = human immunodeficiency virus ; HSCT = hematologic stem cell transplant; NPC = nasopharyngeal carriage.

a. This safety concern has been addressed and will be removed from future versions of the RMP. All primary CSRs are complete in these high-risk populations and SmPC Sections 4.2, 4.4, 4.8 and 5.1 have been or are being updated with information based on results from these studies. These studies include studies 6096A1-4001 (premature infants, primay analysis complete; study ongoing to assess antibody persistance) and 6096A1-3014 (sickle cell disease, completed), and studies in children and/or adults with HIV (6115A1-3002 and 6115A1-3017, both completed) or with HSCT (6115A1-3003, completed).

b. This safety concern has been addressed in study 6096A1-4027. Based on results of the study, it is no longer an important safety concern and will be removed from the list of ongoing safety concerns in future RMPs.

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Pharmacovigilance plans

Table 7. Table of Ongoing and Planned Studies / Activities in the Pharmacovigilance Plan

Study	Objectives	Safety Concerns Addressed	Protocol Status	Planned Dates for Interim Data and Submission of Final Data

Table 7. Table of Ongoing and Planned Studies / Activities in the Pharmacovigilance Plan

Study	Objectives	Safety Concerns Addressed	Protocol Status	Planned Dates for Interim Data and Submission of Final Data
Description of European National Surveillance Systems for Pneumococcal Disease	To monitor PD, including serotype-specific changes, in EU surveillance programs (UK, France, Germany, Norway, Denmark) since launch of 7vPnC (Prevenar).	Vaccine failure in subjects fully vaccinated Effectiveness of 13vPnC Potential changes in epidemiology of non-vaccine type *S pneumoniae*	Reports have been submitted annually	Interim reports: Annual reports from the UK, France, Germany, Norway and Denmark will be submitted annually. . Final report: March 2016 FUMs 19 and 47
Program in Infants, Children, and Adolescents				
Surveillance Network for Rhinopharyngeal Carriage of *Streptococcus pneumoniae* in children with AOM and in healthy children (ACTIV)	To determine nasopharyngeal carriage of *S pneumonia* serotypes in infants and toddlers with AOM and in healthy children	Information on nasopharyngeal carriage of *S pneumoniae* serotypes	Year 11 (2001-present): reporting period: 5 Oct 2011 to 27 April 2012. (13vPnC introduction in France - June 2010).	Interim reports: will be submitted annually Final report: 2016 FUM 19
6096A1-4001 (B1851037): A Phase 4, Open Label, 2-Arm Trial Evaluating the Safety, Tolerability and Immunogenicity of 13-Valent Pneumococcal Conjugate Vaccine in Preterm Infants	To assess safety/immuno-genicity of 13vPnC (3+1 schedule) infants born preterm vs infants born at term	Safety/immuno-genicity in high risk population (preterm infants)	Open label, 2 arm Protocol Amendment 2 (20 June 2012)	Primary endpoint December 2012 (completed) (study ongoing to assess antibody persistence 1 and 2 year(s) after last vaccination)

Table 7. Table of Ongoing and Planned Studies / Activities in the Pharmacovigilance Plan

Study	Objectives	Safety Concerns Addressed	Protocol Status	Planned Dates for Interim Data and Submission of Final Data
6096A1-4002 (B1851044): Post-licensure Evaluation of 13vPnC: Safety of 13vPnC Administered in Routine Use to Infants and Children	To assess safety of 13vPnC in routine use for infants and children	Anaphylaxis/ hypersensitivity Convulsions/ seizures Apnea Unanticipated safety signals	Observational safety study; data collection ongoing Protocol Amendment 2 (26 March 2012)	1st Interim report: Covers the first 12 months of the study submitted November 20 11 2nd Interim report Covers 18 months of the study submitted July 2012 Final report: September 2014 FUM 12
6096A1-4005 (B1851042): A Postmarketing Observational Study Estimating the Impact of Prevnar 13™ (13vPnC) on Invasive Pneumococcal Disease Caused by Vaccine Serotypes of *Streptococcus pneumoniae* After Introduction Into Routine Pediatric Use	To assess impact of 13vPnC on vaccine-type IPD after introduction for routine pediatric use	Vaccine failure in subjects fully vaccinated Effectiveness of 13vPnC	Observational study; data collection ongoing Protocol (15 March 2010)	Final report: March 2016
6096A1-4010 (B1851018): A Phase 4, Postmarketing Study Evaluating the Impact of Prevnar 13™ (13-valent Pneumococcal Conjugate Vaccine; 13vPnC) in Reducing Acute Otitis Media (AOM) and Nasopharyngeal Colonization (NPC) Caused by *Streptococcus pneumoniae* in Healthy Children	To assess impact of 13vPnC on AOM and NPC in healthy children	Effectiveness of 13vPnC Information on NPC in children	Non-therapeutic non-interventional study; ongoing Protocol Amendment 2 (24 May 2011)	Final report: December 2016
6096A1-4018 (B1851041): National Trends in Ambulatory Care Visits for Otitis Media in Children Under the Age of Five in the United States	To assess impact of 13vPnC on AOM in children aged <5 years	Effectiveness of 13vPnC	Non-interventional surveillance; ongoing Protocol (04 June 2010)	Final report: March 2016

Table 7. Table of Ongoing and Planned Studies / Activities in the Pharmacovigilance Plan

Study	Objectives	Safety Concerns Addressed	Protocol Status	Planned Dates for Interim Data and Submission of Final Data
6096A1-4024 (B1851040): Postmarketing Observational Study of the Impact of Prevnar 13™ (Pneumococcal 13-valent Conjugate Vaccine) on Otitis Media in Children	To assess impact of 13vPnC on AOM in children	Effectiveness of 13vPnC	Non-interventional; ongoing Protocol (21 May 2010)	Final report: September 2014
Program in Adults				
6115A1-3001 (B1851020): A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a 13 Valent Pneumococcal Conjugate Vaccine (13vPnC) When Administered Concomitantly With Trivalent Inactivated Influenza Vaccine in Healthy Adults 50 to 59 Years of Age who are Naïve to 23 Valent Pneumococcal Polysaccharide Vaccine and to Evaluate the Immune Response of a Second Dose Of 13vPnC Administered 5 Years After Initial 13vPnC Vaccination	Objective for dose 2 (given 5 years after first dose): To measure the immune response to a second dose of 13vPnC administered 5 years after the initial dose of 13vPnC.	Safety of more than 1 dose of 13vPnC in adults administered >1 year apart	Ongoing (Amendment 2) 13 March 2012	Interim CSR submitted with initial MAA submission. Final report Q2 2014
6115A1-3006 (B1851025): A Phase 4, Randomized, Placebo-Controlled Clinical Trial of 13-valent Pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-Serotype Pneumococcal Community-Acquired Pneumonia (CAP) and Invasive Pneumococcal Disease (IPD)	To evaluate the efficacy of 13vPnC in the prevention of pneumococcal CAP and IPD	Vaccine failure in fully vaccinated subjects Unanticipated safety signals	Parallel group, randomized, placebo-controlled, double-blind; ongoing Amendment 9, (October 2013)	Study report due June 2014 Additional reports by January 2015

Risk minimisation measures

Table 8. Risk Minimization Activities

Safety Concern[a]	Proposed Risk Minimization Activities (Routine and Additional)
Important identified risks:	

Table 8. Risk Minimization Activities

Safety Concern[a]	Proposed Risk Minimization Activities (Routine and Additional)
a) Increased fever rates when coadministered with Infanrix hexa.	The SmPC revisions approved 22 November 2012 in procedure II/56 are as follows: Routine SmPC (Section 4.4) Special warnings and precautions for use When Prevenar 13 is administered concomitantly with Infanrix hexa (DTPa-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa (see section 4.8). (Section 4.8) Undesirable effects In a clinical study in infants vaccinated at 2, 3, and 4 months of age, fever ≥ 38°C was reported at higher rates among infants who received Prevenar (7-valent) concomitantly with Infanrix hexa (28.3% to 42.3%) than in infants receiving Infanrix hexa alone (15.6% to 23.1%). After a booster dose at 12 to 15 months of age, the rate of fever ≥ 38°C was 50.0% in infants who received Prevenar (7-valent) and Infanrix hexa at the same time as compared to 33.6% in infants receiving Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39 °C) and transient.
b) Anaphylaxis/hypersensitivity c) Convulsions/seizures d) Apnoea	These risks are communicated through the label (Sections 4.4 and 4.8 of the SmPC [all 3 safety concerns]; Section 15 of the CDS [convulsions/seizures]; Sections 5 and 15.2 of the CDS [anaphylaxis/ hypersensitivity]; Section 6.1 of the CDS [apnea]) (The post-approval observational safety study 6096A1-4002 is being conducted in at least 43,000 children vaccinated with 13vPnC to monitor the safety profile of 13vPnC The study is designed to evaluate rates of all medically attended events in the hospital and emergency department settings and prespecified events in hospital, emergency department, and outpatient clinic settings. Anaphylaxis, hypersensitivity, seizures, convulsions, wheezing, and apnea events are included as prespecified endpoints in the study. Routine pharmacovigilance to monitor the safety profile of 13vPnC)
Safety Concern[a]	Proposed Risk Minimization Activities (Routine and Additional)
Important Potential Risks	
a) Drug interaction: neurological events of HHE and convulsions with co-administration of 13vPnC and Infanrix hexa.	This risk is being communicated through the label (Sections 4.4, 4.5 and 4.8 of the EU SmPC). The proposed text includes statements on spontaneous reports of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) following concomitant administration of 13vPnC and Infanrix hexa. Routine pharmacovigilance to monitor the safety profile of 13vPnC.

Table 8. Risk Minimization Activities

Safety Concern[a]	Proposed Risk Minimization Activities (Routine and Additional)
b) Lack of effect in subjects who are fully immunized (according to local recommendations).	Routine: SmPC (section 4.4) Special warnings and precautions As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease. (Study 6115A1-3006, a large randomized placebo-controlled efficacy and safety study in approximately 85,000 adults ≥65 years of age is being conducted. Efficacy of 13vPnC in the prevention of first episode of confirmed VT pneumococcal CAP and IPD will be assessed. CSR to be submitted June 2014; additional reports to be submitted by January 2015)
Important missing information:	
a) Unanticipated safety signals (including the onset of rare events)	Unanticipated safety signals (including the onset of rare events) are being monitored through routine pharmacovigilance (infants/children), including wheezing as part of the post-approval safety study (6096A1-4002). Study 6096A1-4002 is monitoring all medically attended events as measured by hospitalizations and emergency room visits, prespecified safety endpoints in the hospital and emergency room setting, and prespecified safety endpoints in the outpatient clinic setting following vaccination with 13vPnC. Wheezing diagnoses are included as prespecified endpoints in the safety assessment. For the adult population, unanticipated safety signals (including the onset of rare events) is being monitored in study 6115A1-3006 (in approximately 85,000 subjects) and through routine phamacovigilance.
b) Effectiveness of 13vPnC (infants/children). Effectiveness of 13vPnC (adults). Long-term vaccine effectiveness.	SmPC (Section 5.1) and PIL language provides information on the efficacy and effectiveness of 7vPnC, the percentage of subjects vaccinated with 13vPnC that have immune responses above the WHO-recommended threshold for efficacy, and the non-inferiority of antibody responses to 13vPnC relative to 7vPnC. In addition, a post-marketing observational study (6096A1-4005) to estimate the impact of 13vPnC on IPD caused by vaccine serotypes after introduction into routine pediatric use. Study 6115A1-3006, a large efficacy and safety study in approximately 85,000 adults ≥65 years of age is being conducted. Final report to be submitted June 2014, additional reports by January 2015. Population-based surveillance of the incidence rates of IPD (in some cases pneumonia and AOM-related outcomes) in 5 European countries (UK, France, Germany, Norway, Denmark), Canada (Quebec), and the USA for 5 years using national surveillance systems. Reports submitted annually, final report due March 2016.

Table 8. Risk Minimization Activities

Safety Concern[a]	Proposed Risk Minimization Activities (Routine and Additional)
c) Potential changes in the epidemiology of non-vaccine *S pneumoniae* serotypes associated with the reduction in disease and nasopharyngeal carriage of serotypes contained in the 13vPnC (infants/children).	The same 5 European population-based surveillance systems for effectiveness evaluation will be used to monitor potential changes in non-13vPnC serotypes for 5 years after 13vPnC introduction. Final report to be submitted 2016.
d) Safety and immunogenicity in high risk populations:	Note: This safety concern has been addressed and is no longer missing information or considered an important safety concern. All studies/primary analyses are complete in these high-risk populations and the SmPC is being updated with information based on results from these studies: 6096A1-4001 (preterm), 6096A1-3014 (SCD), 6115A1-3017 (HIV adult), 6115A1-3002 (HIV children/adults), 6115A1-3003 (HSCT). This will be removed from the list of important safety concerns. Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC, have been or are being updated to include additional information on dosing recommendations, differences in side effects observed and immunogenicity data from completed clinical studies of high-risk populations, including premature infants (primary analysis complete), children with sickle cell disease, children and adults with HIV or with HSCT who are naïve to a pneumococcal vaccine, and adults with HIV infection previously vaccinated with 23vPS.
e) Impact of 13vPnC on nasopharyngeal carriage (infants/children).	Section 5.1 of the SmPC includes information on the impact of Prevenar 13 on NPC in 2 pediatric studies, one conducted in France (ACTIV study) in children with AOM and the other in Israel. Both studies showed that Prevenar 13 reduced NPC of the 6 additional serotypes in 13vPnC combined plus serotype 6C. Ongoing surveillance of nasopharyngeal carriage (NPC) in France through the ACTIV surveillance program comparing nasopharyngeal carriage of *S pneumoniae* and other key commensal bacteria among children 6 to 24 months of age with acute otitis media. Monitoring for replacement of *S pneumoniae* with non-pneumococcal bacteria in the nasopharyngeal flora of children will be conducted in the ACTIV study in France.
f) Effect of antipyretics on immune response to vaccination (Infants/Children)	Note: This has been addressed and is no longer an important safety concern., based on results of study 6096A1-4027 which is now complete. This will be removed from the list of important safety concerns in future RMPs. Update of SmPC Section 4.5 to be implemented.

Table 8. Risk Minimization Activities

Safety Concern[a]	Proposed Risk Minimization Activities (Routine and Additional)
g) Safety of more than 1 dose of 13vPnC in adults administered at >1 year apart	The SmPC (section 4.4) mentions that the need for revaccination with a subsequent dose of Prevenar 13 has not been established in adults 50 years and older. One (1) ongoing clinical study (6115A1-3001) is evaluating the safety of a second dose of 13vPnC administered 5 years after the initial dose. (Study 6115A1-004 extension, which evaluated a second dose of 13vPnC 3 to 4 years after the initial dose is complete and the study report has been submitted.)
h) Vaccine exposure in pregnancy and lactation	Routine pharmacovigilence. Vaccine exposure during pregnancy or lactation will be monitored through the National Pregnancy Registry. In addition, the SmPC (section 4.6) states: Fertility, pregnancy, and lactation There are no data from the use of pneumococcal 13-valent conjugate in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. It is unknown whether pneumococcal 13-valent conjugate is excreted in human milk.

a. Applicable to both infants/children and adults, unless specified.

The CHMP endorsed this advice without changes.

2.5. Changes to the Product Information

The MAH proposed changes to the Product Information (PI). During the procedure, the CHMP requested further amendments to the PI as described in the Appendix 1.

3. Overall conclusion and impact on the benefit/risk balance

The final results from 2 additional studies in high-risk populations (6115A1-3002 and 6115A1-3003), and the 6-month follow-up safety and 1-year antibody persistence and safety data from study 6096A1-3014 (i.e., no study vaccine administered at 1 year) are now available. The variation currently being submitted includes final study reports for these 3 studies:

- 6115A1-3002 (B1851021): HIV-infected individuals aged ≥ 6 years, not previously immunized with a pneumococcal vaccine; final study report.
- 6115A1-3003 (B1851022): recipients of allogeneic hematopoietic stem cell transplant (HSCT) aged ≥ 2 years, who have not received a pneumococcal vaccine since HSCT; final study report.
- 6096A1-3014 (B1851013): children and adolescents aged ≥ 6 to <18 years with SCD, previously immunized with 23vPS; 6-month safety addendum and 1-year final study report).

These studies are submitted in accordance with Article 46 of the Paediatric Regulation (EC) No 1901/2006. Additionally, study 6115A1-3002 is a post-authorisation commitment to the European Union Marketing Authorisation (MEA 013). MEA 013 is fulfilled with the present application.

The CHMP was of the opinion that the study results provided valuable data on risk groups for pneumococcal infections.

HIV-infected children and adults with CD4 ≥ 200 cells/µL (mean 717.0 cells/µL), viral load < 50,000 copies/mL (mean 2090.0 copies/mL), free of active AIDS-related illness and not previously vaccinated with a pneumococcal vaccine received 3 doses of Prevenar 13. As per general recommendations, a single dose of 23-valent pneumococcal polysaccharide vaccine was subsequently administered. Vaccines were administered at 1 month intervals. Immune responses were assessed in 259-270 evaluable subjects approximately 1 month after each dose of vaccine. After the first dose, Prevenar 13 elicited antibody levels, measured by both IgG GMCs and OPA GMTs that were statistically significantly higher when compared to levels prior to vaccination. After the second and third dose of Prevenar 13, immune responses were similar or higher than those after the first dose.

The CHMP was of the opinion that the data in HIV infected subjects were generally in agreement with previously presented data, and the benefit of vaccination is considered clearly demonstrated in this group. The safety data from this study did not give rise to further safety concern, and no new safety signal was detected.

Children and adults with an allogeneic haematopoietic stem cell transplant (HSCT) at ≥ 2 years of age with complete haematologic remission of underlying disease or with very good partial remission in the case of lymphoma and myeloma received three doses of Prevenar 13 with an interval of at least 1 month between doses. The first dose was administered at 3 to 6 months after HSCT. A fourth (booster) dose of Prevenar 13 was administered 6 months after the third dose. As per general recommendations, a single dose of 23-valent pneumococcal polysaccharide vaccine was administered 1 month after the fourth dose of Prevenar 13. Immune responses as measured by IgG GMCs were assessed in 168-211 evaluable subjects approximately 1 month after vaccination. Prevenar 13 elicited increased antibody levels after each dose of Prevenar 13. Immune responses after the fourth dose of Prevenar 13 were significantly increased for all serotypes compared with after the third dose. Functional antibody titers (OPA titers) were not measured in this study.

In the HSCT recipient population, the immune responses were considered adequate by the CHMP, although OPA results are lacking. The presented data support an overall benefit of vaccination in HSCT recipients. The occurrence of some SAEs was addressed in the RSI, and it was concluded that no specific concern was raised due to the results. The data from study 6115A1-3003 support a schedule of four doses of 13vPnC, beginning early after HSCT when risk of infection is highest. The primary series consists of three doses, with the first dose given at 3 to 6 months after HSCT and with an interval of at least 1 month between doses. A fourth (booster) dose is recommended 6 months after the third dose. The proposed dosing schedule was considered adequate by the CHMP.

An open label single arm study in France, Italy, UK, US, Lebanon, Egypt and Saudi Arabia with 2 doses of Prevenar 13 given 6 months apart was conducted in 158 children and adolescents ≥ 6 to < 18 years of age with sickle cell disease who were previously vaccinated with one or more doses of 23-valent pneumococcal polysaccharide vaccine at least 6 months prior to enrolment. After the first vaccination, Prevenar 13 elicited antibody levels measured by both IgG GMCs and OPA GMTs that were statistically significantly higher when compared to levels prior to vaccination. After the second dose immune responses were comparable to those after the first dose. One year after the second dose, antibody levels measured by both IgG GMCs and OPA GMTs were higher than levels prior to the first dose of Prevenar 13, except for the IgG GMCs for serotypes 3 and 5 that were numerically similar.

In Sickle cell disease subjects, the immune responses 1 month after the second dose were assessed in variation II/76. With the present submission, the GMCs at 1 year after dose 2 were generally higher compared to the pre-vaccination levels, but for serotypes 1, 3 and 5 the 95% CI were overlapping. The OPA responses were in agreement with the IgG responses, but the 95% CIs were not overlapping for any serotypes. The CHMP concluded that the final data from the study in sickle cell disease patients confirm the preliminary data submitted with variation II/76.

In addition, the CHMP recommended that the MAH should continue to monitor adverse events in high-risk populations in a separate discussion in next PSURs.

The benefit / risk balance for Prevenar 13 remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to include the final results from the paediatric studies 6115A1-3002 (B1851021) conducted in HIV-infected individuals, 6115A1-3003 (B1851022) conducted in recipients of allogeneic hematopoietic stem cell transplant (HSCT) and 6096A1-3014 (B1851013) conducted in children and adolescents with sickle cell disease (SCD). The Package Leaflet is updated accordingly. With the submission of the final study results for study 6115A1-3002, the MAH fulfils MEA 013.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.