16 December 2010

EMA/830044/2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Synflorix

pneumococcal polysaccharide conjugate vaccine (adsorbed)

Procedure No.: EMEA/H/C/000973/II/0016

Note

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

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1. Scientific discussion

1.1. Introduction

No new data were provided with this type II variation. The data filed under variation II/16 were previously fully reviewed under the follow-up measures (FUM) number 005 and 006.

The two studies in this application include **10PN-PD-DIT-015** and **10PN-PD-DIT-016.**

10PN-PD-DIT-015 was an open controlled study with three parallel groups The safety and immunogenicity of 10Pn-PD-DiT co-administered with DTPa-HBV-IPV/Hib following a 3-dose primary vaccination schedule (2, 4, 6 months) in preterm versus full term born subjects less than 6 months of age was evaluated.

10PN-PD-DIT-016 was the booster vaccination study of study 015. It was a phase III open study conducted to assess the safety and immunogenicity following a booster dose of 10Pn-PD-DiT co-administered with a booster dose of DTPa-IPV/Hib in preterm born children at 16-18 months of age following primary immunisation in study -015 (see Figure 1 and Table 1 for study details).

Figure 1 Study design of studies 10PN-PD-DIT-015 and -016.

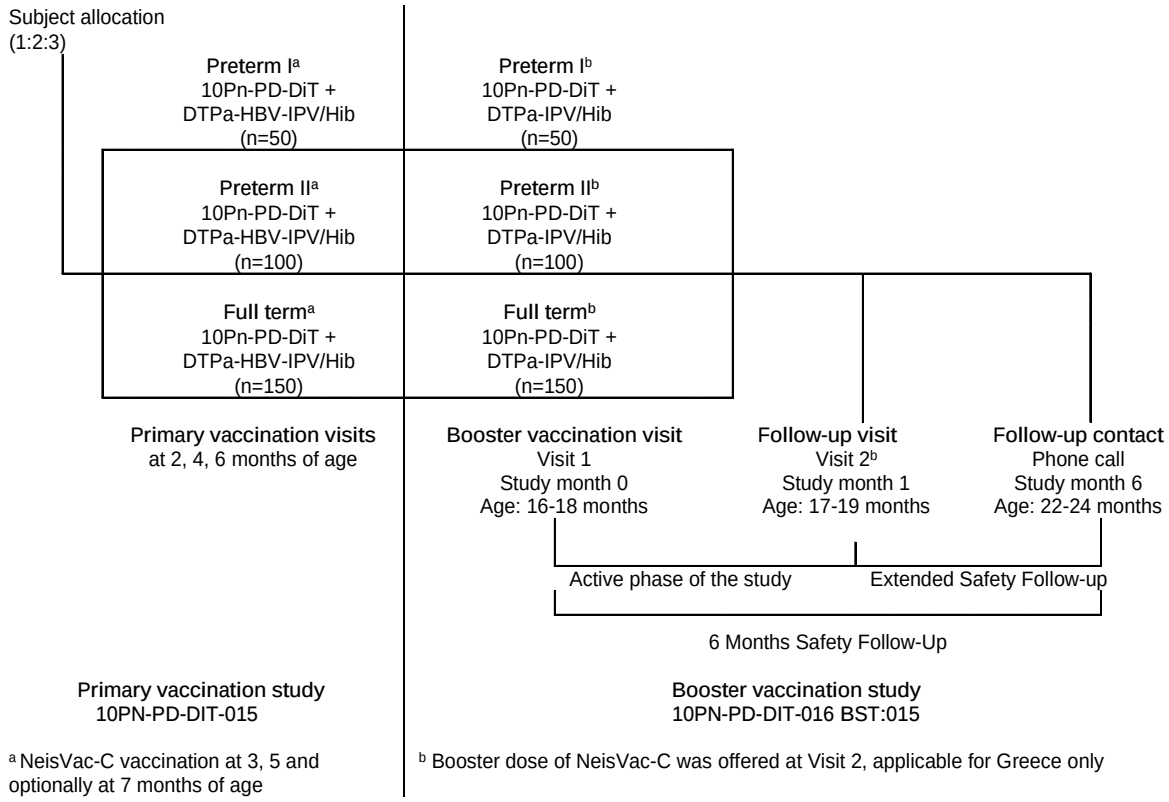


Table 1: Overview of the clinical trials

Study (country)	Design **Main study objectives**	**Population** (Age at time of first dose) *Vaccine schedule*	**Study groups**	**Number of subjects** Total vaccinated cohort	 ATP cohort for immunogenicity
10PN-PD-DIT-015 (Spain, Greece)	Open, controlled, 3-parallel groups Primary objective: o Evaluation of safety and reactogenicity of *Synflorix* when administered as a 3-dose primary vaccination course and co-administered with DTPa-HBV-IPV/Hib vaccine in preterm infants Key secondary objective: o Assessment of the immunogenicity of *Synflorix* when co-administered with DTPa-HBV-IPV/Hib vaccine in preterm infants, one month post dose III vaccination	Healthy preterm and term infants (8 to 16 weeks) *2 - 4 - 6 months*	**Preterm I group (PT1):** very preterm infants born after a gestation period of 27-30 weeks (189-216 days). **Preterm II group (PT2):** mild preterm infants born after a gestation period of 31-36 weeks (217-258 days). **Full term group (FT):** infants born after a gestation period of more than 36 weeks (more than 258 days). All subjects received *Synflorix* co-administered with DTPa-HBV-IPV/Hib given at 2, 4 and 6 months of age*	50 87 149	42 82 132
10PN-PD-DIT-016 **(Spain, Greece)**	Open, controlled, 3-parallel groups Primary objective: o Evaluation of the safety and reactogenicity of a booster dose of Synflorix co-administered with a booster dose of DTPa-IPV/Hib vaccine in preterm born children at 16-18 months of age Key secondary objectives: o Assessment one month post-booster vaccination the immunogenicity of a booster dose of Synflorix co-administered with a booster dose of DTPa-IPV/Hib vaccine in preterm born children at 16-18 months of age. o Assessment prior to the booster dose of the antibody persistence 10 to 12 months after the completion of the 3-dose primary vaccination course with Synflorix co-administered with Infanrix hexa in preterm infants.	Preterm and term infants (16-18 months) Single booster	**Preterm I group (PT1):** very preterm infants born after a gestation period of 27-30 weeks (189-216 days). **Preterm II group (PT2):** mild preterm infants born after a gestation period of 31-36 weeks (217-258 days). **Full term group (FT):** infants born after a gestation period of more than 36 weeks (more than 258 days).	44 72 129	44 69 127

All subjects were planned to be vaccinated with a licensed meningococcal vaccine, NeisVac-C, at 3-5 months of age. At the discretion of the investigator preterm infants were offered a third dose of meningococcal vaccine (NeisVac-C) at ± 7 months of age at Visit 6, after the blood sampling. The NeisVac-C vaccine was not considered as a study vaccine.

Clinical aspects

III.3.2 Clinical efficacy

Methods

Assays used to assess anti-pneumococcal antibodies

All serological assays used to evaluate the anti-pneumococcal antibody and Opsonophagocytic assay (OPA) responses were performed in GSK Biologicals' laboratory, using standardized and validated procedures with adequate controls.

Antibody concentrations as measured by Enzyme-linked Immunosorbent Assay (ELISA) and OPA against all vaccine serotypes and vaccine related serotypes 6A and 19A were evaluated in both studies.

In both studies, the analysis of the immunogenicity was performed according to each of the groups (Preterm I, Preterm II and Full term) on the According-to Protocol (ATP) cohort for immunogenicity (primary analysis), and in study 016 on the ATP cohort for persistence. In addition, in study 015 this analysis of immunogenicity was also performed on the Total Vaccinated Cohort, as more than 5% of the vaccinated subjects were excluded from the ATP cohort for immunogenicity.

The immune responses to the pneumococcal serotypes were measured by

1. ELISA against the 10 vaccine serotypes and the vaccine related serotypes 6A and 19A. The percentages of subjects reaching an antibody concentration of $\geq$0.20 μg/ml and the geometric mean concentrations (GMCs) were evaluated one month after completion of the primary vaccination in study 015, and were evaluated pre- and one month post-booster vaccination in study 016, and

2. OPA against the 10 vaccine serotypes. The percentage of subjects reaching an OPA titre of at least 8 and the geometric mean OPA titres (GMT) were evaluated one month after completion of the primary vaccination in study 015, and were evaluated one month post-booster vaccination in study 016.

ELISA for measurement of anti-protein D IgG antibodies
Anti-protein D antibodies were measured using an ELISA assay developed by the Marketing Authorisation Holder (MAH). The concentration of specific Protein D antibody was determined using a reference serum. The cut-off of the assay was 100 EL.U/mL.

Assays used to assess the immune response to concomitant vaccines
All assays used to evaluate the immune response to co-administered antigens were performed at GSK Bio laboratory using standarized validated procedures with adequate controls.

The immune responses to co-administered vaccine antigens were measured by

1. ELISA against the Hib polysaccharide polyribosyl ribitol phosphate (PRP). The assay cut-off was 0.15 µg/mL.
2. ELISA against pertussis components pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN). The cut-off of the test was 5 EL.U/mL.

3. ELISA against the diphtheria and tetanus components and expressed in IU/mL, with respect to a reference serum. It is generally accepted that for both diphtheria and tetanus, antibody concentrations ≥0.01 IU/mL, as measured by in vivo neutralisation tests, are protective. An antibody concentration of 0.1 IU/mL by ELISA (corresponding to approximately 3 times the lower quantitation limit of the assays) was arbitrarily and conservatively set as the cut-off (for both anti-diphtheria and anti-tetanus ELISAs).
4. Virus micro-neutralisation test adapted from the World Health Organisation Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis - Standard Procedure for Determining Immunity to Poliovirus using the Microneutralization Test (WHO/EPI/GEN 93.9) was used to assess the antibodies against polio virus types 1, 2 and 3. The lowest dilution at which serum samples were tested was 1/8, from which a test was considered positive. Titres were expressed as the reciprocal of the highest dilution of serum showing 50% virus neutralising effect.
5. ELISA (developed by GSK Bio) against the Hepatitis B component of the vaccine was used to measure the antibodies to the HBs antigen. Concentrations of 10 mIU/mL were considered as protective.

Study populations

Total vaccinated cohort

- The Total Vaccinated cohort (TVC) included all vaccinated subjects. The TVC for analysis of safety included all subjects with at least one vaccine administration documented and the TVC for analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. The TVC analysis was performed per treatment actually administered.

ATP cohort for immunogenicity (primary study population)

- The ATP cohort for analysis of immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available. This cohort included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination

ATP cohort for antibody persistence (Study 10PN-PD-DIT-016 only)

- The ATP cohort for analysis of antibody persistence included all subjects included in the ATP cohort for analysis of safety for whom assay results were available for antibodies against at least one study vaccine antigen component for the blood sampling taken before the administration of the study booster dose (pre-booster blood sampling

Inclusion/exclusion criteria

The primary vaccination and booster studies were conducted in healthy preterm and full term male and female children. In study 015, all preterm infants had to be medically stable to be enrolled (medically stable refers to the condition of premature infants who do not require significant medical support or ongoing management for debilitating disease and who have demonstrated a clinical course of sustained recovery). Exclusion criteria used in the studies aimed to prevent administration of the vaccines to those individuals with medical conditions that might potentially interfere with the evaluation of the immune response; to those individuals in whom previous exposure to the vaccine antigens through vaccination or disease would prevent interpretation of the results and to those individuals at risk of possible adverse reactions to the vaccine.

Results

Subject eligibility and attrition from the studies

In study **10PN-PD-DIT-015**, a total of 286 subjects were enrolled (50 subjects in the Preterm I group, 87 subjects in the Preterm II group and 149 subjects in the Full term group) and received at least one dose of study vaccine. A total of 270 subjects (94.4%) (48 subjects in the Preterm I group, 83 subjects in the Preterm II group and 139 subjects in the Full term group) completed the study. One subject in the preterm I group was withdrawn due to a SAE.

Out of the 286 subjects in the Total vaccinated cohort, 281 (98.3%) met the eligibility criteria for the inclusion in the ATP cohort for safety and 256 (89.5%) met the eligibility criteria for the inclusion in the ATP cohort for immunogenicity. The most common reason for elimination from the ATP cohort was serological data missing (n=17).

Among the 286 subjects vaccinated in the primary vaccination study 015 and planned to be enrolled in the booster **study 10PN-PD-DIT-016**, 245 (85.7%) subjects participated in the booster vaccination study (44 out of 50 in the Preterm I group, 72 out of 87 in the Preterm II group and 129 out of 149 in the Full term group). Forty-one subjects (6 in the Preterm 1 group, 15 in the Preterm II group and 20 in the Full term group) did not participate in the booster vaccination study. The most common reasons for not participating were 1) subjects were not willing to participate (n=24), and 2) subjects lost to follow-up (n=15). Among these, 1 subject died during the primary vaccination study

Out of the 245 subjects enrolled in study 016, 234 (95.5%) completed the active phase of the study and 229 (93.5%) subjects were contacted during the extended safety follow-up. Out of the 245 subjects in the Total vaccinated cohort, 245 (100%) met the eligibility criteria for the inclusion in the ATP cohort for safety/persistence and 240 (98.0%) met the eligibility criteria for the inclusion in the ATP cohort for immunogenicity.

Demographic characteristics

Both studies were conducted in Greece and Spain with ~ 40% of subjects enrolled in Greek study centres and ~60% in Spanish study centres overall.

In study 015, the age of infants at first vaccination ranged from 7 - 23 weeks. The mean weight at first vaccination was 3.1 kg in the Preterm I group, 4.2kg in the Preterm II group and 5.2kg in the Full term group. The mean weight at birth was 1.2 kg in the Preterm I group, 2.0kg in the Preterm II group and 3.2kg in the Full term group. The mean gestational age was 28.6 weeks in the Preterm I group, 33.5 weeks in the Preterm II group.

In study 10PN-PD-DIT-016, the mean age at booster vaccination was 16.8 months; with ages ranging from 16-19 months.

The majority (>88%) of subjects who participated in the primary and booster clinical studies were White/Caucasian. Male: Female ratio was approximately 2:3.

Immunogenicity results

Immunogenicity results were presented according to the three study groups (treatment allocation was1:2:3)

- **Preterm I (PT1)**: very preterm infants born after a gestation period of 27-30 weeks (189-216 days).
- **Preterm II (PT2)**: mild preterm infants born after a gestation period of 31-36 weeks (217-258 days).

- **Full term (FT)**: infants born after a gestation period of more than 36 weeks (more than 258 days) (control group).

Study 10PN-PD-DIT 015 - Primary vaccination

ELISA results

The GMCs of antibodies against the vaccine pneumococcal serotypes and the percentage of subjects with antibody concentrations ≥ 0.20 µg/ml one month post-dose 3 are presented in Figures 1 and 2.

For the Full term group, for each of the vaccine serotypes, one month post-dose 3, at least **93.9%** of the subjects had antibody concentrations ≥ 0.2 µg/ml.

For the PT1 group, at least **92.7%** of the subjects had antibody concentrations ≥ 0.2 µg/ml. Antibody GMCs were numerically lower for all serotypes in the PT1 group (except for serotype 14 vs. PT 2) and highest in the Full term group. The antibody GMCs were significantly lower for serotypes 4, 5 and 9V in the PT1 group compared to the Full term group (no overlap of 95% CIs).

For the PT2 group, at least **95.1%** of the subjects had antibody concentrations ≥ 0.2 µg/ml. The GMCs were lower for serotype 9V than those in the Full term group (no overlap of 95% CIs).

Figure 1: Percentage of subjects reaching GMCs ≥ 0.2 µg/ml for vaccine serotype in both preterm and full term infants, one month post-primary vaccination - Study 10PN-PD-DIT-015

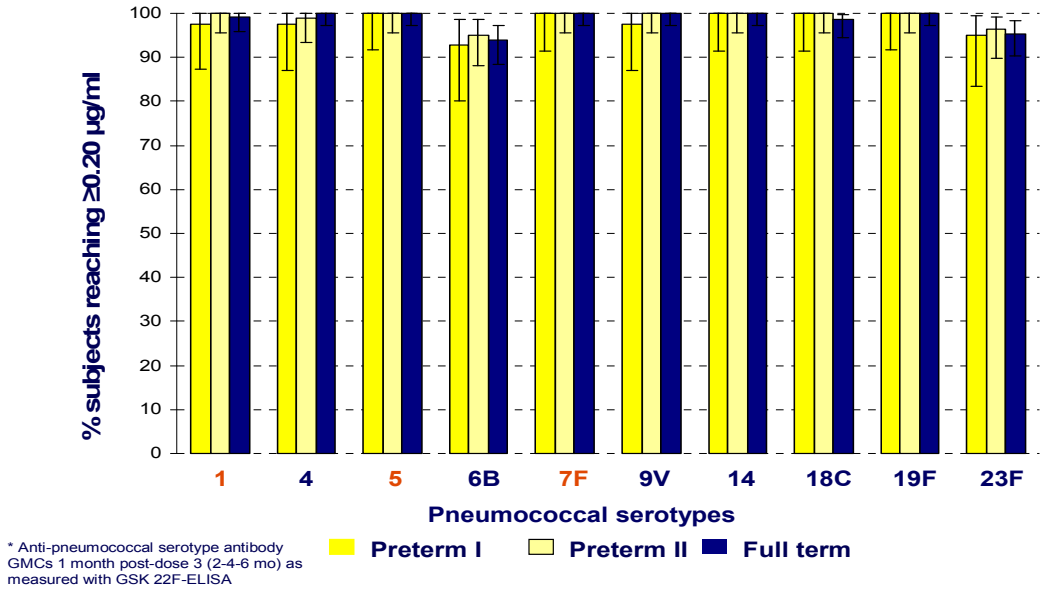
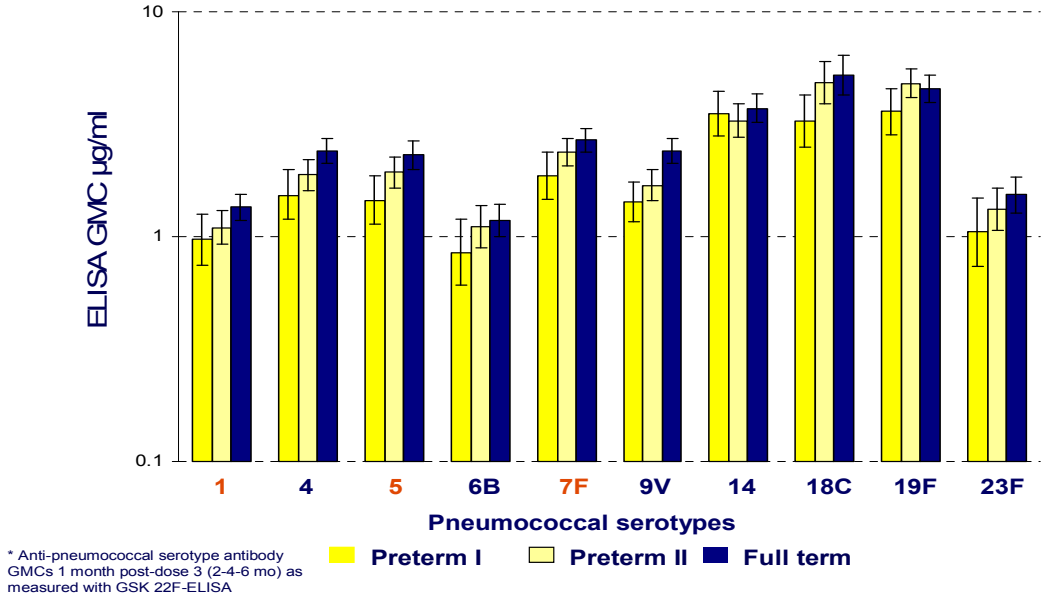


Figure 2: Antibody levels (GMCs) for vaccine serotype in both preterm and full term infants one month post-primary vaccination - Study 10PN-PD-DIT-015 Study 10PN-PD-DIT-015



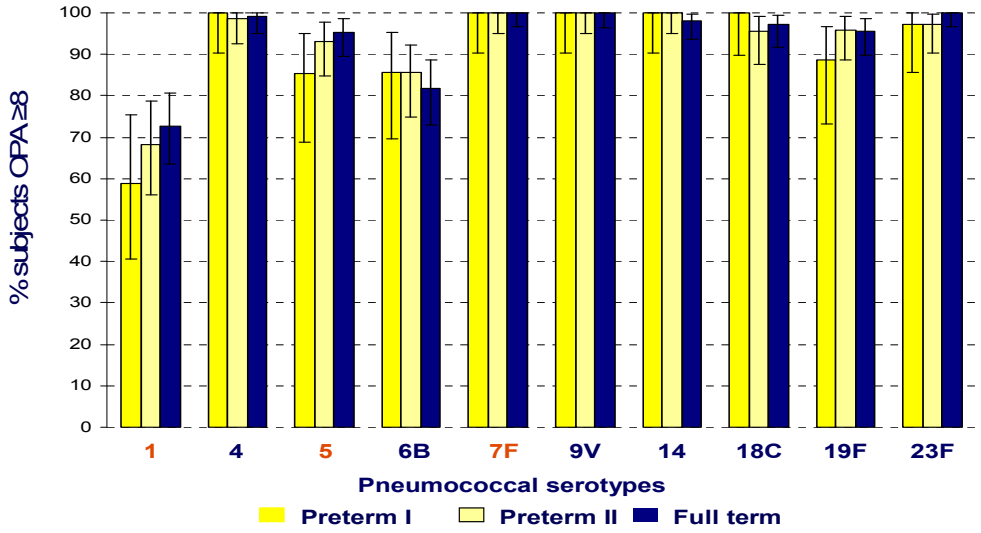
OPA results

Post-primary OPA titres against the vaccine pneumococcal serotypes and percentage of subjects with OPA titre ≥ 8 are presented in Figures 3 and 4. One month post-dose 3, for each of the vaccine pneumococcal serotypes, at least **95.4%** of the subjects in the Full term group had OPA titres ≥ 8, except for serotypes 1 (72.7%) and 6B (81.7%).

In the PT1 group at least **88.6%** of the subjects had OPA titres ≥ 8, except for serotypes 1 (58.8%), 5 (85.3%) and 6B (85.7%). The OPA GMT was lower for serotype 5 in the PT1group compared to that in the Full term group (no overlap of 95% CIs).

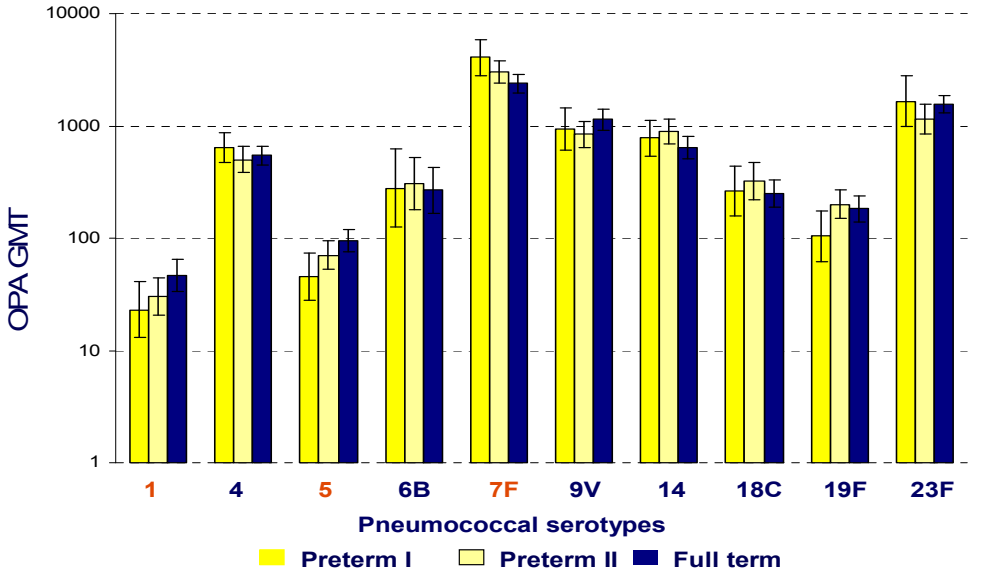
In the PT2 group at least **93.2%** of the subjects had OPA titres ≥ 8, except for serotypes 1 (68.1%) and 6B (85.5%).

Figure 3: Percentage of subjects OPA GMTs >8 for vaccine serotype in both preterm and full term infants, one month post-primary vaccination - Study 10PN-PD-DIT-015.



*1 month post-dose 3 (2-4-6 mo)

Figure 4: OPA titres for vaccine serotypes one month post-primary vaccination - Study 10PN-PD-DIT-015



*1 month post-dose 3 (2-4-6 mo)

The GMCs of antibodies against cross-reactive pneumococcal serotypes 6A and 19A, measured by ELISA and OPA were low in all groups without significant differences between infant groups .

One month post dose-3, all subjects in each of the infant groups had measurable antibodies against protein D (≥100 EL.U/mL) .

The immunogenicity results for the pneumococcal antigens and protein D for the Total vaccinated cohort were in line with those observed for the ATP cohort for immunogenicity

Co-administered vaccines

All subjects were seroprotected/seropositive for all antibodies against the antigens in the DTPa-HBV IPV/Hib vaccine, except one subject in the Preterm I group who was not seroprotected against polio type 3. The anti-PRP GMCs were numerically lower in the very preterm group, but for all the other antigens the GMC/GMTs were in the same range in all three vaccine groups

In general, the immunogenicity results for the co-administered antigens, for the Total vaccinated cohort were in line with those observed for the ATP cohort for immunogenicity. However, in the Preterm I group, the percentage of subjects with titres ≥ 8 against polio 2 antigens and the GMTs, one month post-dose III tended to be lower than those for the ATP cohort for immunogenicity

Study 10PN-PD-DIT 016 - Booster vaccination

Persistence of anti-pneumococcal antibodies (ELISA)
A decline in antibody GMCs was observed in the time period between primary and booster vaccination for each of the vaccine serotypes in all three groups. Antibody GMCs observed prior to the booster vaccination were in the same range in all three groups for each of the vaccine serotypes except for **serotype 5** in Preterm I group (0.24 vs. 0.40) and **serotype 9V** in Preterm II group (0.42 vs. 0.60) for which a lower GMC was observed as compared to the Full term group (no overlap of CIs).

Prior to the booster vaccination 1 approximately 10-12 months post completion of the primary vaccination course, at least **95.3%** of subjects still had ELISA antibody concentrations ≥ 0.05µg/ml for each of the vaccine serotypes except for serotype 1 in all three groups (at least 85.3%) and serotype 4 in the Preterm I group (93.0%). At least **63%** of subjects still had antibody concentrations ≥0.20ug/ml for each of the vaccine serotypes except for **serotype 1** (range 37%-44%) and **serotype 4** in Preterm I group (54%) and in Preterm II group (59%).

Prior to the booster vaccination, at least 76.8% and 65.1% of subjects in each of the three groups still had antibody concentrations ≥ 0.05 µg/ml and at least 24% had antibody concentrations ≥ 0.20 µg/ml against serotype 6A and serotypes 19A, respectively.

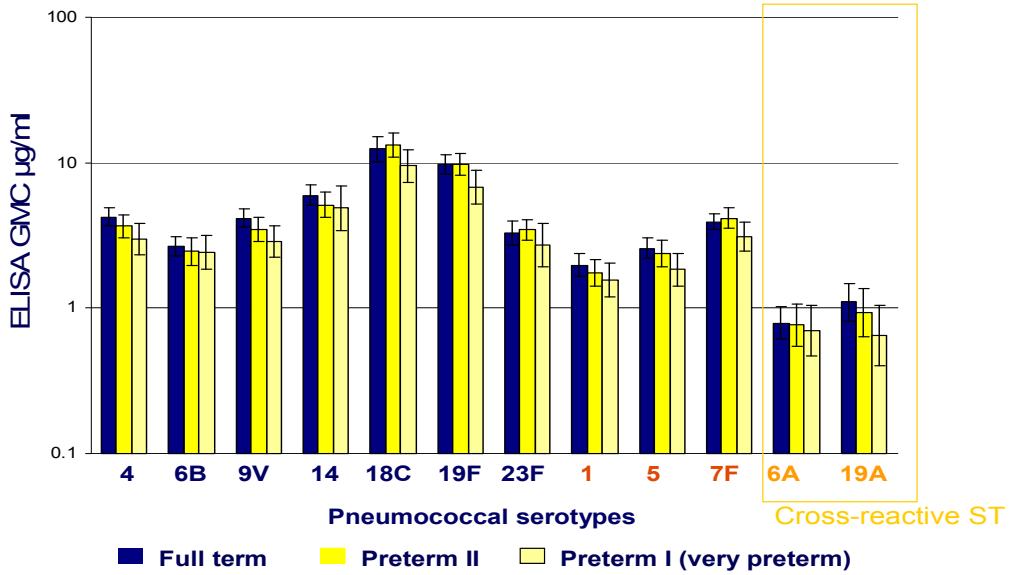
Prior to the booster vaccination, 85.5% of subjects in the Preterm II group and at least 92.7% of subjects in the Preterm I group and the Full term group still had anti-PD antibodies ≥ 100 EL.U/ml.

Booster response to the pneumococcal vaccine (ELISA)

ELISA results
After the booster dose in study 10PN-PD-DIT-016, there was a robust increase of ELISA antibody GMCs observed between the pre- and post booster responses for each vaccine serotype in all infant groups, with increases in GMCs of between 5.7 and 23.6 fold, indicative of immunological memory.

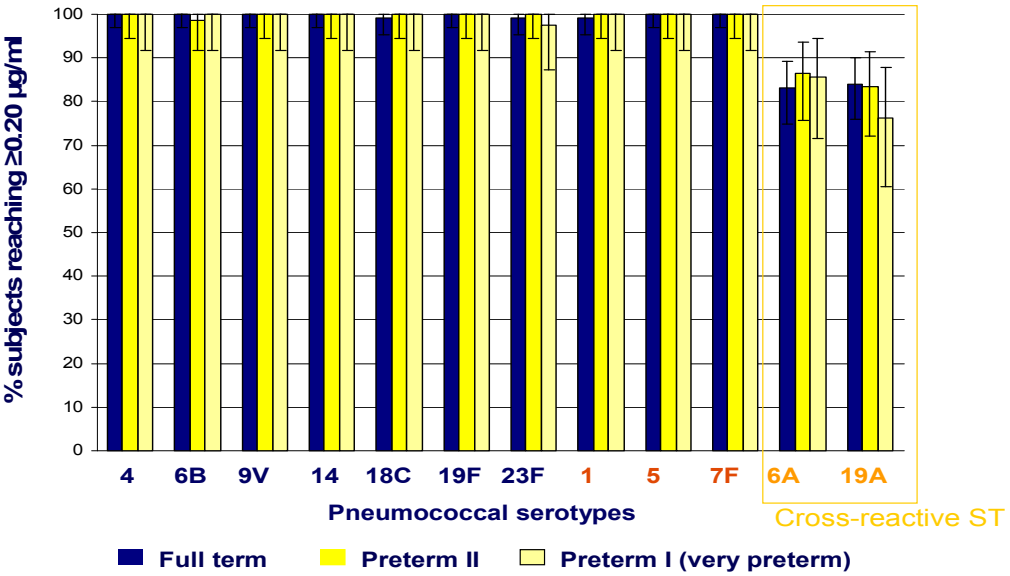
There were no significant differences between groups in post-booster antibody GMCs (all 95% CIs overlap) (Figure 5).

Figure 5: ELISA GMCs in both preterm and full term infants one month post-booster vaccination - Study 10PN-PD-DIT-016



All subjects in very preterm and preterm groups had GMCs ≥ 0.2 µg/ml for each vaccine serotype except for serotype 23F in the very preterm group (97.6%) and serotype 6B in the preterm group (Preterm II group; 98.5%) (Figure 6)

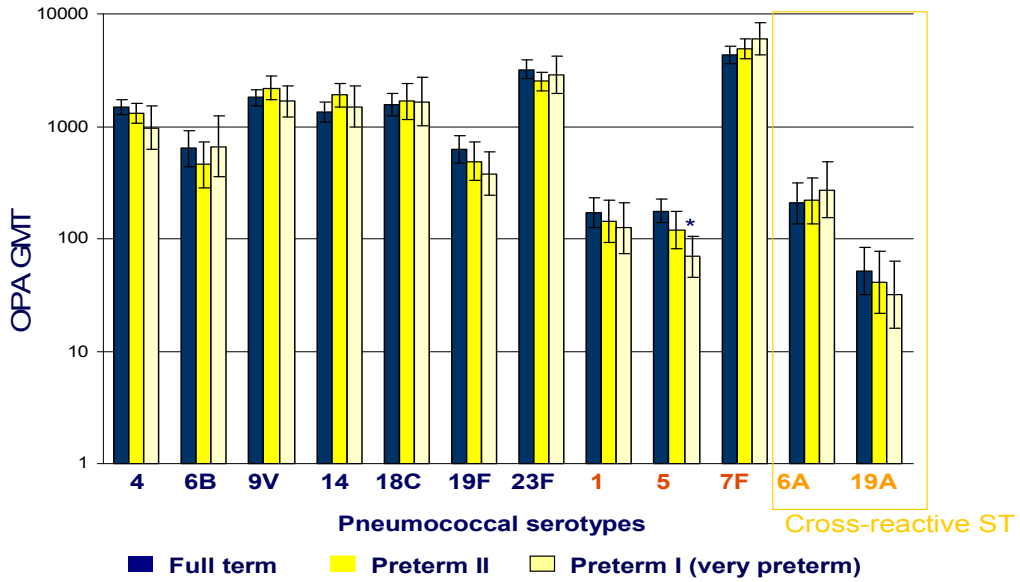
Figure 6: Percentage of subjects reaching GMCs ≥ 0.2 µg/ml in both preterm and full term infants, one month post-booster vaccination - Study 10PN-PD-DIT-016



OPA results

There were no significant differences between groups in post-booster OPA GMTs, except for **serotype 5**, whose OPA GMTs were lower in Preterm I group compared to Full Term group (no overlap of 95% CIs) (Figure 7).

Figure 7: OPA titres one month post-booster vaccination - Study 10PN-PD-DIT-016.



Increases in OPA GMTs post booster were compared to those attained post-primary. Robust increases of OPA GMTs were also seen for each vaccine serotype in both the preterm and very preterm groups comparing one month post-primary vaccination titres to one month post-booster titres.

Post booster OPA responses observed in the very preterm and preterm infant groups were in the same range as those observed in the full term group, with at least 91.9% of all subjects achieving OPA titres ≥ 8 for all vaccine serotypes.

Booster responses and high seroposivity rates were observed post booster for non-vaccine serotypes 6A and 19A. The post booster antibody GMCs and GMTs did not show significant differences between groups (overlap of 95% CI) (Figures 5 and 6). More than 76.2% of all subjects had an ELISA $\geq$ 0.2μg/ml and more than 57.7% of all subjects had an OPA GMT $\geq$ 8 for both non-vaccine serotypes 6A and 19A .One month post-booster vaccination, all subjects in each of the three groups (except one subject in the Full term group) had anti-PD antibodies ≥ 100 EL.U/ml.

As regards the co-administered vaccine, all subjects were seroprotected/seropositive for all antibodies against the antigens in the DTPa- PV/Hib vaccine after the booster dose without any noticeable difference between the groups.

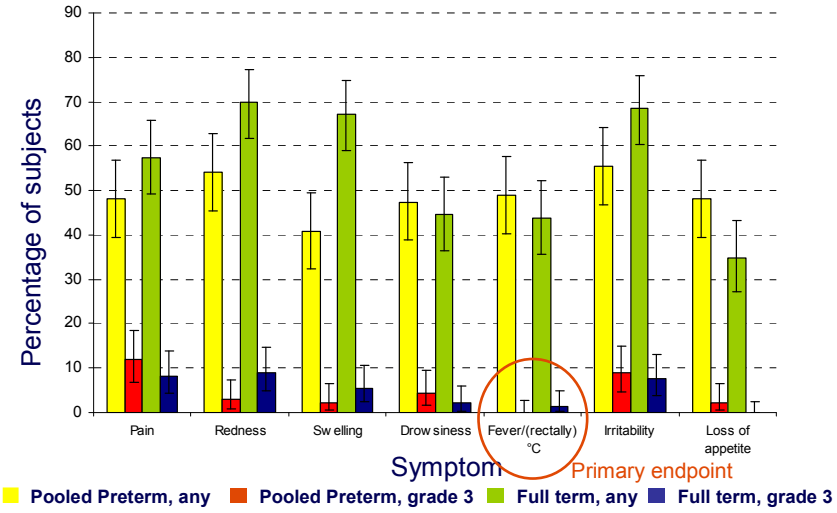
III.3.3 Clinical safety

The main conclusions on safety of *Synflorix* administered to preterm infants administered according to a 3+1 schedule are derived from studies 10PN-PD-DIT-015 and -016 and are summarized below.

Study 015: primary vaccination of preterm born infants

The most frequently reported local solicited adverse events (AEs) were redness and pain in the pooled preterm group and redness followed by swelling in the full term group. The incidence of local and general AEs was similar across all infant groups. However, some differences in reactogenicity were recorded between the study groups (pooled preterm group compared to the full term group) including the incidence of grade 3 fever, the incidence of redness and swelling, and the incidence of any solicited or unsolicited general or local AE being higher in the full term group (Figure 8). Two cases of Grade 3 fever were reported from subjects in the full term group, of which one was assessed by the investigator to be causally related to vaccination. The use of any prophylactic antipyretic in relation to vaccination was similar in both groups.

Figure 8: Percentage of subjects reporting local and general symptoms (any and grade 3 intensity) during the 4-day post-vaccination period following at least one dose of primary vaccination - Study 10PN-PD-DIT-015 (total vaccinated cohort)



During the primary vaccination course 12.4% and 19.0% of doses in the pooled preterm group and full term group, respectively, were followed by at least one unsolicited AEs. The most frequently reported unsolicited AES were upper respiratory tract infection (URTI) in the pooled preterm group and injection site nodules and URTI in the full term group.

One fatality was reported during the study. A subject in the Preterm I group died 25 days after the third dose of study vaccines. The medical diagnosis was choking due to aspiration and was not considered by the investigator to be causally related to vaccination.

A total of 31 subjects (18 (13.1%) infants in the pooled preterm group, and 13 (8.7%) infants in the full term group) reported non-fatal SAEs. The SAEs case reports included apnoea, bronchiolitis, tracheitis bronchospasm, breath holding and choking. Of these, one subject (from the Preterm group) reported a SAE that was considered by the investigator to be causally related to vaccination (i.e. pyrexia). All the reported SAEs resolved without sequelae.

Overall the reactogenicity profile of 10Pn-PD-DiTb as a 3-dose primary vaccination when given to preterm infants was as well tolerated as when given to full term infants, and consistent with the safety profile observed in previous studies.

Study 016: booster vaccination of preterm born infants
The most frequently reported solicited local AE in both groups was pain. Lower incidences of redness and swelling (any and grade 3) were observed in the pooled Preterm group than in the Full term group (no overlap of 95% CI). A maximum of 4.5% of subjects in the pooled Preterm group and 15.6% of subjects in the Full term group reported at least one grade 3 solicited local AE, regardless the injection site.

As with the primary vaccination, the most frequently reported solicited general AE post booster vaccination in both study groups was irritability. Solicited general AEs were reported within the same range in both study groups. Grade 3 solicited general AEs were reported in maximum 1.8% subjects across groups and most of these were considered to be causally related to vaccination. A fever > 39°C (rectal temperature) was reported in 7.1% subjects in the pooled Preterm group and 4.9% in the Full term group. Only one subject in the Full term group reported grade 3 fever (rectal temperature > 40°C) which was considered by the investigator to be causally related to vaccination.

14.7% of subjects in the pooled Preterm group and 18.6% of subjects in the Full term group reported at least one unsolicited AE within the 31-day post-vaccination period. Only one subject in the Full term group reported at least one grade 3 unsolicited AE, and no SAEs were reported during the active phase of the booster study

Overall incidences of AE (either solicited or unsolicited) tended to be lower in the Preterm pooled compared to the Full term group. All SAEs resolved without sequelae.

Overall the reactogenicity profile of 10Pn-PD-DiT as booster vaccination when given to preterm infants was as well tolerated as when given to full term infants, and consistent with the safety profile observed in previous studies**.**

Assessment of events following administration of 10Pn-PD-DiT vaccine to preterm infants during post-marketing surveillance (PMS)
Since the launch of Synflorix until 10 June 2010, there have four PMS cases reported in preterm infants. Of these reported cases, one case featured the event "apnoea", one case featured the event "Sudden Infant Death Syndrome", one case featured the event "Crying, Trance" and one case featured the event "Convulsion, Gaze palsy, Muscle Spasms, Tremor".

The current PMS data do not suggest cases observed in preterms as a particular safety concern or as unexpected.

2. Discussion and Conclusion

Study 015 was well conducted and enrolled both very preterm infants born after a gestation period of 27-30 weeks and mild preterm infants born after a gestation period of 31-36 weeks. Full term infants constituted the control group. Antibody response induced by 10Pn-PD-DiT was measured by both ELISA and OPA, which is satisfactory.

The 10-valent pneumococcal vaccine proved to be immunogenic in all three vaccine groups, although numerically lower antibody GMCs were observed in the pre-term infant groups compared to the full term infants, with statistically significant differences for antibodies against serotypes 4, 5, 7F and 9V in the very preterm group. However, differences between groups in terms of percentage of subjects with antibody concentrations ≥ 0.20µg/ml remained small. Importantly, OPA responses observed in the

Preterm I and the Preterm II groups were in the same range as those observed in the Full term group. Actually, numerically higher OPA GMTs to some serotypes (serotypes 4, 7F, 14 and 19F) were seen in the Preterm 1 group compared with the Full term group. As noted during the registration procedure, the OPA responses were very poor for serotypes 1 and 5 (in all vaccine groups). Therefore, the Company was asked to submit data from the ongoing booster study (10PN-PD-DIT-016), to ensure that the premature infant population achieves a comparable post-booster response as the full term infants.

As regards the co-administered vaccine, all subjects were seroprotected/seropositive for all antibodies against the antigens in the DTPa-HBV IPV/Hib vaccine, except one subject in the Preterm I group who was not seroprotected against polio type 3. The anti-PRP GMCs were numerically lower in the very preterm group, but for all the other antigens the GMC/GMTs were in the same range in all three vaccine groups.

The final safety results of study 10PN-PD-DIT-015 highlighted differences between the study groups as the incidence of fever was higher in the pooled Preterm group and the incidence of any solicited or unsolicited general or local AE was higher in the Full term group. The use of any or prophylactic antipyretic in relation to vaccination was similar in both groups. The most frequently reported unsolicited AE in both groups was upper respiratory infections. Altogether 31 subjects reported at least one SAE; 18 out of 137 vaccinated subjects in the pooled Preterm group and 13 out of 149 vaccinated subjects in the Full term group. Among these one case of pyrexia in the Pre term group was considered related to vaccination. The preterm group included one case of apnoea, 3 cases of bronchiolitis, 2 cases of breath holding, one case of asthma and one case of tracheitis. None of these cases were assessed as vaccine related and all resolved without sequele. The SAEs case reports in Full term infants included bronchiolitis, tracheitis, bronchospasm, breath holding and choking. Similarly, cases of fever convulsions were recorded in the Full term group. The occurrence of apnoea is a specific known adverse event especially in premature children, but will also be an imminent risk in the full term infants. The CIOMS reports did not include information of gestational time and therefore it was not possible to determine whether the reported cases belonged to Preterm group I or II. The current SmPC in section 4.4 *Special warning and precautions for use* appropriately highlights the potential risk of apnoea in preterm infants Apnoea and neurological events in relation to vaccination should be continuously closely monitored and reported on in future PSURs.

In conclusion no new significant or clinically relevant adverse events were identified.

The post-booster **study 016** enrolled 95% of 268 subjects primed with 10Pn-PD-DiT in study 015. The primary aim was to evaluate whether the immune response of booster dose after 3-dose primary vaccination yielded a comparable response in premature infants and in full term infants. Antibody response induced by the booster dose was measured by both ELISA and OPA, which is satisfactory. However, antibody persistence prior to the booster dose was only tested by ELISA.

A similar decline in antibody concentrations was seen in all groups for all vaccine serotypes during the pre-booster period. The persistence of ELISA IgG antibody concentrations was acceptable in all three study groups and for all vaccine serotypes with at least 95.3% of subjects having detectable antibodies ($\geq$0.05µg/ml) except for serotype 1 (all groups) and serotype 4 (preterm I group). At least 63% had antibody concentrations $\geq$0.20µg with the exception of **serotype 1** (37% of subjects in the Preterm group I and 44% in the Full term group). As regards GMCs numerically lower concentrations was observed in the pre-term infant groups compared to the full term infants. Only for serotype 5 and serotype 9V these differences reached statistical significance (no overlap of 95% CIs) in the preterm group I and II, respectively.

One month after the third primary vaccination dose in study 10PN-PD-DIT-015 there was a trend for lower antibody GMCs in the preterm infants groups. Antibody GMCs were significantly lower for serotypes 4, 5 and 9V in the PT1 group compared to FT group (no overlap of 95% CIs). However, after the booster dose robust increase of antibody GMCs was seen for all serotypes without any significant differences between groups (all 95% CIs overlap). Overall, the lowest GMCs were noted for serotype 1 in all groups.

Importantly, post-booster OPA responses observed in the Preterm I and the Preterm II groups were in the same range as those observed in the Full term group. Thus data showed that that the premature infants had been adequately primed. As noted during the registration procedure, the OPA responses were lowest for serotypes 1 and 5 (in all vaccine groups). However, for serotype 1 a good booster response was seen although the GMTs were still low. In this study, the lowest post-booster OPA GMTs were observed for serotype 5, which was evident in the preterm groups I (GMT 69) and II (GMT 120). However, still 94% and 96% of these subject, respectively, attained the OPA threshold $\geq$8.

As regards the co-administered vaccine all subjects were seroprotected/seropositive for all antibodies against the antigens in the DTPa-IPV/Hib vaccine after the booster dose without any noticeable difference between the groups.

In conclusion the results in study 016 showed that a booster dose of 10Pn-PD-DiT vaccine at Month 16-18 induced satisfactory immune responses against all vaccine serotypes and in all vaccine groups including the preterm children. The lowest functional immune responses were observed for serotypes 1 and 5, which were somewhat more pronounced in the very preterm infants. Still the majority of these subjects attained the OPA titre threshold of $\geq$8. It can be concluded that the immune responses elicited by a fourth dose of 10Pn-PD-DiT in premature infants was comparable to that of full term infants and indicate that these infants were adequately primed.

Study 016 evaluated post-booster responses in preterm infants who are at higher risk of experiencing apnoea when receiving vaccination during the first six months of life. At time of the booster dose the occurrence of apnoea is of less concern and no such event was recorded in the study.

Some differences were recorded between the study groups as the incidence of fever >39^{o}C was higher in the pooled Preterm group (7.1% vs. 4.9%) and the incidence of any solicited or unsolicited general or local AE was higher in the Full term group. Few grade 3 systemic events were reported. The use of any or prophylactic antipyretics in relation to vaccination was similar in both groups. It is of note that the overall incidence of fever >39^{o}C was lower after primary vaccination (1% in the pooled preterm group and 2.1% in the Full term group) than that noted following the booster dose.

The most frequently reported unsolicited AE in both groups was upper respiratory infections or tonsillitis. No SAE was reported during the active study phase whereas 4 SAEs were reported during the follow-up safety phase. All of these SAEs were considered unrelated to vaccination.

CHMP concluded that no safety concerns were identified during this booster study.

On 16 December 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet. Update section 4.2, 4.8 and 5.1 of the SmPC to include information on preterm infants based on the data provided in response to FUM 005 and FUM 006 that have been assessed by the Rapporteur and reviewed by the CHMP.