EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/125685/2015
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 13

(Pneumococcal saccharide conjugated vaccine, adsorbed)

Procedure No. EMEA/H/C/001104

P46 017.1

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

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I. INTRODUCTION

On 28 October 2011, the Marketing Authorisation Holder (MAH) submitted the following completed paediatric trial for Prevenar 13 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use: Wyeth Study 6096A1-3010-US (Pfizer Study B1851009) entitled, "A Phase 3, Open-Label, Single-Arm Trial Evaluating the Safety, Immunogenicity, and Impact of 13-valent Pneumococcal Conjugate Vaccine in Alaskan Native Children." The study was also a Post Marketing Commitment (FUM 017).

On 19 January 2012, the CHMP adopted the following conclusions:

Study 6096A1-3010 was undertaken with the primary objective to assess the impact of 13vPnC on the incidence of invasive pneumococcal disease (IPD) in the Yukon Kuskokwinm delta region due to the 13 vaccine S pneumoniae serotypes. Furthermore, it was included in the Risk Management Plan (RMP) to address the "missing information" safety concern of "safety of more than 4 doses of CRM-based pneumococcal vaccine."

A significant failure of the study was that enrolment was limited to only 373 subjects, 182 of which completed all of the planned vaccinations within the protocol…. No direct sample size calculations were performed regarding the primary objective of the study; however, at the initiation of the study, it was estimated that approximately 2500 subjects would be enrolled. Given the rather small sample size, it is uncertain whether any meaningful conclusions can be drawn from the data obtained.

The CHMP also requested the following clarification:

The MAH should discuss the adequacy of the study to fulfill its obligation as a pharmacovigilance activity in the RMP. In addition, the MAH should discuss what other sources may be accessed to address the missing information of "safety of more than 4 doses of CRM-based pneumococcal vaccine."

II. SCIENTIFIC DISCUSSION

Study 3010 was not designed specifically to evaluate the safety of more than 4 doses of CRM-based pneumococcal vaccine. However, the study design did offer the opportunity to collect data that could contribute to a better understanding of this issue. It is for this reason that Study 3010 is mentioned in the RMP as addressing the safety of more than 4 doses: the mention was made for completeness of information and was not meant to indicate that the study would be able to provide a comprehensive evaluation of this issue.

Other studies that provide information regarding the safety of more than 4 doses of CRM-based pneumococcal vaccines include Study 6096A1-3011 and Study 6096A1-3021.

Study 6096A1-3011

Study 3011 was a Phase 3 open-label trial evaluating the safety, tolerability, and immunogenicity of 13vPnC in children aged 15 months to 17 years.

Submission of this study report was also a Post Marketing Commitment. (FU2 18.1).

The following reports relating to this study were previously submitted to the European Authorities:

☐ EMEA/H/C/1104 FUM 18, study 3011 CSR (cohort 1) in December 2009.
☐ EMEA/H/C/1104 FU2 018.2, study 3011 CSR safety addendum (cohort 2 and 6-mo follow up for cohort 1) in December 2010.

Assessment Reports were received for both submissions (EMEA/H/C/1104 FUM 18, AR; and EMEA/H/C/1104 FU2 018.2, AR).

The study enrolled subjects in 4 age groups, 2 of which provide data relevant to the present discussion. Group 1 enrolled subjects >15 months to <2 years of age who had previously received at least 3 doses of marketed 7vPnC, and group 2 enrolled subjects >2 years to <5 years of age who had received at least 3 doses of 7vPnC. Subjects in group 1 were to receive
2 doses of 13vPnC given at least 56 days apart, while subjects in group 2 were to receive 1 study dose of 13vPnC.

Study 3011 was originally designed to enroll 125 subjects in group 1 and 182 subjects in group 2. However, after the requisite numbers of subjects were enrolled in these groups, the protocol was amended to increase the sample size of each age group to 300. Subjects enrolled in Groups 1 and 2 before this amendment were identified as cohort 1, while those enrolled after the amendment were identified as cohort 2; data were analyzed separately for the two cohorts.

Safety results for this study were summarized for all subjects by group and cohort. In addition, exploratory analyses were performed for subgroups of subjects according to the number of previous doses of 7vPnC they had received. Separate reactogenicity and adverse event summaries were produced for each subgroup; however, because the number of previous doses was not controlled in the study design, no formal statistical within-group comparisons were performed for number of previous doses received.

Table 1 provides an overview of the number of subjects enrolled in each subgroup. As can be seen from the table, across both cohorts, a total of 82 (37+45) subjects in group 1 had received 3 previous doses of 7vPnC and could potentially have received a fourth and fifth dose of CRM-based pneumococcal conjugate (PnC) vaccine during the study. Similarly, a total of 220 (89+131) subjects in group 1 had received 4 previous doses of 7vPnC and could potentially have received a fifth and a sixth dose of CRM-based vaccine. Finally, across both cohorts, a total of 277 (172+105) subjects in group 2 had received 4 previous doses of 7vPnC and would have received a fifth dose of CRM-based vaccine during the study. Thus, overall, a total of 579 subjects in this study were available to provide information regarding the safety of >4 doses of CRM-based pneumococcal vaccine.

Table 2. Number of Subjects Enrolled in Subgroups by Number of Previous Doses of 7vPnC – Study 6096A1-3011

Number of Previous Doses of 7vPnC	Cohort 1		Cohort 2	
	Group 1	Group 2	Group 1	Group 2
3	37	--	45	--
4	89	172	131	105

Safety was evaluated based on information regarding local reactions, systemic events, and adverse events experienced after each study vaccination. The summaries of data by group and cohort, as well as the results from the subgroup analyses revealed no safety signals of concern. In these children >15 months to <5 years of age, the incidence and severity of local reactions and systemic events after a fourth, fifth, or sixth dose of CRM-based PnC vaccine were similar to those observed in infants and young children who received up to 4 doses of 13vPnC in clinical studies of 13vPnC. Overall, the safety profile of 13vPnC remains unchanged. Complete results of the subgroup analyses are reported in the clinical study report (CSR) for Study 3011 (cohort 1) and in the CSR addendum (cohort 2).

Study 6096A1-3021

Study 3021 was an open-label trial that was designed to evaluate the concentration of antibodies to the 13vPnC vaccine serotypes among children who had received one of 3 regimens of pneumococcal conjugate vaccine in study 6096A1-008: 4 doses of 13vPnC, 4 doses of 7vPnC, or 3 infant doses of 7vPnC followed by 1 toddler dose of 13vPnC (7vPnC/13vPnC). Study 3021 also evaluated the immunogenicity and safety of a single dose of 13vPnC administered to these children >24 months after the toddler dose in study 008.

Study 6096A1-3021 was a Post Marketing Commitment (FUM) and the full study report was submitted in June 2011. A CHMP opinion was adopted in August 2011. The opinion requested the information from the study be included in the European SPC and this amendment was submitted as Variation II41 which received a CHMP positive opinion in February 2012.

A total of 258 subjects received a single dose of 13vPnC in study 3021, which for all subjects represented a fifth dose of CRM-based pneumococcal vaccine. All subjects were between 3 and 4 years of age (mean age = 3.4 years) at the time of vaccination in this study. Safety data were summarized for all subjects vaccinated in the study, and were also summarized by treatment regimen in study 008: 130 subjects had received 4 doses of 13vPnC, 64 subjects had received 4 doses of 7vPnC, and 64 subjects had received 7vPnC/13vPnC in that study.

Safety was evaluated based on information regarding local reactions, systemic events, and adverse events. Overall, the results revealed no safety signals. In these children 3 to 4 years of age receiving a fifth dose of PnC vaccine, the incidence and severity of local reactions, systemic events, and adverse events were similar to those observed in infants and young children who received up to 4 doses of 13vPnC in previous studies of 13vPnC. Overall, the observations made in this study do not alter the safety profile of 13vPnC. Complete results for study 3021 are reported in the clinical study report.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Included in the RMP for Prevenar 13 was the safety concern of "missing information" related to "safety of more than 4 doses of CRM-based pneumococcal conjugate vaccine" for which Study 6096A1-3010 was noted as the pharmacovigilance activity to address this piece of missing information. At the time of assessment of the CSR, it was noted that only 137 subjects who were potentially exposed to more than 4 doses of such vaccine given the failure of the study to complete the projected enrolment.

The MAH has now summarized data from 2 additional studies with relevant data for the safety concern. Studies 6096A1-3011 and 6096A1-3021 supply data for an additional 579 + 258 subjects. The total number of subjects receiving more than 4 dose of CRM-based vaccine therefore approaches 1000. This total includes infants and children up to 5 years of age. No specific safety concerns were identified during the 3 separate analyses which have been assessed in different procedures.

The further discussion by the MAH is appreciated, and this procedure is considered complete.

Fulfilled: X

No further action required

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable.