EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2015
EMA/124579/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Prevenar

(Suspension for injection, Pneumococcal saccharide conjugated vaccine, adsorbed)

Procedure No. EMEA/H/C/000323

P46 130

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

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I. Executive Summary

No SmPC and PL changes are proposed.

II. Recommendation [1]

The data from this study do not warrant any changes to the SmPC or PIL.

III. Introduction

On 6 February 2012, the MAH submitted a completed paediatric study for Prevenar, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

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

IV. Scientific Discussion

Information on the pharmaceutical formulation used in the study
In Europe, Prevenar (PCV7) is indicated for children aged 2 months to 5 year. Available commercial supply of PCV7 (routine use) was used in this study.

Clinical aspects

1. Introduction

The MAH submitted a final report for:

- B1841001 (0887X1-4596-RU) Prevenar POST-licensure Safety Study in Russia: Frequency of Fever Post Vaccination

2. Clinical study

- **Description**

Pfizer's 7-valent pneumococcal conjugate vaccine (PCV7, Prevenar®), indicated for the prevention of invasive disease caused by *Streptococcus pneumoniae*, was granted a license by the Russian Ministry of Health and Social Development (Roszdravnadzor) on 29 January 2009. As part of a postlicensure commitment requested by the Regulatory Authorities of the Russian Federation, Pfizer conducted a prospective, observational, non-interventional study of Prevenar in the context of the routine immunization schedules of the Russian Federation (Protocol 0887X1-4596-RU). The study has now been completed, and final data are available. The purpose of this Clinical Overview is to summarize the results of Study 0887X1-4596-RU.

- **Methods**

- Objective(s)

Primary
The primary objective of the study was to estimate the incidence of febrile reactions of ≥38°C to ≤39°C; >39°C to ≤40°C; >40°C occurring within 2 days following vaccination with Prevenar (PCV7) co-administered with other routine childhood vaccines under the conditions of routine daily use in the Russian Federation within the licensed indication.

Secondary
The secondary objective was to observe the frequency and severity of other local and/or systemic events and undesirable events and undesirable effects for two days after routine vaccination with PCV7.

[1] *The recommendation from section V can be copied in this section*

a) Local reaction: Redness or induration ≥2cm in diameter, swelling including extent of swelling, transient tenderness and tenderness that interfered with limb movement.
b) Systemic event: to monitor the rate of other systemic events such as restless sleep, decreased appetite, unusual irritability/fussiness/crying, vomiting, diarrhoea, drowsiness, other.

- Study design

This was a prospective, observational, non-interventional, non-randomized study of the safety of Prevenar (PCV7) in children from 3 months up to 23 months of age. See Figure 1 for a schematic view of the current study. Subjects received Prevenar vaccinations as standard care. Available commercial supply of PCV7 (routine use) was used for this study and the schedule within the prescribing information was followed.
Subjects participated in the study for up to 1.5 years (maximum 18 months) duration to allow for 30 days follow up after the last dose.

- Study population /Sample size

One hundred (100) children were to be enrolled at four sites with 50 infants starting the primary series (3-11 months old) and another 50 infants/children receiving 'catch-up doses' starting at 12 months (12-23 months old).

- Treatments

As this was an observational study, no specific interventional procedures were performed at visits, but information was collected. Visits were not protocol driven and corresponded with proposed PCV7 vaccination schedule.

Figure 1: Study Flow Chart

Visit[a]	1	2[b]	3	4[b]	5	6[b]	7	8[b]	Follow-up[b]
Child's age at enrollment	All ages				3-6 months & 7-11 months		7-11 months & 12-23 months		All ages
Study Procedures	Dose 1	Dose 1 + 2 days	Dose 2	Dose 2 +2 days	Dose 3	Dose 3 + 2 days	Dose 4	Dose 4 + 2 days	Last dose[c] + 30 days
Informed consent [d]	X								
Demographics	X								
Medical history	X								
Vaccination History	X	X	X	X	X	X	X	X	
Post vaccination observation to assess acute reactions (at least 30 minutes)[e]	X		X		X		X		
Diary Card Presented	X		X		X		X		
Diary Card Retrieved			X	X (12-23 months)	X	X (7-11 months)	X	X (3-6 months)	
Concomitant medications	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X

a. Visits were not protocol driven and corresponded with proposed PCV7 vaccination schedule
b. Visits 2, 4, 6, 8 and follow -up could be performed by telephone.
c. Last dose is dose 4 for children aged 3-6 months, dose 3 for children aged 7-11 months, dose 2 for children aged 12-23 months
d. Informed consent to be signed prior to protocol-required data being recorded
e. Observations to include oral temperature, local reaction and systemic events
Dose 1 above refer to Prevenar.

- Outcomes/endpoints

The primary endpoint for this study was the incidence of febrile reactions of ≥38°C to ≤39°C; >39°C to ≤40°C; >40°C occurring within 2 days following vaccination with Prevenar.
The secondary endpoints were the frequency of other local reactions (redness, swelling, tenderness) and systemic events (restless sleep, decreased appetite, unusual irritability/fussiness/crying, vomiting, diarrhoea) occurring within the 2-day post vaccination period.

- Statistical Methods

The analysis was descriptive with no hypothesis testing.
Data tabulations: For quantitative data, number of subjects (n), mean and standard deviation (SD), median, minimum, maximum, and number of missing data are presented. For qualitative data, number

of subjects (n), frequency and percentage on available data, and number of missing data are presented.
Within cohorts, 2-sided 95% confidence limits were provided for rates of febrile reactions. These confidence intervals (CIs) were based on the one-sample Wilson Score method without continuity correction.

- **Results**

- Recruitment/ Number analysed

One hundred (100) children were to be enrolled at four sites with 50 infants starting the primary series (3-11 months old) and another 50 infants/children receiving 'catch-up doses' starting at 12 months (12-23 months old). The number of subjects vaccinated with PCV7 at each dose is shown in Table 4 below.

Table 4. Number (%) of Subjects Vaccinated with PCV7 at Each Dose

	Primary [3-6 months] (N=14)	Catch-up [7-11 months] (N=31)	Catch-up [12-23 months] (N=55)
Dose 1	14 (100%)	31 (100%)	55 (100%)
Dose 2	13 (92.9%)	29 (93.5%)	54 (98.2%)
Dose 3	13 (92.9%)	27 (87.1%)	--
Dose 4	7 (50.0%)	--	--

- Efficacy results

Not applicable

- Safety results

Primary objective - Febrile reactions

The primary objective of this study was to estimate the incidence of febrile reactions (defined as temperatures ≥38°C) occurring within 2 days after vaccination with PCV7 co-administered with other routine childhood vaccines. For each dose, the timeframe of interest comprised a total of 3 days, i.e., Day 1 through Day 3, with Day 1 being the day of vaccine administration (Table 7). All reports of fever were for temperatures of ≥38°C to ≤39°C, except for 3 reports of fever >39°C to ≤40°C after dose 1 in the catch-up cohorts (Table 7). All of the subjects with fever >39°C to ≤40°C received concomitant vaccinations after dose 1. The highest incidence of any fever ≥38°C was observed after dose 2 for the primary cohort (3 subjects, 23.1%), after dose 1 for the 7-11 month catch-up cohort (6 subjects, 19.4%), and after dose 1 for the 12-23 month catch-up cohort (3 subjects, 5.5%). No clear influence of concomitant vaccinations on the incidence of febrile reactions was detected in this study; however, the numbers of subjects receiving concomitant vaccinations in each cohort were generally too low to draw conclusions.

Table 7. Febrile Reactions Occurring From Day 1 Through Day 3

		Primary [3-6 months] (N=14)	Catch-up [7-11 months] (N=31)	Catch-up [12-23 months] (N=55)
Dose 1	Any Fever ≥38°C	2 (14.3%)	6 (19.4%)	3 (5.5%)
	≥38°C to ≤39°C	2 (14.3%)	5 (16.1%)	1 (1.8%)
	>39°C to ≤40°C	-	1 (3.2%)	2 (3.6%)
		(N=14)	**(N=29)**	**(N=54)**
Dose 2	Any Fever ≥38°C	3 (23.1%)	3 (10.3%)	0
	≥38°C to ≤39°C	3 (23.1%)	3 (10.3%)	0
		(N=13)	**(N=26)**	
Dose 3	Any Fever ≥38°C	2 (15.4%)	0	
	≥38°C to ≤39°C	2 (15.4%)	0	
		(N=7)		
Dose 4	Any Fever ≥38°C	0 (0.0)		

Secondary objective

The secondary objective of this study was to observe the frequency and severity of local reactions, systemic events, and undesirable effects (i.e., adverse events) occurring within 2 days after routine vaccination with PCV7. Information regarding these events was also collected and summarized for the period through 7 days after vaccination (i.e., Days 1 to 8). Local reactions and systemic events reported for Days 1 to 3 and for Days 1 to 8 are summarized for all cohorts and all doses in Table 8.

Table 8. Local Reactions and Systemic Events Reported After Each Dose – Number (%) of Subjects

	Primary [3-6 months]	Catch-up [7-11 months]	Catch-up [12-23 months]
Dose 1	**(N=14)**	**(N=31)**	**(N=55)**
Day 1 to Day 3			
Fever	2 (14.3%)	6 (19.4%)	3 (5.5%)
Local reactions	2 (14.3%)	13 (41.9%)	21 (38.2%)
Solicited systemic events (including fever)	6 (42.9%)	17 (54.8%)	27 (49.1%)
Day 1 to Day 8			
Local reactions	2 (14.3%)	13 (41.9%)	21 (38.2%)
Solicited systemic events	6 (42.9%)	18 (58.1%)	29 (52.7%)
Dose 2	**(N=13)**	**(N=29)**	**(N=54)**
Day 1 to Day 3			
Fever	3 (23.1%)	3 (10.3%)	0 (0.0)
Local reactions	3 (23.1%)	5 (17.2%)	16 (29.6%)
Solicited systemic events (including fever)	6 (46.2%)	8 (27.6%)	12 (22.2%)
Day 1 to Day 8			
Local reactions	3 (23.1%)	5 (17.2%)	16 (29.6%)
Solicited systemic events	6 (46.2%)	8 (27.6%)	13 (24.1%)
Dose 3	**(N=13)**	**(N=26)**	
Day 1 to Day 3			
Fever	2 (15.4%)	0 (0.0)	
Local reactions	3 (23.1%)	3 (11.5%)	
Solicited systemic events (including fever)	6 (46.2%)	5 (19.2%)	
Day 1 to Day 8			
Local reactions	3 (23.1%)	3 (11.5%)	
Solicited systemic events	6 (46.2%)	5 (19.2%)	
Dose 4	**(N=7)**		
Day 1 to Day 3			
Fever	0 (0.0)		
Local reactions	1 (14.3%)		
Solicited systemic events	2 (28.6%)		
Day 1 to Day 8			
Local reactions	1 (14.3%)		
Solicited systemic events	2 (28.6%)		

Note: Local reactions include both solicited and unsolicited local reactions.

Local Reactions – All local reactions occurred between Day 1 and Day 3, and therefore the frequencies of local reactions reported between Day 1 and Day 8 are the same as the frequencies reported between Day 1 and Day 3. In the primary cohort (3-6 months), local reactions were reported for 2 to 3 subjects (14.3% to 23.1%) after each dose. In the catch-up 7-11 month cohort, the frequency of local reactions decreased with each dose (41.9%, 17.2%, and 11.5% for dose 1, dose 2, and dose 3, respectively). In the catch-up 12-23 month cohort, local reactions were reported for 38.2% and 29.6% of subjects after dose 1 and dose 2, respectively. Most local reactions were of mild or moderate intensity (<2.5 cm or [2.5 to <5 cm], respectively, for measurable reactions). Severe reactions (≥5 cm for measurable reactions) were reported in the catch-up 12-23 month cohort only: after dose 1, severe redness was reported for 3 subjects, while severe swelling, tenderness, and haematoma were reported for 1 subject each; after dose 2, severe swelling and severe induration were reported for 1 subject each.

Systemic Events – In the primary cohort, solicited systemic events were reported for 42.9% to 46.2% of subjects after each dose in the primary series and for 28.6% of subjects after the toddler dose. In the catch-up 7-11 month cohort, the frequency of systemic events decreased across the doses (54.8%, 27.6%, and 19.2% for dose 1, dose 2, and dose 3, respectively). In the catch-up 12-23 month cohort, systemic events were reported for 49.1% and 22.2% of subjects after dose 1 and dose 2, respectively. In the primary cohort, the most frequently reported types of systemic events were unusual irritability, unusual crying, and restless sleep, all of which were reported for between 7.1% and 28.6% of subjects after each dose, except after dose 3, when restless sleep was reported for 46.2% of subjects. In each of the follow-up cohorts, the most frequently reported types of systemic events after each dose were restless sleep and unusual crying, each reported for between 11.5% and 32.3% of subjects after each dose. Most systemic events were reported as mild or moderate. Overall, there were 26 reports of severe systemic events, as summarized in Table 9.

Table 9. Number of Severe Systemic Events Reported During the Study

Systemic Event	Total Number of Reports	Cohort		
		Primary [3-6 months] (N=14)	Catch-up [7-11 months] (N=31)	Catch-up [12-23 months] (N=55)
Unusual crying	10	3	2	5
Restless sleep	8	1	2	5
Unusual irritability	5	2	0	3
Unusual fussiness	3	2	0	1

Adverse Events - Adverse events (AEs) occurring within 7 days after administration of each dose of study vaccine and serious adverse events occurring within 30 days after vaccination were to be reported and recorded on CRFs. In addition, information regarding AEs and serious adverse events occurring throughout the study was to be captured to the extent that this was feasible.
The numbers and percentages of subjects reporting adverse events and adverse events considered related to study vaccine by the investigator are summarized in Table 10 for each dose and each cohort. In the primary cohort, the most frequently reported types of AEs included injection site erythema (3 reports) and atopic dermatitis (3 reports, 2 of which were considered related to study vaccine). In the catch-up cohort 7-11 months, the most frequently reported type of AEs was infections and infestations (7 reports). Related AEs included body temperature increase (2 reports), and crying, atopic dermatitis, and gait disturbance (1 report each). In the catch-up cohort 12-23 months, the most frequently reported types of AEs were infections and infestations (6 reports) and skin and subcutaneous tissue disorders (5 reports). AEs considered related to study vaccine were rash and body temperature increased (1 report each).

Table 10. Other Adverse Events Reported After Each Dose – Number (%) of Subjects

	Primary [3-6 months]	Catch-up [7-11 months]	Catch-up [12-23 months]
Dose 1	**(N=14)**	**(N=31)**	**(N=55)**
All adverse events	2 (14.3%)	7 (22.6%)	6 (10.9%)
Related adverse events	1 (7.1%)	2 (6.5%)	1 (1.8%)
Dose 2	**(N=13)**	**(N=29)**	**(N=54)**
All adverse events	3 (23.1%)	3 (10.3%)	5 (9.3%)
Related adverse events	0 (0.0%)	0 (0.0%)	1 (1.9%)
Dose 3	**(N=13)**	**(N=26)**	
All adverse events	2 (15.4%)	4 (15.4%)	
Related adverse events	1 (7.7%)	2 (7.7%)	
Dose 4	**(N=7)**		
All adverse events	0 (0.0%)		
Related adverse events	0 (0.0%)		

Two serious adverse events were reported during the study, neither of which was considered to be related to study vaccine. One subject in the catch-up 7-11 month cohort was hospitalized with an upper respiratory tract infection 4 days after dose 1. The infection resolved in 5 days. One subject in the catch-up 12-23 month cohort was hospitalized with acute sinusitis 7 days after dose 1. The subject recovered within 2 weeks. No subjects died during the study and no adverse events resulted in withdrawal from the study.

3. Discussion on clinical aspects

The safety data from Study 0887X1-4596-RU are consistent with the known safety profile of Prevenar (PCV7). The study did not highlight any new safety concern for vaccination with Prevenar co-administered with other routine childhood vaccines.

V. Rapporteur's Overall Conclusion and recommendation

- **Overall conclusion**

The current study did not highlight any new safety concerns regarding the vaccination with Prevenar (PCV7) concomitantly with other routine childhood vaccinations in the subjects under study. However, the total number of subjects involved in this study is by far too small to draw a valid conclusion about the vaccine's safety profile among Russian infants and toddlers.

- **Recommendation**

The data from this study do not warrant any changes to the SmPC or PIL.
No further action required.

VI. Request for supplementary information

None