21 July 2016
EMA/CHMP/536289/2016
Human Medicines Development and Evaluation

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Prevenar 13

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Procedure no: EMEA/H/C/001104/P46/059

Note

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

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

1. Introduction

On January 22, 2016, the MAH submitted a completed paediatric study for Prevenar 13, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that B1851140 A Phase 4/3, Open-label, Single-arm, Multicenter Study To Describe The Safety And Immunogenicity Of 13-valent Pneumococcal Conjugate Vaccine In Adults 50 To 65 Years Of Age And In Children 6 To 17 Years Of Age In India is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation of Prevenar 13 was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- B1851140. Final Report, Pediatric Subjects Aged 6 to 17 Years: A Phase 4/3, Open-Label, Single-Arm, Multicenter Study to Describe the Safety and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine in Adults 50 to 65 Years of Age and in Children 6 to 17 Years of Age in India;

2.3.2. Clinical study

B1851140. Final Report, Pediatric Subjects Aged 6 to 17 Years: A Phase 4/3, Open-Label, Single-Arm, Multicenter Study to Describe the Safety and Immunogenicity of 13-valent Pneumococcal Conjugate Vaccine in Adults 50 to 65 Years of Age and in Children 6 to 17 Years of Age in India

Description

Methods

Objective(s)

Primary Safety Objective:

Pediatric Cohort, 6 to 17 Years of Age

To describe the safety profile of 13-valent pneumococcal conjugate vaccine (13vPnC) in pediatric subjects 6 to 17 years of age.

Primary Immunogenicity Objective:

Pediatric Cohort, 6 to 17 Years of Age

To describe the immune responses to the 13 pneumococcal serotypes induced by 13vPnC in pediatric subjects 6 to 17 years of age.

Study design

This was a Phase 4/3, open-label, single-arm, multicenter study to describe the safety and immunogenicity of 13vPnC in pediatric subjects aged 6 to 17 years in India.

Study population /Sample size

Approximately 200 subjects aged 6 to 17 years of age were to be enrolled in the pediatric cohort.

Inclusion Criteria: Subjects must have met all of the following inclusion criteria to be eligible for enrollment into the study.

1. Evidence of a personally signed and dated ICD indicating that the subject or the subject's parent/legal guardian had been informed of all pertinent aspects of the study. If a subject or the subject's parent/legal guardian was illiterate, he/she must have made his/her mark (eg, thumbprint) on the ICD and it must have been signed and dated by an impartial witness who was present throughout the entire informed consent process. If consent was provided by a subject's parent/legal guardian, the subject's assent may also have been required depending on local requirements.

2. Male or female children 6 to 17 years of age at the time of enrollment.

3. Healthy subjects, including subjects with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease 12 weeks before receipt of 13vPnC, were eligible.

4. Subjects or the subjects' parent(s)/legal guardian(s) who were willing and able to comply with scheduled visits and other study procedures.

5. Subjects or subjects' parent(s)/legal guardian(s) were expected to be available for the duration of the study.

6. Male and female subjects of childbearing potential and at risk for pregnancy must have agreed to use a highly effective method of contraception throughout the study.

Female subjects who were not of childbearing potential (ie, met at least 1 of the following criteria):

☐ Had not experienced menarche (the first menstrual cycle);

☐ Had undergone a documented hysterectomy and/or bilateral oophorectomy;

☐ Had medically confirmed ovarian failure; or

☐ Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may have been confirmed by having a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

7. Negative urine pregnancy test for all female subjects who were of childbearing potential.

Exclusion Criteria: Subjects presenting with any of the following were not included in the study:

1. Subjects or parents/legal guardians who were investigational site staff members or relatives of those site staff members or subjects who were Pfizer employees directly involved in the conduct of the trial.

2. History of severe adverse reaction, including hypersensitivity such as anaphylaxis, associated with a vaccine or vaccine component.

3. Any severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or 13vPnC administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the subject inappropriate for entry into this study.

4. Immunocompromised persons with known or suspected immunodeficiency or who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer, human immunodeficiency virus (HIV) infection, or autoimmune disease.

5. Severe chronic disorder, including metastatic malignancy, severe chronic obstructive pulmonary disease requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder which, in the investigator's opinion, precluded the subject from participating in the study.

6. Documented *Streptococcus pneumoniae* infection within the past 5 years before 13vPnC administration.

7. Receipt of any plasma products or immunoglobulins within 60 days preceding 13vPnC administration or anticipated receipt before study completion.

8. Vaccination with any licensed or investigational pneumococcal vaccine within the last year.

9. Participation in other studies within 28 days before the current study began and/or during study participation. Participation in observational studies was permitted.

10. Permanent residence in a nursing home, or other residential care facility. An ambulatory subject who was a resident of a retirement home or village was eligible for the study.

11. Pregnant females; breastfeeding females; males and females of childbearing potential and at risk for pregnancy who were unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study.

Treatments

All pediatric subjects received a single dose (0.5 mL) of 13vPnC intramuscularly into the thigh or the deltoid muscle as appropriate for the subject, at Visit 1. 13vPnC was provided as a 0.5-mL dose in a prefilled syringe. Commercial 13vPnC was provided by the sponsor to each study site. The vaccine was labeled in accordance with local regulations.

Outcomes/endpoints

Immunogenicity Evaluations: One (1) blood sample of approximately 10 mL of blood was collected immediately before vaccination at Visit 1 and another blood sample (10 mL) was collected 1 month after vaccination at Visit 2 from 200 pediatric subjects for the assessment of immune responses.

The protocol-specified window for blood draw of 28 to 42 days after Visit 1 was expanded in the statistical analysis plan (SAP) by 1 extra day before and 14 days after (ie, the window for blood draw was 27 to 56 days after vaccination).

Antibody-mediated opsonophagocytic activity (OPA) against each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) was measured using a serotype-specific microcolony opsonophagocytic activity (mcOPA) assay. Results were expressed as geometric mean titers (GMTs) for each serotype. An OPA titer was defined as the interpolated reciprocal serum dilution that would result in complement-mediated killing of 50% of the bacteria in each mcOPA assay. The lower limit of quantitation (LLOQ) in titers for each serotype was set as follows: serotype 1, 18; serotype 3, 12; serotype 4, 21; serotype 5, 29; serotype 6A, 37; serotype 6B, 43; serotype 7F, 113; serotype 9V, 141 serotype 14, 35; serotype 18C, 31; serotype 19A, 18; serotype 19F, 48; and serotype 23F, 13.

Recent communications with the US Food and Drug Administration (FDA) (Center for Biologics Evaluation and Research [CBER]) concerning the OPAs for pneumococcal serotypes 7F and 9V have included an adjusted analysis for assay linearity, and resulted in revision of the LLOQs for these 2 assays. The revised LLOQ for serotype 7F was a titer equal to 113 (previously 210), and the revised LLOQ for serotype 9V was a titer equal to 141 (previously 345). OPA titers above the LLOQ were considered accurate and their quantitated values will be reported. Titers below the LLOQ or denoted below limit of quantitation (BLQ) were set to 0.5 × LLOQ for analysis.

Safety Evaluations: A medical history was collected and a physical examination was performed on all pediatric subjects at Visit 1. Significant medical history and observations from the physical examination were to be documented in the case report form (CRF).

AEs (serious and nonserious) were reported and recorded on the CRF from the signing of the ICD to Visit 2 (28 to 42 days after Visit 1). Acute reactions within the first 20 minutes after study vaccine administration were assessed and documented on the AE CRF. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative began from the time that the subject provided informed consent, which was obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product and continued through 28 calendar days after the last administration of the investigational product. SAEs that occurred to a subject after the active reporting period ended were reported to the sponsor if the investigator became aware of them; at a minimum, all SAEs that the investigator believed had at least a reasonable possibility of being related to investigational product were reported to the sponsor.

Statistical Methods

For the immunogenicity analyses, 2 analysis populations were defined for the pediatric cohort: the evaluable immunogenicity population and the all-available immunogenicity population. The evaluable immunogenicity population was considered the primary analysis population.

The immunogenicity endpoints for the pediatric cohort were as follows:

☐ Serotype-specific OPA antibody titers at both visits (immediately before and approximately 1 month after vaccination).

☐ Serotype-specific fold rises in antibody titers from immediately before to approximately 1 month after vaccination.

☐ The proportion of subjects achieving serotype-specific OPA titers ≥LLOQ approximately 1 month after vaccination.

☐ Reverse cumulative distribution curves (RCDCs) presented graphically for each serotype.

Immunogenicity analysis summaries were produced for the evaluable immunogenicity population and the all-available immunogenicity population.

Serotype-specific OPA titers were logarithmically transformed for analysis. For each serotype, GMTs at both visits (prevaccination and 1 month postvaccination) were calculated.

Two-sided 95% confidence intervals (CIs) were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. The serotype-specific fold rises in antibody titers from prevaccination to 1 month postvaccination were summarized by geometric means and corresponding 95% CIs for each serotype. The proportion of subjects achieving an OPA titer ≥LLOQ

1 month after vaccination along with 2-sided 95% CIs for each of the 13 serotypes contained in 13vPnC was calculated.

The safety endpoint for the pediatric cohort was the proportion of subjects reporting AEs and SAEs within approximately 1 month after 13vPnC administration. AEs were to be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA version 18.1). The relationship between AEs and study vaccine was to be characterized as related or not related as described in the protocol. The severity of AEs was to be characterized as mild, moderate, severe, and life threatening.

The AEs were to be summarized by the total subjects in the safety population in the pediatric cohort. In addition, tables for related events, and events characterized as severe were to be tabulated for those events occurring during the study. The AEs collected from the signing of the ICD to the postdose follow-up were to be listed.

SAEs were to be summarized for subjects in the safety population. In addition, a listing of SAEs was generated from the Global Clinical Database (GCD).

All summaries were to display the number and percentage of subjects experiencing at least 1 event for each preferred term, arranged by system organ class, and the number of occurrences of the event.

The proportion of subjects reporting AEs and SAEs within approximately 1 month after 13vPnC administration was to be calculated and summarized in the tables.

There was no formal hypothesis testing for the AE data.

CHMP comment: The methodology used in this study is in agreement with previous studies, and raise no questions.

Results

Recruitment / Number analysed

Subject Disposition and Demography:

- A total of 200 subjects were enrolled and consented. All subjects were vaccinated and all subjects completed the study.
- There were no subjects discontinued from the study.

- Of the 200 subjects who received vaccination, 53.5% were female and 46.5% were male. All of the subjects were of Asian race from the Indian subcontinent and were of non-Hispanic/non-Latino ethnicity. Overall, the mean age at vaccination was 9.7 year

Immunogenicity results

Pneumococcal OPA Antibody GMTs and GMFRs Pneumococcal OPA antibody GMTs before and approximately 1 month after vaccination for the evaluable immunogenicity population of pediatric subjects 6 to 17 years of age are presented in Table 1. There was a numerical increase in GMTs from before vaccination to approximately 1 month after vaccination for all 13 serotypes.

Table 1. Pneumococcal OPA Antibody GMTs - Evaluable Immunogenicity Population - Age Group: 6 to 17 Years

Serotype	Sampling Time[a]	n[b]	GMT[c]	(95% CI[d])
1	Before vaccination	194	11	(9.6, 11.8)
	After vaccination	191	176	(146.1, 212.7)
3	Before vaccination	197	18	(15.3, 22.2)
	After vaccination	200	118	(103.7, 133.6)
4	Before vaccination	176	230	(155.8, 339.2)
	After vaccination	199	7860	(7074.0, 8732.4)
5	Before vaccination	199	19	(16.8, 20.9)
	After vaccination	200	286	(232.9, 351.9)
6A	Before vaccination	170	461	(339.6, 626.8)
	After vaccination	199	9247	(8197.4, 10431.8)
6B	Before vaccination	163	263	(184.2, 376.3)
	After vaccination	195	6755	(6018.5, 7581.7)
7F	Before vaccination	160	742	(585.8, 940.5)
	After vaccination	199	5251	(4787.9, 5758.1)
9V	Before vaccination	183	2097	(1702.4, 2582.9)
	After vaccination	197	7028	(6211.9, 7951.1)
14	Before vaccination	182	1387	(1091.0, 1763.0)
	After vaccination	197	7484	(6586.1, 8503.6)
18C	Before vaccination	154	216	(138.9, 336.6)
	After vaccination	198	8641	(7729.0, 9661.2)
19A	Before vaccination	195	62	(47.2, 80.1)
	After vaccination	197	1928	(1660.6, 2238.5)
19F	Before vaccination	194	265	(201.9, 348.5)
	After vaccination	200	3551	(3099.1, 4069.0)
23F	Before vaccination	184	84	(58.3, 121.4)
	After vaccination	199	4419	(3945.7, 4949.2)

a. SAP-specified timing for blood sample.

b. n = Number of subjects with valid and determinate assay results for the specified serotype at the given timepoint.

c. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specifiedblood draws.

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

Pneumococcal OPA antibody GMTs before and approximately 1 month after vaccination, and GMFRs (after/before vaccination) for the evaluable immunogenicity population of pediatric subjects aged 6 to 17 years are presented in Table 2. The OPA antibody GMTs after vaccination were higher than those before vaccination, with a statistically significant increase in GMTs (lower limit of the 2-sided, 95% CI for the GMFRs >1) for all 13 serotypes. GMFRs ranged from 3.3 (serotype 9V) to 53.3 (serotype 23F).

Table 2. Pneumococcal OPA Antibody GMTs and GMFRs - Evaluable Immunogenicity Population - Age Group: 6 to 17 Years

	Sampling Time[a]								
	Before Vaccination			After Vaccination			Fold Rise (After Vaccination/Before Vaccination)		
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	n[b]	GMFR[e]	(95% CI[d])
1	185	10	(9.5, 11.6)	185	170	(140.8, 206.2)	185	16.3	(13.26, 19.92)
3	197	18	(15.3, 22.2)	197	118	(103.7, 134.0)	197	6.4	(5.23, 7.80)
4	175	234	(158.4, 345.5)	175	7616	(6802.8, 8526.0)	175	32.6	(21.59, 49.08)
5	199	19	(16.8, 20.9)	199	287	(233.0, 352.7)	199	15.3	(12.15, 19.26)
6A	169	470	(346.3, 638.5)	169	8980	(7848.7, 10275.0)	169	19.1	(13.77, 26.48)
6B	160	260	(181.4, 373.0)	160	6466	(5679.9, 7360.2)	160	24.9	(17.19, 35.94)
7F	160	742	(585.8, 940.5)	160	5246	(4723.5, 5826.6)	160	7.1	(5.52, 9.05)
9V	180	2140	(1737.6, 2636.8)	180	7058	(6211.3, 8020.9)	180	3.3	(2.65, 4.10)
14	179	1366	(1072.0, 1740.6)	179	7471	(6524.1, 8555.6)	179	5.5	(4.16, 7.19)
18C	153	211	(135.6, 328.8)	153	8765	(7722.2, 9948.0)	153	41.5	(26.82, 64.25)
19A	192	63	(48.2, 82.2)	192	1965	(1688.2, 2287.3)	192	31.2	(23.38, 41.74)
19F	194	265	(201.9, 348.5)	194	3536	(3077.4, 4062.9)	194	13.3	(9.87, 17.99)
23F	183	83	(57.6, 120.4)	183	4434	(3937.3, 4993.6)	183	53.3	(36.17, 78.40)

a. SAP-specified timing for blood sample.

b. n = Number of subjects with valid and determinate assay results for the specified serotype both before and after vaccination blood draws.

c. Geometric mean titers (GMTs) were calculated using all subjects with available data for both the specified blood draws.

d. Confidence intervals (CIs) are back transformations of a CI based on the Student t distribution for the mean logarithm of the titers, or the mean fold rise.

e. Geometric mean fold rises (GMFRs) were calculated using all subjects with available data from both before and after vaccination blood draws.

OPA Titer ≥LLOQ

The proportion of subjects aged 6 to 17 years in the evaluable immunogenicity population with OPA titers ≥LLOQ before vaccination ranged from 6.7% (serotype 1) to 91.2% (serotype 14).

The proportion of pediatric subjects aged 6 to 17 years in the evaluable immunogenicity population achieving an OPA titer ≥LLOQ 1 month after vaccination is presented in Table 3. The proportion of

subjects achieving OPA titers ☐ LLOQ approximately 1 month after vaccination was ≥91.0% for all 13 serotypes.

Table 3. Subjects Achieving an OPA Titer ≥ LLOQ After Vaccination - Evaluable Immunogenicity Population - Age Group: 6 to 17 Years

Serotype	N[a]	n[b]	%	(95% CI[c])
1	191	177	92.7	(88.0, 95.9)
3	200	199	99.5	(97.2, 100.0)
4	199	199	100.0	(98.2, 100.0)
5	200	182	91.0	(86.1, 94.6)
6A	199	199	100.0	(98.2, 100.0)
6B	195	195	100.0	(98.1, 100.0)
7F	199	199	100.0	(98.2, 100.0)
9V	197	197	100.0	(98.1, 100.0)
14	197	197	100.0	(98.1, 100.0)
18C	198	198	100.0	(98.2, 100.0)
19A	197	195	99.0	(96.4, 99.9)
19F	200	198	99.0	(96.4, 99.9)
23F	199	199	100.0	(98.2, 100.0)

Abbreviations: LLOQ = lower limit of quantitation; OPA = opsonophagocytic activity.

a. N = number of subjects with a determinate antibody titer to the given serotype.

b. n = Number of subjects with an antibody titer ≥ LLOQ for the given serotype.

c. Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.

Safety results

In this population of 200 pediatric subjects aged 6 to 17 years, no subject had an abnormal physical examination or any relevant medical history before vaccine administration. In this study, there were no AEs, SAEs, or deaths reported; there were no other significant AEs reported and no subject was withdrawn from the study due to an AE.

The MAH is requested to comment on the lack of AEs and to provide AE frequency in similar age populations in other trials with similar inclusion/exclusion criteria. The AE definition is consistent with ICH-GCPs. However, the definition and study procedures may not have been applied as it should. The MAH is requested to indicate how compliance with ICH-GCPs was ensured during the study.

2.3.3. Discussion on clinical aspects

The immune responses in terms of OPA titres were significantly higher after vaccination compared to before vaccination. The results do not cause concern regarding immunogenicity. The safety results indicate that safety follow-up practices differ from previously conducted studies, as no adverse events were reported at all, which is unexpected, and raise concern regarding the conduct of the study.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

This procedure is considered fulfilled, A question was raised regarding the safety follow up in the study. The response is assessed below, and the procedure is now considered fulfilled.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

1. The MAH is requested to comment on the lack of AEs and to provide AE frequency in similar age populations in other trials with similar inclusion/exclusion criteria. The AE definition is consistent with ICH-GCPs. However, the definition and study procedures may not have been applied as it should. The MAH is requested to indicate how compliance with ICH-GCPs was ensured during the study.

Assessment of Responses to requested clarifications

1. The MAH is requested to comment on the lack of AEs and to provide AE frequency in similar age populations in other trials with similar inclusion/exclusion criteria. The AE definition is consistent with ICH-GCPs. However, the definition and study procedures may not have been applied as it should. The MAH is requested to indicate how compliance with ICH-GCPs was ensured during the study.

Response

In Study B1851140, the safety of 13-valent pneumococcal conjugate vaccine (13vPnC) was assessed in 200 healthy subjects 6 to 17 years of age in India. Subjects received one dose of 13vPnC (Visit 1) and were followed up for adverse events (AEs) and serious adverse events (SAEs) for approximately one month (until Visit 2). As detailed in the clinical study report (CSR), no AEs were reported in the 6 to 17 year-old cohort. There were no deaths or SAEs reported in this cohort; and no subject in this cohort was withdrawn from the study due to an AE.

Adverse events and serious adverse events were clearly defined in the protocol (Protocol Section 8, Adverse Event Reporting). In accordance with EU Clinical Trial Directive EU ENTR/CT3 (June 2011) and US FDA IND Final Rule (September 2011), an AE was defined in the protocol in Section 8.3 as "any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage." Examples of AEs, as defined in the protocol, included but were not limited to clinically significant symptoms and signs; changes in physical examination findings; and abnormal test findings. An SAE was defined as an untoward medical occurrence that was fatal or life-threatening, resulted in persistent or significant disability/incapacity, or required hospitalization. Other important medical events could be reported as SAEs according to the judgment of the investigator.

The protocol safety endpoint was "Incidence of AEs collected by the investigator after clinical evaluation and in response to nonspecific questions on the subject's health." Safety reporting requirements to meet this endpoint were clearly defined in the protocol. Medical history was collected and a physical examination was performed by the investigator on all subjects at Visit 1 to establish a baseline (Protocol Section: 7.5. Safety Parameters). Subjects were to be observed for at least 20 minutes after 13vPnC administration for any acute reaction and any observations were to be documented as AEs on the case report form (Protocol Section: 6.1, Visit 1). Visit 2 follow-up was conducted 28 to 42 days after vaccination. At this visit, each subject or parent/legal guardian was questioned about AEs in a nonspecific manner, and the investigators were to collect and record information on all AEs and SAEs occurring since vaccination, regardless of their suspected causal relationship to the investigational product. These were to include all AEs directly observed by the investigators and all AEs spontaneously reported by the subject or parent/legal guardian.

Study B1851140 was conducted according to the Good Clinical Practice (GCP) Guideline of the International Conference on Harmonisation (ICH). The investigator training for this study included an investigators' meeting and site initiation visits, with specific training on AE reporting that utilized standard approaches that have been used for all 13vPnC studies globally. During the study, due diligence was conducted by the site monitors to confirm the investigators' understanding of the protocol and AE reporting requirements. From the outset, site monitors were actively engaged in routine clinical research monitoring activities. Review of CRFs early on during site monitoring activities revealed no AE CRF pages were being completed; such was highlighted by the site monitors to the

participating investigators and respective site coordinators to assure elicitation of AEs was being performed as stated in the B1851140 protocol. The participating investigators responded that elicitation of AEs was occurring per protocol. Re-training emphasizing AE reporting was performed. During the conduct of the study, the study team noted that no AEs were being documented among subjects in the pediatric cohort and took a number of actions to ensure full reporting of any AEs. Site monitors performed 100% source data verification. Their monitoring confirmed that there were no AEs documented in the source notes that were not reported in the case report forms. Above and beyond these routine clinical research monitoring activities, the Pfizer Compliance Officer in India contacted the investigators by telephone to confirm their understanding of AE reporting requirements. Some of the points of discussion from the telephone conversations with the investigators which helped to clarify the absence of AEs included comments by investigators that healthy subjects with no pre-existing diseases were being enrolled, and therefore, the lack of any AEs during the short duration of the study (approximately 1 month for each subject) was not unexpected. From these conversations, the Pfizer Compliance Officer was reassured that the subjects' parents/guardians were adequately counselled and questioned by the investigators about AEs.

Study B1851140 also enrolled 1000 adult subjects 50 to 65 years of age; 999 of these subjects received 1 dose of 13vPnC at Visit 1. Although the 12 sites that enrolled adult subjects were different from the 3 sites that enrolled pediatric subjects, the protocol, and the methods and procedures used to collect safety data, were the same for both of the cohorts and investigators received the same training at investigator meetings and site visits. Using the same methods and procedures, while no AEs were reported for subjects in the pediatric cohort, AEs were reported for 7.0% of subjects in the adult cohort.

The assessor has requested that the MAH provide AE frequency data for similar age populations in other trials that had similar inclusion/exclusion criteria. Study 6096A1-3011, conducted in the United States, evaluated the immunogenicity and safety of 13vPnC administered to children and adolescents in 4 different age groups. Data are presented here for 294 subjects aged ≥5 years to <10 years who had previously received at least 1 dose of 7-valent pneumococcal conjugate vaccine (Group 3) and 298 adolescents aged ≥10 years to <18 years who had not previously been vaccinated with any pneumococcal vaccine (Group 4). Subjects in these age groups were administered a single dose of 13vPnC at study entry. Information regarding AEs was to be collected by the investigator from the signing of the informed consent form (ICF) through the visit that was to take place approximately 1 month (28 to 42 days) after vaccination. Complete details of the study methods are described in the clinical study report for Study 6096A1-3011, Group 3 and Group 4 (eCTD module 5.3.5.1), submitted on 30 March 2012 (EMEA/H/C/001104/II/0055) and approved on 17 November 2012.

The method for collection of AE data in Study 6096A1-3011 was similar to that used in Study B1851140, with one important exception. In Study 6096A1-3011, subjects/parents were to assess and record electronic diary (e-diary) symptoms each day for 7 days after vaccination.

In the majority of studies in the 13vPnC program, subjects (or the subjects' parents) were required to enter information into an e-diary daily in response to prompts asking about the occurrence of local reactions at the study vaccine injection site (tenderness, swelling, and redness) as well as systemic events (fever, decreased appetite, irritability, increased sleep, decreased sleep) occurring within a specified number of days after vaccination. By requiring such careful, daily attention to these symptoms, the use of an e-diary could potentially have influenced the way in which subjects/parents paid attention to other symptoms that might have manifested during the first month after vaccination, increasing their vigilance and awareness as to the occurrence of signs and symptoms that might otherwise have gone unnoticed. Similarly, the detailed recording of this information might also have

influenced subjects/parents to report other minor symptoms that they otherwise would have considered too insignificant to mention to the investigator.

At the time the protocol for Study B1851140 was developed and approved for conduct in India, local reactions and systemic events had been collected in all previous pediatric studies using these e-diary collection methods, and the reactogenicity profile of 13vPnC was well-established and satisfactory for all age groups. Differences in the reactogenicity profile were not expected in this pediatric population in India. Therefore, when the protocol for Study B1851140 was submitted to the Health Authority in India, it did not incorporate the use of e-diaries to collect information on local reactions and systemic events and differs in this respect from other studies.

AEs reported within approximately 1 month after vaccination in Study 6096A1-3011 are summarized by MedDRA system organ class (SOC) and preferred term for subjects in Group 3 and Group 4 in Table 4 and Table 5, respectively. The types of AEs reported were largely the types of signs and symptoms that occur frequently in children and adolescents in these age groups. In subjects ≥5 years to <10 years of age, the most frequently reported types of AEs were infections (SOC Infections and Infestations, 10.2% of subjects); Respiratory, Thoracic and Mediastinal Disorders (SOC = 4.8%) including cough (3.4%) and nasal congestion (1%); Gastrointestinal Disorders (SOC = 3.7%), including vomiting (2.7%) and diarrhoea (1.0%); and other common symptoms such as pyrexia (2.4%) and headache (1.0%). Similar conditions were reported in this study for adolescents ≥10 years to <18 years of age: Infections and Infestations (10.4%); Respiratory, Thoracic and Mediastinal Disorders (SOC = 3.7%) including cough and oropharyngeal pain (1.7% each); and Gastrointestinal Disorders (SOC = 3.7%), including vomiting (1.3%) and nausea (1.0%); and other common symptoms such as headache (3.4%) and pyrexia (1.0%).

AEs that were considered related to study vaccine by the investigator were reported for 3 subjects (1.0%) in each age group. The related AE of headache was reported for 2 subjects in Group 3 and 2 subjects in Group 4, and the related AE of nausea was reported for 1 subject in each age group. All other related AEs were reported by 1 subject each (Table 6).

Severe AEs were reported for 2 subjects in Group 3 (appendicitis and eye injury), while no severe AEs were reported for subjects in Group 4. No subjects were withdrawn from the study because of AEs. One SAE was reported for a subject in Group 3; this was the case of appendicitis, which was reported on Day 1 and resolved after 2 days; this SAE was considered not related to study vaccine by the investigator. No SAEs were reported for subjects in Group 4.

Table 4. Adverse Events Reported Within 1 Month After Vaccination – Study 6096A1-3011, Group 3 (Subjects ≥5 Years to <10 Years of Age)

	13vPnC N = 294		
System Organ Class\ Preferred Term	Number of Subjects[a]	%	Number of Events[b]
Any Event	57	19.4	94
Ear and Labyrinth Disorders	1	0.3	1
Ear pain	1	0.3	1
Eye Disorders	2	0.7	2
Conjunctivitis	2	0.7	2
Gastrointestinal Disorders	11	3.7	15
Abdominal pain	1	0.3	1
Abdominal pain upper	1	0.3	1
Diarrhoea	3	1.0	3
Nausea	1	0.3	1
Vomiting	8	2.7	9
General Disorders and Administration Site Conditions	7	2.4	7
Pyrexia	7	2.4	7
Immune System Disorders	1	0.3	1
Seasonal allergy	1	0.3	1
Infections and Infestations	30	10.2	32
Acarodermatitis	1	0.3	1
Appendicitis	1	0.3	1
Dermatophytosis	1	0.3	1
Gastroenteritis viral	2	0.7	2
Influenza	3	1.0	3
Nasopharyngitis	3	1.0	3
Otitis media	3	1.0	3
Pharyngitis	2	0.7	2
Pharyngitis streptococcal	6	2.0	6
Sinusitis	3	1.0	3
Upper respiratory tract infection	2	0.7	2
Viral infection	3	1.0	3
Viral pharyngitis	1	0.3	1
Viral upper respiratory tract infection	1	0.3	1
Injury, Poisoning and Procedural Complications	5	1.7	5
Contusion	1	0.3	1
Eye injury	1	0.3	1
Hand fracture	1	0.3	1
Head injury	1	0.3	1
Periorbital haematoma	1	0.3	1
Musculoskeletal and Connective Tissue Disorders	3	1.0	3
Back pain	1	0.3	1
Neck pain	1	0.3	1
Torticollis	1	0.3	1
Nervous System Disorders	5	1.7	5
Headache	3	1.0	3

Table 4. Adverse Events Reported Within 1 Month After Vaccination – Study 6096A1-3011, Group 3 (Subjects ≥5 Years to <10 Years of Age)

	13vPnC N = 294		
System Organ Class\ Preferred Term	**Number of Subjects[a]**	**%**	**Number of Events[b]**
Presyncope	1	0.3	1
Syncope	1	0.3	1
Renal and Urinary Disorders	2	0.7	2
Dysuria	1	0.3	1
Haematuria	1	0.3	1
Respiratory, Thoracic and Mediastinal Disorders	14	4.8	20
Asthma	1	0.3	2
Cough	10	3.4	10
Epistaxis	1	0.3	2
Nasal congestion	3	1.0	3
Rhinorrhoea	1	0.3	1
Sneezing	1	0.3	1
Wheezing	1	0.3	1
Skin and Subcutaneous Tissue Disorders	1	0.3	1
Eczema	1	0.3	1

a. Number of subjects reporting at least 1 event.
b. The total number of events. Multiple events may be reported by 1 subject.
Program ID: Study 6096A1-3011/CP SAF_AE_GLOBAL.SAS. Runtime ID: 09DEC2011 17:08
Source: CSR for Study 6096A1-3011, Group 3 and Group 4; Table 10-11.

Table 5. Adverse Events Reported Within 1 Month After Vaccination – Study 6096A1-3011, Group 4 (Subjects ≥10 Years to <18 Years of Age)

	13vPnC N = 298		
System Organ Class\ Preferred Term	**Nubmer of Subjects[a]**		**Number of Events[b]**
Any Event	72	24.2	107
Ear and Labyrinth Disorders	1	0.3	1
Eustachian tube dysfunction	1	0.3	1
Gastrointestinal Disorders	11	3.7	13
Abdominal pain	1	0.3	1
Abdominal pain upper	1	0.3	1
Constipation	1	0.3	1
Diarrhoea	1	0.3	1
Nausea	3	1.0	3
Toothache	1	0.3	1
Uvulitis	1	0.3	1
Vomiting	4	1.3	4
General Disorders and Administration Site Conditions	9	3.0	10
Chills	2	0.7	2
Influenza like illness	1	0.3	1
Injection site pain	1	0.3	1
Injection site pruritus	1	0.3	1
Pain	2	0.7	2
Pyrexia	3	1.0	3
Infections and Infestations	31	10.4	35
Acute sinusitis	1	0.3	1
Bronchitis	1	0.3	1
Furuncle	1	0.3	1
Gastroenteritis	1	0.3	1
Influenza	5	1.7	5
Nasopharyngitis	3	1.0	3
Otitis externa	2	0.7	2
Otitis media	2	0.7	2
Otitis media acute	1	0.3	1
Pharyngitis	5	1.7	5
Sinusitis	5	1.7	5
Subcutaneous abscess	1	0.3	1
Upper respiratory tract infection	3	1.0	3
Viral infection	4	1.3	4
Injury, Poisoning and Procedural Complications	9	3.0	9
Arthropod bite	1	0.3	1
Foot fracture	1	0.3	1
Hand fracture	2	0.7	2
Head injury	1	0.3	1
Limb injury	1	0.3	1
Muscle strain	1	0.3	1
Procedural pain	1	0.3	1
Wrist fracture	1	0.3	1
Investigations	1	0.3	1
Heart rate decreased	1	0.3	1

Table 5. Adverse Events Reported Within 1 Month After Vaccination – Study 6096A1-3011, Group 4 (Subjects ≥10 Years to <18 Years of Age)

	13vPnC N = 298		
System Organ Class\ Preferred Term	**Nubmer of Subjects[a]**		**Number of Events[b]**
Musculoskeletal and Connective Tissue Disorders	3	1.0	3
Back pain	2	0.7	2
Musculoskeletal chest pain	1	0.3	1
Nervous System Disorders	14	4.7	16
Dizziness	2	0.7	2
Headache	10	3.4	11
Migraine	1	0.3	1
Somnolence	1	0.3	1
Syncope	1	0.3	1
Psychiatric Disorders	2	0.7	2
Anxiety	1	0.3	1
Depression	1	0.3	1
Respiratory, Thoracic and Mediastinal Disorders	11	3.7	13
Asthma	2	0.7	2
Cough	5	1.7	5
Nasal congestion	1	0.3	1
Oropharyngeal pain	5	1.7	5
Skin and Subcutaneous Tissue Disorders	4	1.3	4
Acanthosis nigricans	1	0.3	1
Acne	2	0.7	2
Rash	1	0.3	1

a. Number of subjects reporting at least 1 event.
b. The total number of events. Multiple events may be reported by 1 subject.
Program ID: Study 6096A1-3011/CP SAF_AE_GLOBAL.SAS. Runtime ID: 09DEC2011 17:08
Source: CSR for Study 6096A1-3011, Group 3 and Group 4; Table 10-12.

Table 6. Listing of Related Adverse Events Reported Within 1 Month After Vaccination – Study 6096A1-3011

Site	Subject	Adverse Event (Preferred Term)	Days Since Last Dose	Duration (days)	Severity	Action
Group 3 (Subjects ≥5 Years to <10 Years of Age)						
023	001464	Headache	6	1	Mild	N
029	001857	Headache	2	1	Moderate	C
		Vomiting	2	1	Moderate	N
034	002181	Diarrhoea	5	2	Mild	N
		Nausea	5	2	Mild	N
		Pyrexia	21	3	Mild	C
Group 4 (Subjects ≥10 Years to <18 Years of Age)						
013	000802	Headache	1	1	Mild	U
		Nausea	1	1	Mild	U
023	001476	Back pain	2	2	Mild	N
		Dizziness	1	2	Mild	N
		Headache	1	2	Mild	C
		Injection site pain	1	2	Mild	N
025	001585	Injection site pruritus	4	1	Mild	N

Abbreviations: C=concomitant medication; N=none; U= unscheduled clinic visit/no tests or procedures.
Source: CSR for Study 6096A1-3011; 16.2.7, AE Listings; Listing of Related AEs (modified).
Program ID: Study 6096A1-3011/CP CDL_AE.SAS. Runtime ID: 10DEC2011 03:05

In conclusion, the methods used for collection of information regarding AEs occurring within 1 month after vaccination in Study B1851140 were very similar to methods used in both pediatric and adult studies in the 13vPnC program, globally. Investigator training was conducted both at the study investigator meetings and at site initiation visits using standard global approaches, and during the study, site monitors held conversations with investigators and site coordinators to confirm that elicitation of AEs was being performed as stated in the B1851140 protocol. Although the lack of AEs among subjects in the pediatric cohort was concerning to the study team, site monitoring and investigator interactions confirmed that the investigators were aware of the reporting requirements, but had no AEs to report.

Assessment: The study has been adequately monitored which resulted in several activities. It appears that the sponsor has actively investigated the lack of AE reports in the study by contacting study investigators, but it is not clear if the safety/reactogencity during the study has been adequately recorded and reported. Thus, the lack of AEs does not seem to be due to investigator lack of training or compliance to the protocol, but this cannot be entirely excluded. The MAH claims that the same methods for collecting safety that was applied in the adult part of the study, was also applied in the adolescent part. However, then we would expect at least some AE reporting. The lack of AEs reporting could be due to investigator lack of training or reminder because some of the investigators that were contacted by the MAH indicated that they did not expect AE to occur, despite very common AE (frequency ≥1/10) being described in the SmPC in the adolescent population.

In the comparison to the paediatric studies in the clinical development program the main difference in reporting was that e-diaries were used in previous studies, while e-diaries were not used in the current study. The MAH correctly pointed out that at the time of Study B1851140, the reactogenicity profile of 13vPnC was well-established and satisfactory for all age groups. It is considered legitimate that the

MAH did not find it necessary to incorporate the use of e-diaries in this study because differences in the reactogenicity profile were not expected in this pediatric population in India.

The lack of e-diaries in this study is considered a probable but partial explanation for the lack of AEs in the study. Indeed, not using e-dairies is not a reliable explanation for the total absence of AE in this study, which is not consistent with safety data obtained in US studies or reported in the SmPC. Differences in the AE frequency across studies are very large (around 20% in US studies vs. 0% in Indian studies and reactogenicity recorded through the diary represents only part of it). Protocol compliance issue (underreporting of AE) therefore remains a likely explanation for the findings.

The previously reported data have already been assessed.

It can be concluded that the reporting rate in this study is lower than expected, which is probably at least partly due to the method of collecting data, i.e. not using e-diaries.

Adverse events as defined in the protocol (including but not limited to clinically significant symptoms and signs) which were to be reported over a very short period of one month, may have been underreported in this study in India compared with the US population aged 6 to 17 years. The MAH should take actions to make sure that study compliance is ensured for any further study. Although no safety concern is expected due to this lack of compliance, it is considered as unacceptable to underreport AE as the overall validity of the data should be preserved (see ICH HARMONISED TRIPARTITE GUIDELINE; THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE EFFICACY – M4E(R1)). If non-compliance issues are suspected again this could trigger a GCP inspection.'