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Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Synflorix

pneumococcal polysaccharide conjugate vaccine (adsorbed)

**Procedure No.:** EMEA/H/C/000973/II/0014

## Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

# 1. Scientific discussion

## *1.1. Introduction*

The aim of this type II variation is to update the Summary of the Product Characteristics in section 4.2 with a recommendation for use of Synflorix with 2+1 schedule in routine infant immunization programmes based on the availability of immunogenicity data following primary vaccination and booster vaccination in subjects receiving Synflorix according to a 2+1 or 3+1 schedule. Two clinical trials were already presented in the registration file: the 2-dose primary vaccination study **10PN-PD-DIT-002** and the 2-dose data from study **10PN-PD-DIT-011** including a *post-hoc* head to head comparison with Prevenar. The more recent study **10PN-PD-DIT-046** is the 2-3 years follow-up of study 002 and provides new data on persistence of antibodies for 2-3 years after a booster dose at 11-12 months of age and an anamnestic response to an additional challenge dose (long-term immune response). Due to the shortness of time since licensure of Synflorix, there are currently no effectiveness data available.

In addition, this variation application aims to update section 5.1 to reflect immunogenicity data on the 2-dose primary schedule and the new immunological data from study 10PN-PD-DIT-046. The Package Leaflet has also been updated to reflect the total number of vaccine doses given to children.

## *1.2. Clinical aspects*

**Clinical studies supporting the proposed changes**

Study 002 was part of the initial registration file in Europe and compared the post-primary and post-booster immunogenicity following a 2+1 and 3+1 schedules for 10Pn-PD-DiT. A *post-hoc* analysis of study 011, was performed upon request of CHMP and provided a head to head comparison between 10Pn-PD-DiT and Prevenar following two vaccine doses administered according to a 2, 4 month schedule. The recent study 046 assessed the persistence and immunological memory following 2+1 and 3+1 vaccination and is the follow-up of study 002. An overview of the studies submitted is presented in Table 1.

Only the new data presented in the Clinical Study Report of study 10PN-PD-DIT-046 are assessed in full in the current variation application. The data from studies 002 and 011 are presented first since they evaluate short term immunogenicity. Subsequently the new data from study 046 on longer term immunogenicity are evaluated.

**Table 1: Overview of studies evaluating 2+1 vaccination schedule**

| Study | Design | Primary efficacy objective | Age | Total cohort | ATP cohort |
|---|---|---|---|---|---|
| **10PN-PD-DIT-002**<br>(Denmark, Norway, Slovakia, Sweden) | Open, randomised<br><br>10Pn-PD-DiT + Infanrix hexa or Infanrix IPV/Hib at 2-4-11 months<br><br>10Pn-PD-DiT + Infanrix hexa or | <u>Primary objective</u><br>Assessment of post-dose 2 immune response elicited by 10Pn-PD-DiT administered at a 2-4-11 months schedule co-administered with DTPa-combined vaccine | Healthy infants<br>8 to 16 weeks<br><br>2-4-11 months | 175 | 153 |

| | | | | | |
|---|---|---|---|---|---|
| | Infanrix IPV/Hibat 2-4-11months) | | 2-3-4-11 months | 176 | 153 |
| **10PN-PD-DIT-011** (Germany, Poland, Spain) | Open, randomized, controlled<br><br>2-4-6 months*<br><br>(*MenC given at 2 and 4 months) | <u>Primary objective:</u><br>Non-inferiority of 10Pn vs. Prevenar, both co-administered with DTPa-combined and Hib-MenC vaccines, in terms of post-immunization febrile reactions with rectal temperature >39°C | Healthy infants<br>6 to 16 weeks<br><br>10Pn + Infanrix hexa + Meningitec<br><br>10Pn + Infanrix hexa + NeisVac-C<br><br>10Pn + DTPa-HBV-IPV + Hib-MenC<br><br>Prevenar + DTPa- HBV-IPV + Hib-MenC | <br><br>385<br><br>387<br><br>386<br><br>390 | <br><br>169<br><br>175<br><br>173<br><br>170 |
| **10PN-PD-DIT-046 (follow-up study 002)** (Slovakia, Sweden) | Open , randomized<br><br>2-4-11 months + dose 24-34 months after last dose<br><br>2-3-4-11 months + dose 24-34 months after last dose<br><br>Unprimed + 2 doses at 36-46 months of age and 38-48 months of age | <u>Primary objective</u>:<br>Assessment of the immune responses:<br>- following vaccination with an additional dose of 10Pn given at 36-46 mo of age in children previously vaccinated in study -002 with either a 3- or 2-dose primary schedule<br>- following vaccination with a single dose of the 10Pn in age-matched unprimed children. | Healthy children 36 to 46 months<br><br>2+1 group<br><br>3+1 group<br><br>Unprimed group | <br><br>51<br><br>59<br><br>62 | <br><br>50<br><br>57<br><br>60 |

**Good clinical practice**

All studies were carried out by experienced investigators and all these studies were conducted in accordance with Good Clinical Practice (GCP) guidelines. The protocols reflected the Declaration of Helsinki and its amendments as well as the GCP guidelines in use at the study outset.

**Methods to evaluate immunogenicity**

Total IgG antibodies specific to serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F were each measured by 22F-inhibition ELISA. The antibody concentration was determined by logistic log comparisons of the ELISA curves with the standard reference serum 89-SF for which concentration of IgM and IgG to the 10 serotypes was known in µg/ml. The cut off of the assay was 0.05 µg/ml.

*S. pneumoniae* opsonophagocytic activity (OPA) was measured by a killing assay using a human HL-60 cell line. The cut-off of the assay was an opsonic titre of 8.

The ELISA antibody concentrations and OPA against the cross-reactive serotypes 6A and 19A were also determined (cut-off of the assay was 0.05 µg/ml for ELISA and 8 for OPA).

Anti-PD antibodies were determined by an ELISA assay (GSK Biologicals). Specific PD antibodies were determined using a standard reference serum. The cut-off of the assay was 100EL U/ml.

The B-cell enzyme-linked immunospot (ELISPOT) assay allows the quantification of antigen specific memory B-cells after *in vitro* differentiation of B memory cells into antibody secreting plasma cells. The results are expressed as the frequencies of antigen-specific memory B-cells within the total memory B-cell population.

All serological assays used were performed in GSK Biologicals laboratory using standardised and validated procedures with adequate controls.

**Methods used to evaluate efficacy**

Antibody concentrations as measured by ELISA and OPA against all vaccine serotypes and vaccine related serotypes 6A and 19A were evaluated in all studies. The analysis was performed on the ATP cohort for immunogenicity but, in study 046, the ATP cohort for persistence included all subjects in the ATP cohort for safety with assay data for at least one vaccine serotype or protein D. The immune responses as measured by ELISA were evaluated in terms of percentages of subjects reaching an antibody concentration of $\geq$0.20 $\mu$g/ml, and the geometric mean antibody concentrations (GMC). The percentage of subjects reaching an OPA titre of 8 and the geometric mean OPA titres (GMT) against the 10 vaccine serotypes one month after vaccination in studies 002 and 046 and two months post-dose 2 in the *post-hoc* analysis of study 011 were assessed. If more than 5 % of the vaccinated subjects with immunogenicity results were excluded from the ATP cohort of immunogenicity, a secondary analysis of immunogenicity was conducted on the Total Vaccinated cohort that included all vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

The GMC/T calculations were performed by taking the anti-$\log_{10}$ of the mean of the $\log_{10}$ titer/ concentration transformations. Antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC/T calculation.

In all studies and for each group, seropositivity rates with exact 95% CI and geometric mean antibody concentration/titre (GMC/T), with 95% CI, were calculated using standard methods.

**Populations evaluated**

Studies were conducted in healthy male and female children after checking eligibility criteria at study entry. In studies 002 and 011, exclusion criteria aimed to prevent administration of the candidate vaccine to individuals with medical conditions that might potentially interfere with the evaluation of the immune response; those in whom previous exposure to the vaccine antigens through vaccination or disease would prevent interpretation of the results and those individuals at risk of possible adverse reactions to the vaccine. Studies 002, 011 and 046 were conducted in EU countries; Denmark, Germany, Norway, Poland, Slovakia, Spain and Sweden. The majority (>90%) of subjects who participated in the clinical studies were White/Caucasian. Males and females were approximately equally represented in all studies.

The inclusion/exclusion criteria were similar across all studies with exception of the age range for enrolment and the vaccines given prior to clinical trials.

**Statistical methods**

The following descriptive analyses were common to all studies. For each treatment group, at each time-point that a blood-sample result was available:

- Antibody GMCs/GMTs with 95% CIs was tabulated.
- Percentage of subjects with pneumococcal antibody concentrations ≥0.20 µg/ml with exact 95% CIs was calculated for each serotype.
- Percentage of subjects with OPA titers ≥8 with exact 95% CIs was calculated for each serotype.

Additional comparative, inferential analyses were performed in all studies, but are not reported here as the results are not directly relevant to the current application.

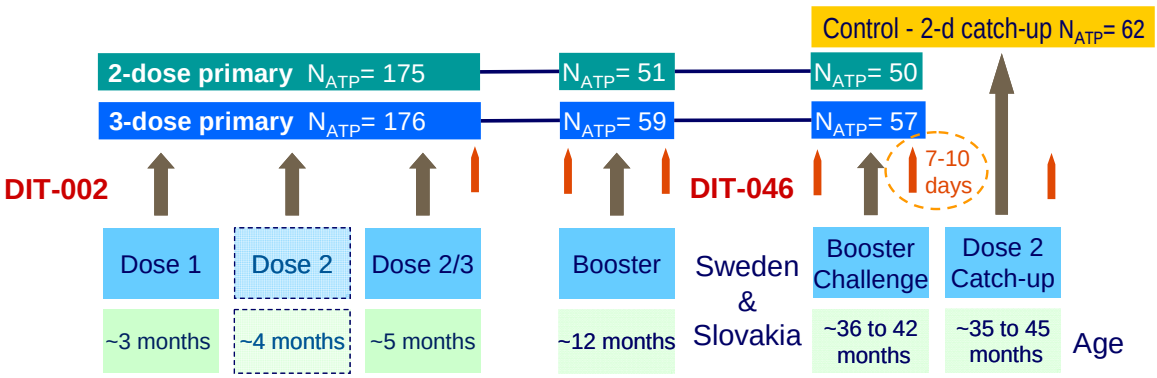
**Study objectives of studies 10PN-PD-DIT-002 and -011**

***Study 10PN-PD-DIT-002***

Study 002 is an open, randomised clinical phase III trial with two parallel groups. The design is summarised in Table 1 above and in Figure 1.

The primary objective was to assess the post-dose 2 immune response elicited by 10Pn-PD-DiT administered according to a 2-4-11 month schedule. Secondary immunogenicity objectives included evaluation of immunogenicity of 10Pn-PD-DiT in the 2-3-4-11 month schedule and evaluation of persistence of the immune response at 11 months of age. Safety and reactogenicity of the vaccine were also evaluated in this study.

**Figure 1: Study design of study 002 and 046**




***Study 10PN-PD-DIT-011***

Study 011 is an open, randomised, controlled study with four parallel groups: (i) Group Pn-Men: 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + Meningitec, (ii) Group Pn-Neis:10Pn-PD-DiT+ DTPa -HBV-IPV/Hib + NeisVac-C, (iii) Group Pn-HibC: 10Pn-PD-DiT + DTPa-HBV-IPV + Hib-MenC and (iv) Group Pr-HibC: Prevenar + DTPa -HBV-IPV + Hib-MenC. The study vaccines were administered at 2-4-6 months of age with the exception of Neisvac-C and Meningitec, for which two doses were administered at 2 and 4 months of age.

The primary objective was to demonstrate that 10Pn-PD-DiT, when administered as a 3-dose primary course, is non-inferior to Prevenar, both co-administered with DTPa-HBV-IPV and Hib-MenC vaccines, in terms of post-immunization febrile reactions with fever > 39.0°C (measured rectally). Immunogenicity of 10Pn-PD-DiT was also evaluated in this study.

This study is the only study to date that included a Prevenar group and where a blood sample was collected after the second dose. Immunogenicity was evaluated 1 month after the third dose as a secondary objective and 2 months after the second dose in a *post-hoc* analysis. After the second

primary dose, anti-pneumococcal immune responses were analyzed for a random subset of sera (about one-third) from the 10Pn-PD-DiT groups and all available sera from Prevenar vaccines.

**RESULTS - 10PN-PD-DIT-002 and -011**

**Study 10PN-PD-DIT-002 (Denmark, Norway, Slovak Republic, Sweden)**
A total of 351 subjects were vaccinated in the study and received at least one dose of 10-Pn-PD-DiT. The mean age at first vaccination was 12.1 weeks (SD±1.91). Among 342 subjects who completed the study, a total of 9 subjects were withdrawn and one subject from the 3+1 group was withdrawn due to an SAE and two subjects (one in each group) were withdrawn due to a non-SAE.

Out of 351 subjects, 312 (88.9%) met the eligibility criteria for inclusion in the ATP cohort for immunogenicity.

***Comparison of immune responses with 10Pn-PD-DiT following 2+1 and 3+1 vaccination schedule***

Post primary:
One month post primary vaccination at least 92.8% in the 2+1 group and 96.1% of subjects in 3+1 group reached the ELISA antibody threshold of ≥0.20 µg/ml against each of the serotypes, **except for serotypes 6B** (2- dose group: 55.7%; 3 -dose group: 63.l %) **and 23F** (2 dose group: 69.3%; 3 dose group: 77.4 %). For most serotypes, post primary ELISA GMCs were higher (no overlap of CIs) after the 3 dose priming than after the 2 dose priming, particularly for 18C and for 19F. One month post-primary vaccination at least 20% and 42.7% of subjects had antibody concentrations ≥ 0.20 µg/ml against serotypes 6A and 19A, respectively.

There was a lower percentage of subjects with OPA titers ≥8 in 2-dose primed subjects compared to 3-dose primed subjects for serotypes 6B, 18C and 23F (74.4%, 82.8%, 86.3% respectively for the 2-dose schedule and 88.9%, 96.2%, 97.7%, respectively for the 3-dose schedule).

Pre-booster:
In the time period after primary and before booster vaccination, a decline in ELISA GMCs was observed in both groups for all serotypes, except 6B and 23F. Persistence of the immune response was evaluated at 11 months of age, in both groups the rate with concentrations ≥0.20µg/ml was at least 78.9% in the 2-dose group and at least 89.3% in the 3-dose group **except for serotypes 1, 6B and 23F** (51.7%, 65.6%, 71.5%, respectively for the 2-dose schedule and 68.7%, 76.0%, 78.4%, respectively for the 3-dose schedule).

The persistence of OPA immune response by serotype varied widely. At least 45.1% in the 2-dose groups and at least 42.1% in the 3 dose group remained at an OPA titre ≥ 8, **except for serotypes 1, 4 and 18C** in the 2 dose group (9.6%, 39.4%, 24.6%, respectively) and **except for serotypes 1, 5 and 18C** in the 3 dose group (15.7%, 41.5%, 49.3%, respectively). The OPA GMTs were particularly low for serotypes 1, 4, 5, 18 C and 19F in both groups. For all serotypes except 23F, GMTs were higher in the 3-dose group.

Post-booster:
A booster dose to subjects primed with either 2 or 3 doses elicited increases in antibody concentration against all antigens. One month after the booster dose the percentage of subjects with antibody concentrations ≥0.20µg was at least 95.9% for each of the vaccine serotypes in both groups with **the exception of serotype 6B** which was 88.5% in the 2-dose group, and 96.6% in the 3 dose group.

For most serotypes the ELISA GMCs were higher following the 3-dose primary vaccination course and similarly also post-booster vaccination, **except for serotype 1**.

An increase in OPA GMTs was observed for all serotypes. At least 82.6% of subjects in the 2-dose group and 90.8% in the 3-dose group had OPA activity ≥8 after primary vaccination, **except for serotypes 5 and 6B**. A trend for higher OPA GMTs measured post-primary and post-booster was observed in the 3+1 groups compared to the 2+1 group.

Serotypes 6A and 19A
One month post-primary vaccination, at least 20% and 42.7% of subjects had antibody concentrations ≥0.20 µg/ml against serotypes 6A and 19A, respectively, in both groups. Post-booster vaccination, at least 63.6% and 81.4% of subjects reached antibody level ≥0.20 µg/ml against serotypes 6A and 19A, respectively. After primary vaccination at least 39.8% and 12.8% of subjects had OPA titre ≥ 8 against serotypes 6A and 19A, respectively, in both groups. One month post booster vaccination, at least 57.1% and 24.4% of subjects had OPA titre ≥ 8 against serotypes 6A and 19A, respectively. The GMTs observed after the booster dose in the 2-dose primary schedule remained below those observed after the booster dose in the 3-dose schedule.

Protein D: Overall 98.0% of subjects in the 2-dose priming group and all subjects in the 3-dose priming group were seropositive for anti-PD antibodies. Prior to the booster dose, 90.1% of subjects in the 2-dose group and 95.3% in the 3-dose group remained seropositive for anti-PD antibodies, whereas one month post booster vaccination all children except one in the 2-dose priming group had anti-PD antibodies ≥ 100 EL U/ml.

In conclusion, for most serotypes, the ELISA GMCs were higher following 3-dose primary vaccination course compared to the 2-dose primary course. The same trend was observed post-booster vaccination, except for serotype 1. The difference between groups became less marked after the booster dose for both ELISA and OPA, but was still significant for percentage of subjects reaching ELISA/OPA thresholds for serotypes 6B (ELISA) and 5 (OPA).

**Study 10PN-PD-DIT-011 (Germany, Spain, Poland)**

A total of 1572 subjects were enrolled. Due to the findings of an audit, 24 subjects from one centre were eliminated from the total vaccinated cohort, leaving 1548 subjects for analysis. Of these, 1158 received at least one dose of 10Pn-PD-DiT. The mean age of first vaccination was 8.1 weeks (SD ± 2.23 weeks). Forty-nine subjects were withdrawn, three due to SAE (2 subjects in the Pn-Neis group and 1 subject in the Pn-HibC group). A total of 1499 subjects completed the study.

Overall 698/1548 (45.1%) met the eligibility criteria for inclusion in the ATP cohort for immunogenicity. A total of 766 subjects were not planned to have any blood sampling and received a specific elimination code.

- ***Post-hoc head to head comparison of 10Pn-PD-DiT and Prevenar after 2 primary doses***

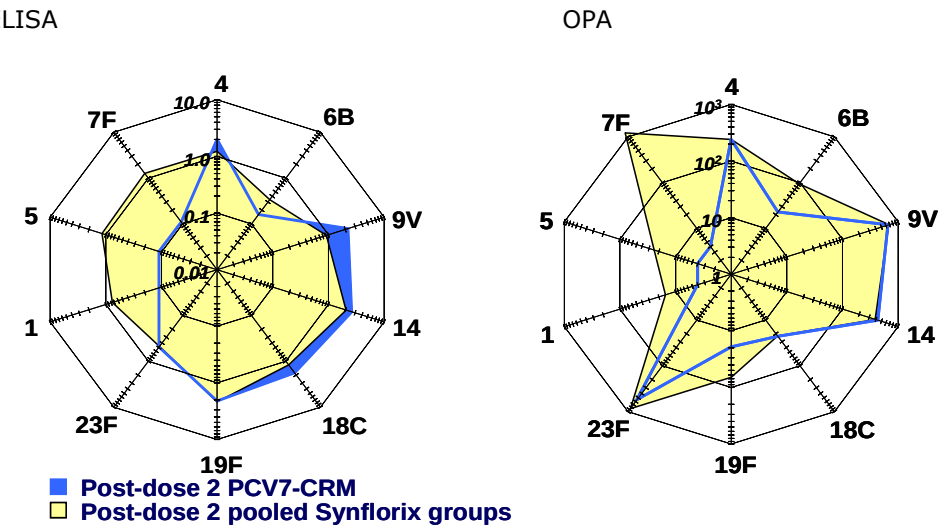
Study 011 evaluated the immune responses in infants vaccinated with either Prevenar or 10Pn-PD-DiT at 2, 4 and 6 months of age. A ***post-hoc*** analysis of the immunogenicity data measured 2 months after the second vaccine dose was performed to provide comparative data with Prevenar.

For each of the 7 serotypes in common, the percentage of subjects with antibody concentration ≥ 0.20µg/ml after the second dose was within the same range for both vaccines **except for the**

**serotypes 6B** (higher for 10Pn 64% vs. 31% for Prevenar) **and 18C** (higher for Prevenar 98% vs.10 Pn 87%). The corresponding percentage for serotype 23F was 75% for both vaccines. Antibody GMCs were similar in both groups, but with one serotype (6B) higher for 10Pn-PD-DiT and with 4 of 7 serotypes (4, 9V, 14 and 18C) higher for Prevenar (Figure 2).

For each of the serotypes common to both vaccines, the OPA GMTs and the percentages of subjects reaching OPA GMTs ≥ 8 after the second dose were within the same range for both vaccines, with the exception of serotypes 6B, 19F and 23F for which the responses were higher with 10Pn-PD-DiT. The OPA GMTs against serotype 18C were similar for both vaccines with a higher OPA seropositivity rate in the Prevenar group (75% vs. 61%).

**Figure 2: Study 011: Post-hoc head-to-head immunogenicity of 10Pn-Pd-DiT and Prevenar in ELISA (GMC) and OPA (GMT) after 2 doses**




The ratios of the GMCs and GMTs elicited by two doses of 10Pn-PD-DiT compared to two doses of Prevenar are presented for each serotype in Table 2.

**Table 2: Study 011: ELISA/OPA responders and ELISA GMCs/OPA GMTs to the 7 common serotypes in Prevenar and 10Pn-PD-DiT after two primary vaccine doses**

| Serotypes | 4 | 6B | 9V | 14 | 18C | 19F | 23F |
|---|---|---|---|---|---|---|---|
| **ELISA GMC (µg/ml)** | | | | | | | |
| 10Pn-PD-DiT | 1.23 | 0.34 | 0.92 | 2.09 | 1.21 | 2.17 | 0.47 |
| Prevenar | 2.02 | 0.16 | 2.24 | 2.63 | 1.79 | 2.10 | 0.49 |
| Ratio (10Pn-PD-DiT/Prevenar) | **0.61** | **2.13** | **0.41** | **0.79** | **0.68** | **1.03** | **0.96** |
| **% ELISA >0.20 µg/ml** | | | | | | | |
| 10Pn-PD-DiT | 98.2 | 64.1 | 95.2 | 98.8 | 87.1 | 95.9 | 75.3 |
| Prevenar | 99.4 | 30.7 | 97.0 | 98.2 | 97.6 | 99.4 | 75.9 |
| **OPA GMT** | | | | | | | |
| 10Pn-PD-DiT | 239.1 | 94.2 | 675.4 | 385.9 | 22.4 | 65.8 | 860.4 |
| Prevenar | 241.6 | 22.8 | 658.4 | 432.2 | 22.8 | 19.3 | 556.6 |
| Ratio (10Pn-PD-DiT/Prevenar) | **0.99** | **4.13** | **1.03** | **0.89** | **0.98** | **3.41** | **1.55** |
| **% OPA >8** | | | | | | | |
| 10Pn-PD-DiT | 96.6 | 62.8 | 98.6 | 97.3 | 60.6 | 84.1 | 96.6 |
| Prevenar | 96.1 | 34.9 | 99.4 | 94.2 | 74.7 | 67.9 | 88.7 |

One month post-dose 3 at least 92.5% of the study subjects who received 10Pn-PD-DiT in both groups had antibody concentrations ≥ 0.20 µg/ml against each of the vaccine serotypes **except for serotype**

**6B** (87.3% or 88.6% in 2 out of the 4 groups). OPA titers ≥ 8 were observed for at least 90.4% of each of the serotypes **except serotypes 1** (50.3% to 54.3%), **5** (86.5% to 92.8%) and **6B** (81.8% to 87.8%).

One month after the third vaccine dose, all subjects vaccinated with 10Pn-PD-DiT except one in the Pn-HibC group had measurable concentrations of antibodies against protein D (≥ 100 ELU/ml).

**STUDY 10PN-PD-DIT-046 (Slovakia and Sweden)**

**Design**
Experimental design: phase III, open, controlled, multi-centre, long-term follow-up study of study 002 with three parallel groups:

- **10Pn-2d group**: subjects previously vaccinated with the 10Pn-PD-DiT vaccine according to a 2+1 schedule, receiving one dose of 10Pn-PD-DiT.
- **10Pn-3d group**: subjects previously vaccinated with the 10Pn-PD-DiT vaccine according to a 3+1 schedule, receiving one dose of 10Pn-PD-DiT.
- **Unprimed group**: age-matched* subjects not previously vaccinated with any pneumococcal vaccine receiving two doses of 10Pn-PD-DiT.

*Age-matching was ensured by the enrolment of subjects 36-46 months of age. In order to ensure the appropriate treatment allocation ratio, the investigator was instructed to enrol one subject in the unprimed group for each subject enrolled in the 10Pn-2d group.

Each subject was being offered vaccination against hepatitis A and/or hepatitis B or against chickenpox.

**Blood samples**

For serology
• before vaccination (Day 0) and 7-10 days following the Day 0 vaccination in all groups
• one month after the second vaccination in the unprimed group

For memory B-cell quantification (serotypes 6B, 18C, 19F and 23F), in all groups
• before vaccination (Day 0)
• 7-10 days following the Day 0 vaccination

**Study objectives**
*Primary objectives:*

- To assess the immune responses following vaccination with a booster dose of the 10Pn-PD-DiT vaccine administered at 36-46 months (i.e. 24 to 34 months after the last dose given in study 002) of age in children previously vaccinated with the 10Pn-PD-DiT vaccine in study 002 according to either a 3-dose or 2-dose primary vaccination within the first 6 months of age and booster vaccination at 11 months of age and to assess the immune responses following vaccination with a single dose of 10Pn-PD-DiT in age-matched unprimed children.

*Secondary objectives:*

- To assess the antibody persistence 24-34 months following vaccination in study 002 with the 10Pn-PD-DiT vaccine according to either a 3-dose or 2-dose primary vaccination within the first 6 months of age and booster vaccination at 11 months of age.

- To evaluate the safety, reactogenicity and immunogenicity of the 10Pn-PD-DiT vaccine when given as a 2-dose vaccination course to unprimed children in their 4th year of life.

- To assess the safety and reactogenicity of a booster dose of the 10Pn-PD-DiT vaccine administered at 36-46 months of age in children previously vaccinated with the 10Pn-PD-DiT vaccine in study 002 according to either a 3-dose or 2-dose primary vaccination within the first 6 months of age and booster vaccination at 11 months of age

**Additional inclusion/exclusion criteria specific to study 046**

*Inclusion:*

- Male or female between, and including, ± 36-46 months of age at the time of vaccination.
- For primed subjects: having completed the full vaccination course with the 10Pn-PD-DiT vaccine in study 002.

*Exclusion:*

- For primed subjects: administration of any pneumococcal vaccine since the end of study 002.
- For unprimed subjects: previous vaccination with any pneumococcal vaccine.

**Study population**

The analysis was performed on the ATP cohort for analysis of immunogenicity and on the ATP cohort for analysis of antibody persistence, according to the objective.

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, *i.e*. the subjects for whom assay results were available for antibodies against at least one vaccine serotype or protein D after vaccination.

The ATP cohort for analysis of antibody persistence, 2-3 years after study 002, comprised all subjects included in the ATP cohort for analysis of safety for whom assay results were available for at least one vaccine serotype or protein D before the administration of the additional dose of 10Pn-PD-DiT.

**Criteria for evaluation**

***Immunogenicity*:**

- Antibody concentrations against serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (22F-ELISA), prior to, 7-10 days post-dose 1 and one month post-dose *2* (unprimed group only*).*
- Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, prior to, 7-10 days post-dose 1 and one month post-dose 2 (unprimed group only).
- Antibody concentrations and opsonophagocytic activity (OPA) against cross-reactive pneumococcal serotypes 6A and 19A, prior to, 7-10 days post-dose 1and one month post-dose 2 (unprimed group only).
- Antibody concentrations against protein D (ELISA), prior to, 7-10 days post-dose 1and one month post-dose 2 (unprimed group only).
- Quantification of memory B-cells that produce antibodies against vaccine pneumococcal serotypes 6B, 18C, 19F and 23F (ELISPOT assay), prior to, and 7-10 days post-dose 1.

***Safety/Reactogenicity:***

- Occurrence of solicited local and general (any and grade 3) adverse event within 4 days after each vaccination.
- Occurrence of unsolicited adverse events within 31 days after each vaccination.
- Occurrence of serious adverse events after vaccination throughout the entire study period.

**Statistical methods**

***Sample size***

The sample size of the 10Pn-2d and 10Pn-3d groups was contingent on the number of subjects who received a full vaccination course with the 10Pn-PD-DiT vaccine in study 002. Slovakian and Swedish study centres were to participate in the current study, and 142 subjects received a full vaccination course in these 2 countries (70 in the 10Pn-2d group and 72 in the 10Pn-3d group). Assuming that around 40% of these subjects would not enter the long-term follow-up study, it was considered that ~85 subjects would receive an additional dose of the 10Pn-PD-DiT vaccine in the present study at 36 to 46 months of age (~42 subjects in the 10Pn-2d group and 43 in the 10Pn-3d group).

Considering that ~85 subjects would be enrolled in the primed groups and 42 subjects would be enrolled in the unprimed group of the current study and considering that up to 10% of the subjects may be excluded from the ATP cohort for analysis of immunogenicity, there would be ~115 evaluable subjects in the current study (~38 subjects in the 10Pn-2d primed group, 39 subjects in the 10Pn-3d primed group and 38 subjects in the unprimed group).

***Statistical analyses***

*Demography:* descriptive analyses were performed.

*Immunogenicity:* descriptive and exploratory inferential analyses were performed:

- Geometric mean antibody concentrations/Geometric mean titres (GMCs/GMTs) and seropositivity rates, were calculated with their 95% CI at each applicable blood sampling time point, for each group, for each serotype (vaccine and cross-reactive) and for protein D.
- The distribution of antibody concentrations/titres was displayed using reverse cumulative distribution curves.
- Descriptive analyses on B-cell memory quantification was performed for each group, at Day 0 and at Day 7-10 post vaccination, and was expressed as frequency of polysaccharide specific memory B-cells.
- The geometric mean of the ratio's (GMR) of OPA titres/ELISA antibody concentrations with the 95% CIs, was tabulated at each applicable blood sampling time point, for each group, for each pneumococcal serotype (vaccine and cross-reactive).

*Safety and reactogenicity:* descriptive analyses were performed (see safety section).

**RESULTS**

***Subject accounting***

A total 172 subjects were enrolled, 110 subjects in the primed groups and 62 children in the unprimed group (Table 3). Of the 171 subjects who completed the study, one subject from the 3+1 group withdrew from the study due to the parents' withdrawal of consent at visit 1.

A total of 167 subjects (97.1%) met the eligibility criteria for inclusion in the ATP cohort for immunogenicity

**Table 3: Number of subjects in study 046**

| Number of subjects: | Total | 10Pn-2d | 10Pn-3d | Unprim |
|---|---|---|---|---|
| Number of subjects planned | 210 | 70 | 70 | 70 |
| Number of subjects enrolled | 172 | 51 | 59 | 62 |
| Number of subjects completed | 171 | 51 | 58 | 62 |
| Total vaccinated cohort | 172 | 51 | 59 | 62 |
| According to Protocol (ATP) cohort for safety / persistence | 172 | 51 | 59 | 62 |
| According to Protocol (ATP) cohort for immunogenicity | 167 | 50 | 57 | 60 |

Among the 241 subjects from study 10PN-PD-DIT-002 who did not participate in this long term follow-up study (124 in the 10Pn-2d group and 117 in the 10Pn-3d group), 208 belonged to centres not willing to participate to the current study, 2 were not eligible, 9 were lost to follow-up and 22 subjects did not want to participate.

***Demographic characteristics***

The mean age at the time of vaccination was 38.8 months (SD ± 2.35 months) and ranged from 36 to 45 months. Between 49.7% and 53.3% of the subjects were males and 95% and 100% of the subjects were White-Caucasians (Table 4).

**Table 4: Demographic characteristics (ATP cohort for immunogenicity)**

| | 2+1 N=50 | | 3+1 N=57 | | Unprimed N=60 | |
|---|---|---|---|---|---|---|
| **Characteristics** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| ***Age*** | | | | | | |
| Mean | 38.1 | - | 38.0 | - | 40.3 | |
| SD | 1.83 | | 1.81 | | 2.56 | |
| Median | 37.5 | - | 38.0 | - | 40.0 | - |
| ***Gender*** | | | | | | |
| Female | 24 | 48.0 | 23 | 40.4 | 31 | 51.7 |
| Male | 34 | 52.0 | 34 | 59.6 | 29 | 48.3 |
| ***Race*** | | | | | | |
| White-Caucasian | 49 | 98.0 | 57 | 100 | 57 | 95.0 |
| Other | 1 | 2.0 | 0 | 0 | 3 | 5 |

***Antibody persistence prior to challenge vaccine dose in the 4th year of life***

ELISA: Persistence of the immune response to the vaccine antigens 24-34 months after completion of the 2-dose or 3-dose primary vaccination course was observed, with at least 60% of subjects had antibody concentrations ≥ 0.20 μg/ml, **except for serotypes 1, 4 and 9V** (24.5%-52.9%) in the 2+1 group and for **serotypes 1 and 4** in the 3+1 group (39.3%-50.8%). Overall, the percentage of subjects with antibody concentrations ≥0.20 μg/ml were higher in the 3+1 group. At least 96.0% of subjects in the 2+1 group had measurable antibody concentrations (≥ 0.05 μg/ml), except for serotypes 1 (86.0%), 4 (83.7%), 6B (89.8%) and 23F (88.0%) in the 2+1 group and was at least 96.6% in the 3+1 group for each vaccine serotype.

Higher antibody GMCs was observed in the 3+1 group as compared with the 2+1 group for all serotypes, except for 19F.

OPA: The percentage of subjects in the 2+1 group with an OPA titre ≥8 24-34 months after vaccination in study 002 was at least 95.2% for serotypes 7F, 9V and 14, at least 66.7% for serotypes 19F and 23F and ranged from 12.5% to 48.8% for serotypes 1, 4, 5, 6B and 18C in the 2+1 group. In the 3+1 group, the corresponding percentages were at least 98.1% for serotypes 7F, 9V and 14, at least 67.3% for serotypes 6B, 19F and 23F and ranged from 21.4% to 38.2% for serotypes 1, 4, 5 and 18C. At the pre-booster time point, a decline in OPA GMTs was observed for all vaccine serotypes, especially for serotypes 1, 4, 5, 6B and 18C in the primary 2-dose group and for serotypes 1, 4, 5 and 18C in the primary 3-dose group.

Higher OPA GMTs was observed in the 3+1 group compared to the 2+1 group for all serotypes except for serotype 4, 7F, 9V and 23F.

Although there was a trend towards lower antibody levels and functional immune responses for most serotypes at this time point in the 2+1 primed children compared to 3+1 primed children, waning of immunity occurred at similar pace for both groups.

Serotype 6A and 19A: A decline of ELISA GMCs was observed in both groups 24-34 months after vaccination. The percentages of subjects with ELISA concentrations ≥ 0.20 µg/ml were 46.9% (6A) and 54.0% (19A) in the 2+1 group and 68.4% (6A) and 50.8% (19A) in the 3+1 group. At least 86.4% remained seropositive ≥ 0.05 µg /ml for each serotype and with both schedules. The percentage of children with OPA titers ≥ 8 in the 2+1 group was 58.5% (6A) and 28.3% (19A) and in the 3+1 group was 64.6% (6A) and 25.0% (19A) . The OPA GMTs for serotype 6A were somewhat lower in the 2-dose group. As regards 19A, GMTs were similarly low in both groups.

Anti-PD: The percentage of subjects with anti-PD concentrations ≥100 EL.U/ml observed 24-34 months after booster vaccination was 82.4% in the 2+1 group and 96.6% in the 3+1 group. The GMCs were higher in the 3+1 group.

Before additional vaccination, for each of the vaccine serotypes, the observed percentages of seropositive subjects and ELISA GMCs in the primed groups were higher than in the age-matched unprimed group prior to catch-up vaccination. This observation was less pronounced for OPA titres but also for some of the serotypes, the observed percentages of subjects with OPA titre ≥8 and/or OPA GMTs were higher in the primed groups prior to additional vaccination than those in the age-matched unprimed group prior to catch-up vaccination.

➢ ***Evaluation of immunological memory following challenge vaccine dose in the 4th year of life***

ELISA: The percentage of subjects with antibody concentrations ≥ 0.20 µg/ml, 7-10 days after the challenge dose was comparable in both schedule groups (at least 98.0% in the 2+1 group and 100% in the 3+1 group) (Table 5). In the unprimed group, the percentage of children with antibody concentration ≥ 0.20 µg/ml were lower and ranged from 26.7% to 100%, depending on the serotype.

**Table 5: Difference between 2 and 3-dose primary groups in percentage of subjects with ELISA antibody levels ≥0.20 µg/ml in study 002 and study 046** (ATP cohort for immunogenicity)

| STUDY 002 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 10PN_2d group | | 10PN_3d group | | Difference in % >0.2µg/ml (10Pn_3d - 10PN_2d) | | |
| **Antibody** | **N** | **%** | **N** | **%** | **%** | **95% CI** | |
| **Post-primary** | | | | | | | |
| Anti-1 | 153 | 97.4 | 151 | 98.7 | 1.29 | -2.39 | 5.37 |
| Anti-4 | 153 | 98.0 | 153 | 99.3 | 1.31 | -1.83 | 5.03 |
| Anti-5 | 152 | 96.1 | 149 | 100 | 3.95 | 1.39 | 8.34 |
| **Anti-6B** | **149** | **55.7** | **149** | **63.1** | **7.38** | **-3.76** | **18.35** |
| Anti-7F | 153 | 96.7 | 152 | 99.3 | 2,61 | -0.70 | 6.85 |
| Anti-9V | 152 | 93.4 | 153 | 99.3 | 5.93 | 2.14 | 11.12 |
| Anti-14 | 152 | 96.1 | 152 | 100 | 3.95 | 1.43 | 8.34 |
| Anti-18C | 152 | 96.1 | 153 | 99.3 | 3.29 | -0.09 | 7.77 |
| Anti-19F | 152 | 92.8 | 152 | 96.1 | 3.29 | -2.05 | 9.04 |
| **Anti-23F** | **153** | **69.3** | **152** | **77.6** | **8.35** | **-1.57** | **18.17** |
| **Post-booster** | | | | | | | |
| Anti-1 | 156 | 99.4 | 147 | 100 | 0.64 | -1.91 | 3.54 |
| Anti-4 | 155 | 100 | 147 | 100 | 0.00 | -2.55 | 2.42 |
| Anti-5 | 155 | 100 | 147 | 100 | 0.00 | -2.55 | 2.42 |
| **Anti-6B** | **156** | **88.5** | **147** | **96.6** | **8.14** | **2.37** | **14.53** |
| Anti-7F | 156 | 100 | 147 | 100 | 0.00 | -2.55 | 2.40 |
| Anti-9V | 156 | 99.4 | 147 | 100 | 0.64 | -1.91 | 3.54 |
| Anti-14 | 156 | 99.4 | 147 | 98.6 | -0.72 | -4.25 | 2.31 |
| Anti-18C | 156 | 100 | 147 | 99.3 | 0.68 | -3.75 | 1.73 |
| Anti-19F | 156 | 96.2 | 147 | 98.0 | 1.81 | -2.45 | 6.37 |
| **Anti-23F** | **153** | **96.1** | **147** | **95.9** | **-0.19** | **-5.21** | **4.70** |
| **STUDY 046** | | | | | | | |
| | 10PN_2d group | | 10PN_3d group | | Unprimed group | | |
| **Antibody** | **N** | **%** | **N** | **%** | **N** | **%** | |
| **Pre-additional dose** | | | | | | | |
| Anti-1 | 49 | 32.7 | 57 | 49.1 | 60 | 16.7 | - |
| Anti-4 | 48 | 25.0 | 54 | 37.0 | 60 | 6.7 | |
| Anti-5 | 50 | 62.0 | 57 | 61.4 | 60 | 15.0 | |
| **Anti-6B** | **48** | **60.4** | **57** | **77.2** | **60** | **31.7** | |
| Anti-7F | 49 | 75.5 | 56 | 94.6 | 60 | 18.3 | |
| Anti-9V | 50 | 54.0 | 57 | 78.9 | 60 | 11.7 | |
| Anti-14 | 50 | 74.0 | 56 | 87.5 | 60 | 45.0 | |
| Anti-18C | 50 | 70.0 | 56 | 78.6 | 60 | 13.3 | |
| Anti-19F | 47 | 83.0 | 56 | 83.9 | 60 | 48.3 | |
| **Anti-23F** | **49** | **59.2** | **56** | **64.3** | **60** | **18.3** | |
| **Post-additional dose** | | | | | | | |
| Anti-1 | 50 | 100 | 55 | 100 | 60 | 90.0 | |
| Anti-4 | 49 | 100 | 55 | 100 | 60 | 100 | |
| Anti-5 | 50 | 100 | 55 | 100 | 60 | 78.3 | |
| **Anti-6B** | **50** | **98.0** | **55** | **100** | **58** | **50.0** | |
| Anti-7F | 50 | 100 | 55 | 100 | 60 | 90.0 | |
| Anti-9V | 50 | 100 | 55 | 100 | 60 | 66.7 | |
| Anti-14 | 50 | 100 | 55 | 100 | 60 | 70.0 | |
| Anti-18C | 50 | 100 | 55 | 100 | 59 | 94.9 | |
| Anti-19F | 50 | 100 | 55 | 100 | 59 | 96.6 | |
| **Anti-23F** | **50** | **98.0** | **55** | **100** | **60** | **26.7** | |

A single dose of 10Pn-PD-DiT given during the 4th year of life, as a challenge dose, elicited higher ELISA GMCs 7-10 days following vaccination in 2-dose primed subjects (ranging from 4.00 to 20.28 µg/ml) and 3-dose primed subjects (ranging from 4.72 to 30.55 µg/ml) compared to unprimed subjects (ranging from 0.10 to 2.37 µg/ml) (Table 6).

**Table 6: ELISA GMCs pre and post challenge dose of 10Pn-PD-DiT vaccine during the 4th year of life (Study 046)** (ATP cohort for immunogenicity)

| Serotype | GMC | | |
|---|---|---|---|
| | **10PN_2d group Value (95% CI)** | **10PN_3d group Value (95% CI)** | **Unprimed group Value (95% CI)** |
| **Pre-additional dose** | | | |
| Anti-1 | 0.13 (0.10, 0.17) | 0.17 (0.14, 0.22) | 0-06 (0.05, 0.08) |
| Anti-4 | 0.15 (0.10, 0.23) | 0.19 (0.14, 0.25) | 0.04 (0.03, 0.05) |
| Anti-5 | 0.24 (0.19, 0.31) | 0.33 (0.26, 0.42) | 0.07 (0.05, 0.09) |
| **Anti-6B** | **0.50 (0.29, 0.88)** | **1.01 (0.62, 1.64)** | **0.10 (0.07, 0.13)** |
| Anti-7F | 0.33 (0.24, 0.46) | **0.51** (0.42, 0.61) | 0.08 (0.05, 0.12) |
| Anti-9V | 0.24 (0.18, 0.33) | 0.49 (0.34, 0.69) | 0.05 (0.04, 0.07) |
| Anti-14 | 0.62 (0.39, 0.97) | **1.10** (0.69, 1.75) | 0.25 (0.16, 0.38) |
| Anti-18C | 0.37 (0.26, 0.54) | 0.49 (0.35, 0.70) | 0.06 (0.04, 0.08) |
| Anti-19F | 1.42 (0.80, 2.51) | 1.44 (0.82, 2.53) | 0.23 (0.14, 0.38) |
| **Anti-23F** | **0.41 (0.23, 0.71)** | **0.67 (0.41, 1.11)** | **0.06 (0.04, 0.08)** |
| **Post-additional dose** | | | |
| Anti-1 | 4.06 (3.20, 5.15) | 4.72 (3.77, 5.92) | 0.60 (2.25, 3.51) |
| Anti-4 | 7.54 (5.98, 9.50 | **9.97** (7,68, 12.95) | 2.37 (1.91, 2.94) |
| Anti-5 | 5.38 (4.09, 7.08) | **7.07** (5.51, 9.09) | 0.45 (0.34, 0.59) |
| **Anti-6B** | **4.00 (2.82, 5.69)** | **6.33 (4.75, 8.45)** | **0.20 (0.14, 0.29)** |
| Anti-7F | 6.18 (5.05, 7.56) | **7,27** (5.87, 9.01) | 0.92 (0.67, 1.25) |
| Anti-9V | 7.48 (5.88, 9.51) | **10.17** (7.86, 13.16) | 0.33 (0.23, 0.48) |
| Anti-14 | 13.42 (9.70, 18.55) | **19.67** (14.97, 25.84) | 0.54 (0.34, 0.86) |
| Anti-18C | 17.12 (12.77, 22.94) | **22.62** (17.58, 29.11) | 1.45 (1.01, 2.06) |
| Anti-19F | 20.28 (15.71, 26.19) | **30.55** (24.32, 38.7) | 1.82 (1.27, 2.60) |
| **Anti-23F** | **6.23 (4.34, 8.94)** | **8.42 (6.38, 11.11)** | **0.10 (0.07, 0.15)** |

Marked increases in ELISA GMCs were observed after the challenge dose compared to pre-vaccination time point. The fold increase in ELISA GMCs pre to post vaccination was similar after 2-dose and 3-dose vaccination. The ELISA GMCs of subjects vaccinated with a 2+1 or 3+1 schedule were higher than unprimed subjects for all vaccination serotypes demonstrating the induction of immune memory.

OPA: The OPA responses after the challenge dose are shown in Table 7.

**Table 7: Percentage of subjects with OPA titre ≥8 and OPA GMTs pre and post challenge dose of 10Pn-PD-DiT vaccine during the 4th year of life (Study 046)** (ATP cohort for immunogenicity)

| Serotype | % Subjects OPA titre ≥8 | | | OPA GMT | | |
|---|---|---|---|---|---|---|
| | 2+1 | 3+1 | Unprimed | 2+1 | 3+1 | Unprimed |
| **Pre-additional dose** | | | | | | |
| **1** | 12.8 | 20.0 | 0.0 | 5.5 | 6.2 | 4.0 |
| 4 | 15.9 | 23.1 | 5.2 | 9.6 | 9.5 | 5.1 |
| **5** | 31.9 | 37.0 | 1.7 | 6.7 | 8.0 | 4.1 |
| 6B | 47.6 | **66.7** | 32,7 | 61.5 | **126.3** | 21.6 |
| 7F | 95.6 | 100 | 87.3 | 1329.1 | 1225.5 | 644.2 |
| 9V | 97.7 | 98.1 | 67.3 | 307.4 | 292.3 | 103.1 |
| 14 | 95.1 | 100 | 83.0 | 421.5 | **738.6** | 252.5 |
| 18C | 26.7 | 37.0 | 8.3 | 11.0 | 17.7 | 6.1 |
| 19F | 66.0 | 70.9 | 22.0 | 34.1 | 48.4 | 8.4 |
| 23F | 74.4 | 77.6 | 71.2 | 485.5 | 465.6 | 265.3 |
| **Post-additional dose** | | | | | | |
| **1** | 100 | 100 | 100 | 2342.2 | 2321.5 | 441.1 |
| 4 | 100 | 100 | 100 | 13247.5 | **17732.6** | 9675.9 |
| **5** | 100 | 100 | **94.7** | 991.5 | **1221.1** | 330.0 |
| 6B | **95.7** | **94.4** | **77,8** | 3312.9 | 3136.0 | 438.2 |
| 7F | 100 | 100 | 100 | 20779.0 | 22461.4 | 11048.4 |
| 9V | 100 | 100 | 100 | 21193.6 | 19038.4 | 12217.8 |
| 14 | 100 | 100 | 100 | 14310.0 | 14670.9 | 3948.7 |
| 18C | 100 | 100 | **98.2** | 6095.8 | 6448.7 | 3905.6 |
| 19F | **97.9** | 100 | **89.5** | 2231.5 | **5684.4** | 367.5 |
| 23F | 100 | 100 | 100 | **15688.3** | 13812.6 | 5059.0 |

The percentage of subjects with OPA titre ≥ 8, 7 to 10 days after the challenge dose in the primed groups was 100% for each serotype **except for serotypes 6B** (94.4% in the 3+1 group and 95.7% in the 2+1 group) and **19F** (97.9% in the 2+1 group) (Table 7).

In the unprimed group, 7-10 days after the first vaccination, the observed percentage of subjects with an OPA titre ≥ 8, was at least 94.7% for each serotype, except for serotype 6B (77.8%) and serotype 19F (89.5%).

Marked increases of OPA GMTs were seen after the challenge dose compared to pre-vaccination time point were higher than unprimed subjects for all vaccination serotypes demonstrating the induction of immune memory. The fold increase in OPA GMTs was similar in both vaccination schedules.

Serotypes 6A and 19A: For the cross-reactive serotypes 6A and 19A, a robust anamnestic response indicative of immune memory was also demonstrated for both schedules. The percentage of subjects with antibody concentrations ≥ 0.20 µg/ml, 7-10 days after the challenge dose was 88.0% (6A) and 94% (19A) in the 2+1 group and 92.7% (6A) and 98.2% (19A) in the 3+1 group. Higher ELISA GMCs against serotype 6A were observed in both 2+1 and 3+1 groups compared to the unprimed group (4-fold vs.1.4 fold increase). Similarly for serotype 19A, higher GMCs were observed in the 2-dose and the 3-dose primed subjects (14-fold and 19-fold increase, respectively) compared to unprimed subjects (2.5-fold increase).

The percentage of subjects with OPA titres ≥8 7-10 days after the challenge dose was 97.8% (6A) and 85.4% (19A) in the 2+1 group and 96% (6A) and 92.7% (19A) in the 3+1 group (Table 8). The corresponding percentages in the unprimed group were 86.5% and 81.8 % 7 days after the first dose. OPA GMTs against serotypes 6A and 19A were significantly higher than those in the unprimed children.

Protein D: All subjects in the 2+1 group and 3+1 group had measurable antibodies against protein D (> 100 EL.U/ml). In the unprimed group, 93.3% reached anti-PD ≥ 100 EL.U/ml (Table 9).

**Table 8: Seropositivity rates and GMTs for OPSONO-6A and OPSONO-19A (ATP cohort for immunogenicity)**

| | | | | ≥8 | | | | GMT | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| Antibody | Group | Timing | N | n | % | LL | UL | value | LL | UL |
| OPSONO-6A | 10Pn-2d | PIII(M10) | 35 | 20 | 57.1 | 39.4 | 73.7 | 60.9 | 25.9 | 143.1 |
| | | PIII(M34) | 40 | 23 | 57.5 | 40.9 | 73.0 | 64.3 | 27.1 | 152.7 |
| | | PIV(M34+7) | 45 | 44 | 97.8 | 88.2 | 99.9 | 1639.4 | 958.6 | 2803.9 |
| | 10Pn-3d | PIV(M10) | 44 | 32 | 72.7 | 57.2 | 85.0 | 135.0 | 68.3 | 267.0 |
| | | PIV(M34) | 47 | 30 | 63.8 | 48.5 | 77.3 | 81.5 | 39.7 | 167.5 |
| | | PV(M34+7) | 50 | 48 | 96.0 | 86.3 | 99.5 | 1267.3 | 713.8 | 2250.0 |
| | Unprim | PRE | 50 | 25 | 50.0 | 35.5 | 64.5 | 36.3 | 18.9 | 69.6 |
| | | PI(D7) | 52 | 45 | 86.5 | 74.2 | 94.4 | 389.6 | 215.2 | 705.5 |
| | | PII(M3) | 52 | 50 | 96.2 | 86.8 | 99.5 | 715.2 | 487.3 | 1049.6 |
| OPSONO-19A | 10Pn-2d | PIII(M10) | 36 | 13 | 36.1 | 20.8 | 53.8 | 14.4 | 7.6 | 27.3 |
| | | PIII(M34) | 45 | 12 | 26.7 | 14.6 | 41.9 | 8.0 | 5.2 | 12.2 |
| | | PIV(M34+7) | 48 | 41 | 85.4 | 72.2 | 93.9 | 799.3 | 372.8 | 1713.4 |
| | 10Pn-3d | PIV(M10) | 46 | 25 | 54.3 | 39.0 | 69.1 | 35.9 | 18.0 | 71.6 |
| | | PIV(M34) | 55 | 14 | 25.5 | 14.7 | 39.0 | 8.6 | 5.6 | 13.4 |
| | | PV(M34+7) | 55 | 51 | 92.7 | 82.4 | 98.0 | 1871.6 | 975.8 | 3589.8 |
| | Unprim | PRE | 58 | 7 | 12.1 | 5.0 | 23.3 | 5.4 | 4.2 | 6.9 |
| | | PI(D7) | 55 | 45 | 81.8 | 69.1 | 90.9 | 211.9 | 99.9 | 449.7 |
| | | PII(M3) | 53 | 50 | 94.3 | 84.3 | 98.8 | 406.4 | 227.3 | 726.9 |

**Table 9: Seropositivity rates and GMCs for ANTI-PD antibodies (ATP cohort for immunogenicity)**

| | | | | ≥100 EL.U/mL | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| Antibody | Group | Timing | N | n | % | LL | UL | value | LL | UL |
| ANTI-PD | 10Pn-2d | PIII(M10) | 48 | 47 | 97.9 | 88.9 | 99.9 | 1438.0 | 1018.9 | 2029.4 |
| | | PIII(M34) | 50 | 42 | 84.0 | 70.9 | 92.8 | 301.6 | 219.5 | 414.3 |
| | | PIV(M34+7) | 50 | 50 | 100 | 92.9 | 100 | 1724.1 | 1299.4 | 2287.5 |
| | 10Pn-3d | PIV(M10) | 56 | 56 | 100 | 93.6 | 100 | 2241.3 | 1752.5 | 2866.3 |
| | | PIV(M34) | 57 | 55 | 96.5 | 87.9 | 99.6 | 461.3 | 351.1 | 606.0 |
| | | PV(M34+7) | 55 | 55 | 100 | 93.5 | 100 | 2113.2 | 1651.2 | 2704.5 |
| | Unprim | PRE | 60 | 32 | 53.3 | 40.0 | 66.3 | 110.9 | 88.8 | 138.6 |
| | | PI(D7) | 60 | 56 | 93.3 | 83.8 | 98.2 | 536.3 | 390.7 | 736.2 |
| | | PII(M3) | 60 | 59 | 98.3 | 91.1 | 100 | 960.4 | 752.7 | 1225.5 |

***Immune responses following 2-dose catch-up vaccination with the pneumococcal conjugate vaccine during the 4th year of life (unprimed group)***

Robust increases in ELISA antibody GMCs and OPA GMTs were observed one month after the second dose of vaccine as compared to the pre-vaccination status. All subjects had vaccine pneumococcal antibody concentrations ≥ 0.20 µg/ml for each vaccine serotype **except for serotypes 6B and 23F** (93.3%).

One month after the second dose of vaccine, all subjects had an OPA titre ≥8 for each vaccine serotype **except for serotypes 1** (89.3%), **5** (98.2%) and **6B** (93.0%).

One month after the second dose of vaccine, the observed percentage of subjects with measurable anti-PD antibody concentrations (≥100 EL.U/ml) was 98.3% and the anti-PD GMC was 960.4 EL.U/ml.

Like PCV7 and PCV13, Synflorix was initially registered with a 3+1 schedule for all children aged 6 weeks to 6 months, regardless of the presence of underlying medical conditions such as HIV infection, sickle cell disease, asplenia or chronic disease. There is currently no data in the literature to conclude that PCV effectiveness will be inferior in such high risk populations vaccinated with the 2+1 schedule as compared to the 3+1 schedule. Only limited data have demonstrated that 3-dose primary series induced an acceptable immune response in infants with sickle cell disease vaccinated with PCV7 (Reinert et al PIDJ, 2007). HIV-infected children benefiting from a substantial immune response boostability and anamnestic response after a 3-dose primary course of PCV9 showed substantial protection against IPD (Madhi et al JID, 2009). In addition, the MAH has recently submitted data demonstrating that Synflorix elicits generally robust immune responses in preterm infants after 3+1 schedule when compared to full term infants. Based on these data, the Company has proposed the inclusion for a recommendation of the 3+1 schedule in preterm infants to ensure maximal individual protection, in a separate ongoing type II variation (EMEA/H/C/973/II/16). The currently available data in study 046 show strong immune priming, similar following both 2+1 and 3+1 schedules, and boostability even years after the primary series, supporting the use of the 2+1 schedule in the context of universal mass vaccination. Therefore, in the context of universal mass vaccination programmes, in which herd immunity may also play a role in protecting individuals who are not vaccinated or those with a lower immune response, the Company believes the data to date support the use of the 2+1 schedule with the decision to vaccinate high-risk groups left at the discretion of the national health authorities.

There are also some important practical considerations in favour of making no distinction between high risk and other populations on this issue. Some countries recommend the use of the 2+1 vaccination schedule in children regardless of whether they are high-risk group or not. For instance, high-risk groups in the UK should be given PCV according to the schedule for the routine immunisation

programme at 2, 4 and 13 months of age (Green Book, 2010). In South Africa, in order for HIV-infected children to derive the most benefit from a 3-dose schedule and to fit with the current EPI, the third dose is given at 9 months of age following a 6 and 14 weeks primary vaccination course (Baker L, 2010). More national authorities are considering to include high-risk groups in their routine immunization programmes using the 3-dose schedule as it is already the current practice in the UK and South Africa. In addition, it seems likely that GAVI countries introducing PCV vaccines will largely do so using a 2+1 schedule, without separate specific immunization recommendations for the high risk groups. In the setting of universal mass vaccination (UMV), the herd protection related to the PCV vaccination coverage starts to play role regardless the schedule applied in the country, so it may have additional protective effect for children who are not vaccinated or immunocompromised for any reason. This may provide reassurance that proper protection is provided to all children in UMV settings.

### III.3.3 Clinical safety

***Overview of safety***

Safety data on 10Pn-PD-DiT administered according to a 2+1 schedule are derived from studies 002 and 046. The analyses of reactogenicity and safety were not performed in the post-hoc head-to-head analysis in study 011.

**Study 002**

No clinically relevant differences in the solicited reactogenicity profile were observed between the two vaccination schedules. During the primary vaccination course 27.8% of the doses in the 2-dose and 35,7% of the doses in the 3-dose priming group were followed by at least one unsolicited adverse event (AE). The corresponding frequencies following booster doses were 36.2% and 41%, respectively. A total of 15 subjects: 7 in the 2-dose priming group and 8 in the 3-dose priming group reported non-fatal serious adverse events (SAEs). In all 2 subjects, one in each group, were considered to be causally related to vaccination (i.e. lower respiratory infection and fever convulsions). All SAEs resolved without sequelae.

**Study 011**

The analyses of reactogenicity and safety were not performed in the *post hoc* analysis in study 011. From evaluation of safety and reactogenicity following 3-dose priming in the study 011 in the initial registration file of 10Pn-PD-DiT can be summarized:
The primary objective of this study was to demonstrate that the 10Pn-PD vaccine when administered as a 3-dose primary vaccination course is non-inferior to Prevenar, both co-administered with DTPa-HBV-IPV and Hib-MenC vaccines, in terms of post–immunisation febrile reactions with temperature > 39.0ºC (measured rectally).

A second objective was to assess the safety and reactogenicity of 10Pn-PD-DiT vaccine when co-administered with DTPa-combined and MenC or Hib-MenC vaccines.

***Solicited and unsolicited adverse events***

The overall/dose incidence of AEs (solicited and unsolicited) reported during the 31-day post vaccination period ranged between 82.9% (Pr-HibC group) and 86.0% (Pn-Men group).The most frequently reported solicited local and general AEs were *redness* and *irritability* in all four groups. A low overall/dose incidence of grade 3 solicited local and general AEs was observed, which did not exceed 3.1% and 4.6%, respectively.

Five cases of grade 3 *fever* (> 40ºC) were reported (2 in the Pn-Neis group, 1 in the PnHibC group and 2 in the Pr-HibC group) Antipyretic medication was administered within 4 days of vaccination following 14.0% to 19.2% of the vaccines across the 4 groups.
No fatal events were reported

***Safety conclusions***
The primary objective of the study was met because the upper limit of the 95%CI for the difference (PnHibC minus PrHibC) in terms of percentage of subjects with rectal temperature >39ºC after at least one vaccination dose was 3.32% and therefore below the pre-defined limit of 10%.
The incidence of reported AEs and SAEs in the groups where 10Pn-PD-DiT vaccine was co-administered with DTPa-combined and MenC or Hib-MenC vaccines did not show any significant difference.

**Study 046**

One challenge dose of 10Pn-PD-DiT was given to all subjects at approximately 36-42 months of age. This was the 4$^{th}$ dose to subjects primed with a 2+1 schedule and the 5$^{th}$ dose to subjects primed with a 3+1 schedule. In the unprimed group two 10Pn doses were administered during the 4$^{th}$ year of life.

The analysis of safety was performed on the Total vaccinated cohort (Table 10).

**Table 10: Number and percentage of subjects who received vaccine dose(s) (Total vaccinated cohort)**

| | 10Pn-2d N = 51 | | 10Pn-3d N = 59 | | Unprim N = 62 | | Total N = 172 | |
|---|---|---|---|---|---|---|---|---|
| Total number of doses received | n | % | n | % | n | % | n | % |
| 1 | 51 | 100 | 59 | 100 | 0 | 0.0 | 110 | 64.0 |
| 2 | 0 | 0.0 | 0 | 0.0 | 62 | 100 | 62 | 36.0 |

10Pn-2d= 10Pn-PD-DiT(2-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months) followed by an additional dose of 10Pn-PD-DiT
10Pn-3d= 10Pn-PD-DiT(2-3-4-11 months)+DTPa-(HBV)-IPV/Hib(2-4-11 months) followed by an additional dose of 10Pn-PD-DiT
Unprim = Unprimed / 2 doses of 10Pn-PD-DiT

**Overall incidence of adverse events**

The overall incidence of AEs (solicited and unsolicited), reported during the 31-day post-vaccination period, following each dose and overall is presented in Table 11 and Table 12, for the primed and the unprimed study groups respectively.

Primed groups:

During the 31-day post-vaccination period,

- 92.2% of subjects in the 10Pn-2d group and 89.8% of subjects in the 10Pn-3d group reported at least one AE.
- 29.4% of subjects in the 10Pn-2d group and 32.2% of subjects in the 10Pn-3d group reported at least one grade 3 AE.
- 92.2% of subjects in the 10Pn-2d group and 88.1% of subjects in the 10Pn-3d group reported at least one AE assessed by the investigator to be causally related to the vaccine administration.
- 13.7% of subjects in the 10Pn-2d group and 11.9% of subjects in the 10Pn-3d group reported at least one AE requiring a medical consultation.

Unprimed group:

- 85.5% of documented doses were followed by at least one AE.
- 23.4% of documented doses were followed by at least one grade 3 AE.
- 80.6% of documented doses were followed by at least one AE assessed by the investigator to be causally related to the vaccine administration.
- 17.7% of documented doses were followed by at least one AE requiring a medical consultation.

**Table 11: Incidence and nature of symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period – Primed groups (Total vaccinated cohort)**

| | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| 10Pn-2d | 51 | 47 | 92.2 | 81.1 | 97.8 | 51 | 35 | 68.6 | 54.1 | 80.9 | 51 | 45 | 88.2 | 76.1 | 95.6 |
| 10Pn-3d | 59 | 53 | 89.8 | 79.2 | 96.2 | 59 | 40 | 67.8 | 54.4 | 79.4 | 59 | 52 | 88.1 | 77.1 | 95.1 |

**Table 12: Incidence and nature of symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period – unprimed group (Total vaccinated cohort)**

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | Unprim | 62 | 55 | 88.7 | 78.1 | 95.3 | 62 | 39 | 62.9 | 49.7 | 74.8 | 62 | 52 | 83.9 | 72.3 | 92.0 |
| Dose 2 | Unprim | 62 | 51 | 82.3 | 70.5 | 90.8 | 62 | 27 | 43.5 | 31.0 | 56.7 | 62 | 45 | 72.6 | 59.8 | 83.1 |
| Overall/dose | Unprim | 124 | 106 | 85.5 | 78.0 | 91.2 | 124 | 66 | 53.2 | 44.1 | 62.2 | 124 | 97 | 78.2 | 69.9 | 85.1 |
| Overall/subject | Unprim | 62 | 58 | 93.5 | 84.3 | 98.2 | 62 | 45 | 72.6 | 59.8 | 83.1 | 62 | 55 | 88.7 | 78.1 | 95.3 |

**Solicited local adverse events**

The incidence of each solicited local adverse event reported during the 4-day post-vaccination period, following each dose, overall/dose and overall/subject is shown in Table 13 and Table 14 for the primed groups and the unprimed groups respective.

Primed groups:

- *Pain at injection site* was the most frequently reported solicited local AE in the primed groups (80.4% of subjects in the 10Pn-2d group and, 74.6% of subjects in the 10Pn-3d group).
- Grade 3 solicited local AEs were reported by a maximum of 17.6% of subjects in the 10Pn-2d group and 20.3% of subjects in the 10Pn-3d group.
- Large *swelling* reactions (> 50 mm) following vaccination were reported by 1 subject in the 10Pn-3d group. The lesion had a diameter of 60 mm and had resolved after 1 day.

Unprimed group:

- *Pain at injection site* was the most frequently reported solicited local adverse event (62.1%, overall/dose)
- The overall/dose incidence of grade 3 solicited local symptoms ranged from 4.8% to 13.7% in the unprimed group.

**Table 13: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period – Primed groups (Total vaccinated cohort)**

| | | 10Pn-2d | | | | | 10Pn-3d | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| Pain | All | 51 | 41 | 80.4 | 66.9 | 90.2 | 59 | 44 | 74.6 | 61.6 | 85.0 |
| | Grade 3 | 51 | 3 | 5.9 | 1.2 | 16.2 | 59 | 4 | 6.8 | 1.9 | 16.5 |
| | Medical advice | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| Redness (mm) | All | 51 | 34 | 66.7 | 52.1 | 79.2 | 59 | 35 | 59.3 | 45.7 | 71.9 |
| | >20.0 | 51 | 17 | 33.3 | 20.8 | 47.9 | 59 | 14 | 23.7 | 13.6 | 36.6 |
| | >30.0 | 51 | 9 | 17.6 | 8.4 | 30.9 | 59 | 12 | 20.3 | 11.0 | 32.8 |
| | Medical advice | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| Swelling (mm) | All | 51 | 28 | 54.9 | 40.3 | 68.9 | 59 | 27 | 45.8 | 32.7 | 59.2 |
| | >20.0 | 51 | 11 | 21.6 | 11.3 | 35.3 | 59 | 13 | 22.0 | 12.3 | 34.7 |
| | >30.0 | 51 | 5 | 9.8 | 3.3 | 21.4 | 59 | 9 | 15.3 | 7.2 | 27.0 |
| | Medical advice | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |

**Table 14: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall - Unprimed group (Total vaccinated cohort)**

| | | Unprim | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL |
| **Dose 1** | | | | | | |
| Pain | All | 62 | 45 | 72.6 | 59.8 | 83.1 |
| | Grade 3 | 62 | 5 | 8.1 | 2.7 | 17.8 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |
| Redness (mm) | All | 62 | 36 | 58.1 | 44.8 | 70.5 |
| | >20.0 | 62 | 14 | 22.6 | 12.9 | 35.0 |
| | >30.0 | 62 | 12 | 19.4 | 10.4 | 31.4 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |
| Swelling (mm) | All | 62 | 22 | 35.5 | 23.7 | 48.7 |
| | >20.0 | 62 | 11 | 17.7 | 9.2 | 29.5 |
| | >30.0 | 62 | 5 | 8.1 | 2.7 | 17.8 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |
| **Dose 2** | | | | | | |
| Pain | All | 62 | 32 | 51.6 | 38.6 | 64.5 |
| | Grade 3 | 62 | 1 | 1.6 | 0.0 | 8.7 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |
| Redness (mm) | All | 62 | 33 | 53.2 | 40.1 | 66.0 |
| | >20.0 | 62 | 8 | 12.9 | 5.7 | 23.9 |
| | >30.0 | 62 | 5 | 8.1 | 2.7 | 17.8 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |
| Swelling (mm) | All | 62 | 22 | 35.5 | 23.7 | 48.7 |
| | >20.0 | 62 | 6 | 9.7 | 3.6 | 19.9 |
| | >30.0 | 62 | 4 | 6.5 | 1.8 | 15.7 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |
| **Overall/dose** | | | | | | |
| Pain | All | 124 | 77 | 62.1 | 52.9 | 70.7 |
| | Grade 3 | 124 | 6 | 4.8 | 1.8 | 10.2 |
| | Medical advice | 124 | 0 | 0.0 | 0.0 | 2.9 |
| Redness (mm) | All | 124 | 69 | 55.6 | 46.5 | 64.6 |
| | >20.0 | 124 | 22 | 17.7 | 11.5 | 25.6 |
| | >30.0 | 124 | 17 | 13.7 | 8.2 | 21.0 |
| | Medical advice | 124 | 0 | 0.0 | 0.0 | 2.9 |
| Swelling (mm) | All | 124 | 44 | 35.5 | 27.1 | 44.6 |
| | >20.0 | 124 | 17 | 13.7 | 8.2 | 21.0 |
| | >30.0 | 124 | 9 | 7.3 | 3.4 | 13.3 |
| | Medical advice | 124 | 0 | 0.0 | 0.0 | 2.9 |
| **Overall/subject** | | | | | | |
| Pain | All | 62 | 49 | 79.0 | 66.8 | 88.3 |
| | Grade 3 | 62 | 6 | 9.7 | 3.6 | 19.9 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |
| Redness (mm) | All | 62 | 41 | 66.1 | 53.0 | 77.7 |
| | >20.0 | 62 | 19 | 30.6 | 19.6 | 43.7 |
| | >30.0 | 62 | 15 | 24.2 | 14.2 | 36.7 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |
| Swelling (mm) | All | 62 | 30 | 48.4 | 35.5 | 61.4 |
| | >20.0 | 62 | 15 | 24.2 | 14.2 | 36.7 |
| | >30.0 | 62 | 9 | 14.5 | 6.9 | 25.8 |
| | Medical advice | 62 | 0 | 0.0 | 0.0 | 5.8 |

Unprim = Unprimed / 2 doses of 10Pn-PD-DiT

**Solicited systemic adverse events**

The incidence of solicited general AEs reported during the 4-day post-vaccination period, following each dose, overall/dose and overall/subject is shown in Table 15 for the primed groups.

Primed groups:

- The most frequently reported solicited general adverse events were *irritability* and *drowsiness* (both 39.2%) in the 10Pn-2d group and irritability in the 10Pn-3d group (45.8%).
- None of the subjects reported *fever* > 40°C or any other grade 3 solicited AE subsequently to vaccination.

Unprimed group:

- *Irritability* was the most frequently reported solicited general adverse event.
- None of the subjects reported *fever* > 40°C or any other grade 3 solicited general AEs.

**Table 15: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period – Primed groups (Total vaccinated cohort)**

| | | 10Pn-2d | | | | | 10Pn-3d | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| Drowsiness | All | 51 | 20 | 39.2 | 25.8 | 53.9 | 59 | 23 | 39.0 | 26.5 | 52.6 |
| | Grade 3 | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| | Related | 51 | 20 | 39.2 | 25.8 | 53.9 | 59 | 23 | 39.0 | 26.5 | 52.6 |
| | Grade 3*Related | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| | Medical advice | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| Fever(Rectal) (°C) | All | 51 | 9 | 17.6 | 8.4 | 30.9 | 59 | 5 | 8.5 | 2.8 | 18.7 |
| | >38.5 | 51 | 4 | 7.8 | 2.2 | 18.9 | 59 | 3 | 5.1 | 1.1 | 14.1 |
| | >39.0 | 51 | 3 | 5.9 | 1.2 | 16.2 | 59 | 2 | 3.4 | 0.4 | 11.7 |
| | >39.5 | 51 | 2 | 3.9 | 0.5 | 13.5 | 59 | 1 | 1.7 | 0.0 | 9.1 |
| | >40.0 | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| | Related | 51 | 9 | 17.6 | 8.4 | 30.9 | 59 | 4 | 6.8 | 1.9 | 16.5 |
| | >40.0*Related | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| | Medical advice | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| Irritability | All | 51 | 20 | 39.2 | 25.8 | 53.9 | 59 | 27 | 45.8 | 32.7 | 59.2 |
| | Grade 3 | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| | Related | 51 | 20 | 39.2 | 25.8 | 53.9 | 59 | 25 | 42.4 | 29.6 | 55.9 |
| | Grade 3*Related | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| | Medical advice | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| Loss of appetite | All | 51 | 12 | 23.5 | 12.8 | 37.5 | 59 | 13 | 22.0 | 12.3 | 34.7 |
| | Grade 3 | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| | Related | 51 | 12 | 23.5 | 12.8 | 37.5 | 59 | 13 | 22.0 | 12.3 | 34.7 |
| | Grade 3*Related | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |
| | Medical advice | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |

**Unsolicited adverse events**

For the primed groups, the percentage of subjects reporting the occurrence of unsolicited AEs with causal relationship to vaccination is tabulated per treatment group and as a percentage of subjects in Table 16 and for the unprimed group in Table 17.

Primed groups:

- In the 10Pn-2d and the 10Pn-3d groups, 47.1% and 40.7% of subjects respectively, reported at least one unsolicited AE within the 31-day post-vaccination period. Out of these, 5.9% and 8.5% of the subjects in the 10Pn-2d and the 10Pn-3d group respectively, reported at least one unsolicited AE assessed by the investigator to be causally related to the administration of the 10Pn-PD-DiT vaccine.

- Grade 3 unsolicited AEs were reported in 3.9% and 5.1% of the subjects in the 10Pn-2d and the 10Pn-3d group, respectively and none of them were assessed by the investigator to be causally related to the 10Pn-PD-DiT vaccine.

Unprimed group:

- 40.3% of the administered doses of 10Pn-PD-DiT vaccine were followed by at least one unsolicited adverse event within the 31-day post-vaccination period. Out of these, 8.1% of the doses were followed by at least one unsolicited adverse event assessed by the investigator to be causally related to the administration of the 10Pn-PD-DiT vaccine.
- Grade 3 unsolicited adverse events were reported following 4.8% of the administered doses and none of them were assessed by the investigator to be causally related to the 10Pn-PD-DiT vaccine.

**Table 16: Percentage of subjects reporting the occurrence of unsolicited symptoms with causal relationship to vaccination, within the 31-day(Days 0-30) post-vaccination period classified by MedDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort)**

| | | 10Pn-2d N = 51 | | | | 10Pn-3d N = 59 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 3 | 5.9 | 1.2 | 16.2 | 5 | 8.5 | 2.8 | 18.7 |
| Gastrointestinal disorders (10017947) | Nausea (10028813) | 0 | 0.0 | 0.0 | 7.0 | 0 | 0.0 | 0.0 | 6.1 |
| | Vomiting (10047700) | 0 | 0.0 | 0.0 | 7.0 | 0 | 0.0 | 0.0 | 6.1 |
| General disorders and administration site conditions (10018065) | Injection site haematoma (10022066) | 0 | 0.0 | 0.0 | 7.0 | 0 | 0.0 | 0.0 | 6.1 |
| | Injection site pruritus (10022093) | 1 | 2.0 | 0.0 | 10.4 | 0 | 0.0 | 0.0 | 6.1 |
| | Pyrexia (10037660) | 3 | 5.9 | 1.2 | 16.2 | 1 | 1.7 | 0.0 | 9.1 |
| Infections and infestations (10021881) | Gastroenteritis (10017888) | 0 | 0.0 | 0.0 | 7.0 | 1 | 1.7 | 0.0 | 9.1 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 7.0 | 0 | 0.0 | 0.0 | 6.1 |
| Psychiatric disorders (10037175) | Nightmare (10029412) | 0 | 0.0 | 0.0 | 7.0 | 0 | 0.0 | 0.0 | 6.1 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 0 | 0.0 | 0.0 | 7.0 | 0 | 0.0 | 0.0 | 6.1 |
| | Rhinorrhoea (10039101) | 0 | 0.0 | 0.0 | 7.0 | 1 | 1.7 | 0.0 | 9.1 |
| Skin and subcutaneous tissue disorders (10040785) | Eczema (10014184) | 0 | 0.0 | 0.0 | 7.0 | 1 | 1.7 | 0.0 | 9.1 |
| | Rash erythematous (10037855) | 0 | 0.0 | 0.0 | 7.0 | 1 | 1.7 | 0.0 | 9.1 |

**Table 17: Percentage of doses with unsolicited symptoms with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period classified by MedDRA Primary System Organ Class and Preferred Term - Unprimed group (Total vaccinated cohort)**

| | | Unprim N = 124 | | | |
|---|---|---|---|---|---|
| | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL |
| At least one symptom | | 10 | 8.1 | 3.9 | 14.3 |
| Gastrointestinal disorders (10017947) | Nausea (10028813) | 2 | 1.6 | 0.2 | 5.7 |
| | Vomiting (10047700) | 2 | 1.6 | 0.2 | 5.7 |
| General disorders and administration site conditions (10018065) | Injection site haematoma (10022066) | 2 | 1.6 | 0.2 | 5.7 |
| | Injection site pruritus (10022093) | 1 | 0.8 | 0.0 | 4.4 |
| | Pyrexia (10037660) | 2 | 1.6 | 0.2 | 5.7 |
| Infections and infestations (10021881) | Rhinitis (10039083) | 2 | 1.6 | 0.2 | 5.7 |
| Psychiatric disorders (10037175) | Nightmare (10029412) | 1 | 0.8 | 0.0 | 4.4 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 1 | 0.8 | 0.0 | 4.4 |
| Skin and subcutaneous tissue disorders (10040785) | Eczema (10014184) | 1 | 0.8 | 0.0 | 4.4 |

**Serious adverse events**

Three subjects (one in each treatment group) reported each one SAE during the course of the study. None of these was considered by the investigator to be causally related to vaccination and all subjects recovered uneventfully

**Fatal events:** No fatal SAEs were reported.

**Adverse events leading to premature discontinuation of study vaccine and/or study**

None.

**Concomitant medications**

Antipyretics were given as a therapeutic measure following vaccination in 17.6% and 10.2% of subjects in the 10Pn-2d and in the 10Pn-3d group, respectively (Table 18).

In the unprimed group, antipyretics were given as a therapeutic measure after 12.9% of the first doses and after 1.6% of the second doses; overall following 7.3% of the vaccine doses (Table 19.

**Table 18: Prevalence of concomitant medication during the 4-day (Days 0-3) post-vaccination period – Primed groups (Total vaccinated cohort)**

| | 10Pn-2d | | | | | 10Pn-3d | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| Any | 51 | 9 | 17.6 | 8.4 | 30.9 | 59 | 9 | 15.3 | 7.2 | 27.0 |
| Any antipyretic | 51 | 9 | 17.6 | 8.4 | 30.9 | 59 | 6 | 10.2 | 3.8 | 20.8 |
| Prophylactic antipyretic | 51 | 0 | 0.0 | 0.0 | 7.0 | 59 | 0 | 0.0 | 0.0 | 6.1 |

**Table 19: Prevalence of concomitant medication during the 4-day (Days 0-3) post-vaccination period following each dose and overall – Unprimed group (Total vaccinated cohort**

| | Unprim | | | | |
|---|---|---|---|---|---|
| | | | | 95% CI | |
| | N | n | % | LL | UL |
| **Dose 1** | | | | | |
| Any | 62 | 10 | 16.1 | 8.0 | 27.7 |
| Any antipyretic | 62 | 8 | 12.9 | 5.7 | 23.9 |
| Prophylactic antipyretic | 62 | 0 | 0.0 | 0.0 | 5.8 |
| **Dose 2** | | | | | |
| Any | 62 | 2 | 3.2 | 0.4 | 11.2 |
| Any antipyretic | 62 | 1 | 1.6 | 0.0 | 8.7 |
| Prophylactic antipyretic | 62 | 0 | 0.0 | 0.0 | 5.8 |
| **Overall/dose** | | | | | |
| Any | 124 | 12 | 9.7 | 5.1 | 16.3 |
| Any antipyretic | 124 | 9 | 7.3 | 3.4 | 13.3 |
| Prophylactic antipyretic | 124 | 0 | 0.0 | 0.0 | 2.9 |
| **Overall/subject** | | | | | |
| Any | 62 | 10 | 16.1 | 8.0 | 27.7 |
| Any antipyretic | 62 | 8 | 12.9 | 5.7 | 23.9 |
| Prophylactic antipyretic | 62 | 0 | 0.0 | 0.0 | 5.8 |

MAH´s safety conclusions

Primed groups:

- After vaccination with additional dose of 10Pn-PD-DiT (4th or 5th dose respectively) in the fourth year of life, 92.2% of subjects in the 10Pn-2d group and 89.8% of subjects in the 10Pn-3d group reported at least one AE (solicited or unsolicited, local or general).
- The most frequently reported solicited local AE was *pain* in both primed groups and the most frequently reported solicited general adverse events were *irritability* and *drowsiness* in the 10Pn-2d group and *irritability* in the 10Pn-3d group.
- Large *swelling* reactions were reported by 1 subject in the 10Pn-3d group.
- No cases of grade 3 *fever* (rectal temperature >40°C) were reported in any of the primed groups.
- The observed percentage of subjects reporting at least one unsolicited AE within 31 days after additional vaccination was 47.1% in the 10Pn-2d group and 40.7% in the 10Pn-3d group. Up to 5.1% of the primed subjects reported at least one unsolicited AE with grade 3 intensity. Unsolicited AEs considered by the investigator to be causally related to vaccination were reported by 5.9% and 8.5% of the subjects in the 10Pn-2d and the 10Pn-3d group respectively.

Unprimed group:

- Overall 85.5% of documented doses were followed by at least one adverse event.
- *Pain* was the most frequently reported solicited local AE was and *irritability* was the most frequently reported solicited general adverse event.
- Large *swelling* reactions were reported by 1subject.
- None of the subjects reported *fever* >40°C or any other grade 3 solicited general AEs
- The observed percentage of administered doses followed by at least one unsolicited adverse event within 31 days after vaccination was 40.3%.

Three subjects (one in each treatment group) reported each one SAE during the course of the study. None of these was considered to be causally related to vaccination and all subjects recovered uneventfully.

**Efficacy / Immunogenicity discussion**

In **study 002**, it was demonstrated that the 2+1 schedule results in lower immune responses than the 3+1 schedule. The real problematic serotypes include **serotypes 6B and 23F** with low post-primary GMCs in both schedules, but in particular in the 2-dose schedule with only 56% and 69% of subjects having ELISA GMCs above the 0.20 µg/ml threshold. These findings are consistent with studies conducted with Prevenar, which also showed a reduced immune response, in particular for serotypes 6B and 23F, with the 2+1 schedule compared with the 3+1 schedule.

Post-booster, the significant differences between the two dose regimens remained for **serotype 6B** with lower ELISA GMCs and OPA GMTs, 88.5% (vs. 96.6% (3-dose)) of subjects achieving GMCs $\geq$0.2µg/ml and 81% (vs. 90.3% (3-dose)) of subjects achieving OPA GMTs $\geq$8 in the 2-dose schedule. For serotype 1 only ~80% of subjects had OPA GMT $\geq$1:8 in both schedules, whereas there was a difference seen for **serotype 5** (87% (2-dose) vs. 97.5% (3-dose)). Overall the post-boost ELISA GMCs and OPA GMTs were lower with the 2+1 schedule vs. the 3+1 schedule, except for some serotypes that were in the same range. Thus, the differences between schedules remained after the booster dose for the 10Pn-PD-DiT vaccine. The immune responses after the booster dose were comparable for all serotypes following a two- or three-dose series.

In **study 011** a direct comparison of post-dose 2 responses between the 10Pn-PD-DiT and Prevenar was made (post-hoc analysis). The results were somewhat surprising showing that the immune responses were not that different for the two vaccines and the functional immune response were higher for three serotypes in the 10Pn group namely 6B, 19F and 18C. However, the low serotype 6B GMCs seen in the Prevenar groups of the GSK trials differ from published data which might be due to technical particularities with the GSK 22F-ELISA. Overall, antibody GMCs for 4 serotypes (4, 9V, 14 and 18C) were higher in the Prevenar group, GMCs for 6B were higher in the 10Pn group and GMCs for types 19F and 23F were in the same range for both vaccines. As regards OPA, GMTs were higher for serotypes 6B, 19F and 23F in the 10Pn group, but for other types in the same range. The OPA GMTs in study 011 were overall lower than those seen in study 002 (except for serotypes 7F and 23F).

Recent licensure of Prevenar 13 in December 2009 has as yet not allowed the MAH to perform a head to head comparison between 10Pn-PD-DiT and Prevenar 13. However, the MAH reviewed published comparative data on Prevenar 7 and Prevenar 13 used in a 3-dose priming schedule (2-4-6 months, Spain) (Diez-Domingo et al, 2009) and in a 2-dose-priming schedule (2-4-12 months, UK) (Paradiso et al 2010) and noted some similarities with the comparative data on Prevenar and the 10Pn-PD-DiT vaccine. In the Spanish trial it was shown that the immune responses after two primary doses of Prevenar 13 were similar to those after two doses of Prevenar 7 in terms of the number of subjects with ELISA antibody concentration $\geq$0.35 µg/ml, although the GMCs for all common serotypes following two doses of Prevenar 13 were lower than observed for Prevenar 7. In the second head to head study in the UK with a 2+1 schedule it was found that the OPA GMTs were higher for serotype 6B in those who received two doses of Prevenar 13 in comparison with Prevenar 7. For other serotypes OPA GMTs were either lower or similar to GMTs following two doses of Prevenar.

**STUDY 10PN-PD-DIT-046 (Slovakia and Sweden)**

Antibody persistence:
Persistence of ELISA antibody response above the threshold level ≥0.20ug/ml prior to administration of the challenge dose at 36-46 months of age varied widely by serotype. For both schedules low proportions of subjects remained at the antibody threshold level for **serotypes 1 and 4** (and **9V** for the 2+1 dose group) ranging from 25% to 54% in the 2+1 group and 37% to 49% in the 3+1 group, whereas for the other serotypes this figure was at least 60%. Overall, the percentage of subjects with antibody concentrations ≥0.20 µg/ml and ELISA GMCs were higher for each of the serotypes in the 3+1 group. In comparison, the unprimed group had very low baseline ELISA antibody concentrations, except for serotypes 14 and 19F. For 6B it is noted that 32% of unprimed subjects had antibody concentrations ≥0.2 µg/ml.

Similarly, with respect to the more important functional immune responses, the percentage of subjects with OPA titres ≥8 were always higher in the 3+1 group (except for 23F). Also the OPA GMTs were higher in the 3+1 group, except for serotype 4, 7F, 9V and 23F where the GMTs were in the same range. Remarkably low OPA titres were observed for serotypes 1, 4, 5, 18C and 19F in both schedule groups. The same pattern was observed in the unprimed group.

As regards the `problematic´ **serotypes 6B and 23F** noted during the primary/booster series, the differences in immune response by schedule was no longer apparent for serotype 23F. In contrast for serotype 6B, differences remained**,** the percentage of subjects with antibody concentrations ≥0.20 µg/ml was 60.4% (2+1 group) and 77.2% (3+1 group) and that with OPA titres ≥8 was 47.6% and 66.7%, respectively.

The persistence data must be assessed together with the robust anamnestic responses as demonstrated for all serotypes after a challenge dose of 10Pn-PD-DiT vaccine given 24-34 months after completion of the 2-dose or 3-dose primary vaccination series.

Post-challenge vaccine dose in the 4$^{th}$ year of life:
Seven to 10 days following the challenge dose, brisk anamnestic ELISA and OPA responses were observed for all serotypes, including 6B and 23F, regardless of primary vaccination schedule used. However, ELISA GMCs were again nominally higher in the 3+1 group than those in the 2+1 group, but the clinical relevance of these differences could be questioned taking the more important functional immune response into consideration. The OPA GMTs and proportion of subjects with OPA titres ≥8 were in the same range in both primed groups, **except for 19F** (higher GMTs in the 3+1 group 5684 vs. 2231 in the 2+1 group). For serotypes 6B and 23F the OPA GMTs were even somewhat higher in the 2+1 group.

Compared with the unprimed group, the proportion of subjects with ELISA concentrations ≥0.20µg/ml and OPA titres ≥8 was higher for the majority of serotypes in the primed groups, although 100% of unprimed subjects also achieved the OPA threshold for 6 of the 10 serotypes. However, as regards ELISA GMCs and OPA GMTs substantially higher antibody levels were always reached in the primed groups. These data indicate a similar induction of immunological memory after primary vaccination according to a 2+1 or 3+1 schedule. The data suggest that comparable long-term protection can be obtained with both vaccination schedules. Considering the lower post-primary and post-booster immune responses noted with the 2+1 schedule, the MAH proposed, that this alternative schedule should only be used as part of the routine infant immunisation program, since the benefit of herd protection can be taken advantage of it.

Surveillance data are available from Quebec where a PCV 7 infant immunisation program using a 2+1 schedule was implemented in 2004. The experience in Quebec showed that PCV7 in a 2+1 schedule was highly efficacious against invasive pneumococcal disease (IPD) due to vaccine serotypes (VST) in children <5 years (VE: 97%). A case control study, where IPD cases were reported in children aged 2-59 months during the years 2005-2007, showed a VE of 60% against overall IPD and 92% against VST IPD. Of note is that an increase in the incidence of IPD in children < 5 years of age has been reported in Quebec since 2006. The increase is due to serotypes not included in PCV7, including serotypes 19A and 7F.

In June 2009 Synflorix replaced PCV7 in the infant immunisation program in Quebec and the first post-marketing data were provided in the MAH´s response. An ecological comparative analysis of impact of PCV7 and Synflorix on IPD was performed. IPD data was collected up to June 2010. Post-booster impact of vaccination was not evaluated.

During the surveillance period, a total of 21 cases of IPD were recorded in the PCV7 cohort (2 VST cases of 19F) and 8 cases in the Synflorix cohort (2 VST cases of 7F).

Based on the distribution of cases of IPD and the length of follow up for the two cohorts, the incidence rate of IPD cases in infants of 6 to 11 months of age was calculated. In this age group, only two IPD cases (non-vaccine serotypes (NVST) 23B and 15A) were reported in the Synflorix cohort yielding an incidence rate of 18.1 cases/100 000 child-years of follow-up. In the PCV7 cohort, although there were no VST IPD cases reported, the overall incidence rate was higher (59.4 cases/100 000 child-years of follow-up).

In children 0-6 months of age, who had not completed the primary vaccination course, a similar number of IPD cases was reported in the PCV7 and Synflorix cohort (8 vs. 6), with predominantly NVST. Regarding VST cases, there were two cases of 7F IPD in the Synflorix cohort (one in a 1-month-old child and one in a 3-month-old) and two cases of 19F IPD in the PCV7 cohort (one in a less than 1-month old child and one in a 2-month old).

These preliminary short-term data showed that following the 2-dose primary series of Synflorix, no IPD cases due to vaccine serotypes were reported. However, these results were obtained in an epidemiological situation where the circulation of the PCV7 serotypes has been substantially reduced by the direct and indirect effects of an universal mass immunisation (UMV) program with a high PCV7 vaccine uptake. Although there was evidence of 19F and 7F circulation, no data were given for the other two additional serotypes in Synflorix (serotypes 1 and 5). It would have been reassuring if the data on Synflorix had suggested protection against serotypes 1 and 5 for which the vaccine-induced OPA responses are the lowest. Of note is that there were no cases of 19A IPD reported in Synflorix primed infants vs. 7 cases in PCV7 primed children. This finding requires monitoring during a longer-term period and post-booster data to conclude that Synflorix would exert cross-protection against serotype 19A.

Apart from the herd effect, other confounding factors of the study were discussed by the MAH, such as the truncated follow-up for the Synflorix cohort, incomplete recording of vaccination status and lack of case data on clinical severity as well as the influence of external factors such as the concurrent A/H1N1 epidemic.

In conclusion a preliminary post-marketing analysis of the impact of Synflorix vs. PCV7 in the context of 2+1 used in a routine immunization in Quebec was reported. The post-dose 2 data in the Synflorix

cohort showed promising results, which, however, must be confirmed by data from longer-term surveillance and from the ongoing RCT studies in Finland. Currently no effectiveness data on the 2+1 schedule are currently available from the still blinded Finnish studies.

Upon request the MAH´s provided a useful review upon which it can be concluded that the importance of maintaining antibody levels above a specific threshold to uphold protection against VST IPD, for example, at a pre-booster time point is not known. The relationship between persistence of functional OPA responses and protection is even less well understood. The establishment of an immune memory and maintenance of boostability appears to be very important for short and longer-term protection against invasive pneumococcal diseases. The data from several countries applying the 2+1 schedule in UVM support the effectiveness of PCV vaccines.
As regards mucosal disease (AOM and pneumonia) even less is known about the relationship between antibody levels and protection. The current data provide no clear answer.

There are no data on Synflorix with respect to vaccine safety or immunogenicity in infants/children with increased risk for pneumococcal infection. Only limited immunogenicity data are available on children with sickle cell disease following a 3-dose primary series with PCV7, which showed an acceptable immune response. In the study by Madhi et al concerning PCV7 vaccination of older HIV infected children ($\geq$ 5 years), it was concluded that "HIV-infected vaccinees experience a partial loss of anamnestic responses to PCV. The optimal timing and frequency of booster vaccination as well as the responses to them among HIV-infected children need to be determined". Regrettably, there are currently no data from studies evaluating PCV efficacy/effectiveness in high risk children.

In the setting of national immunisation programs with high vaccine uptake, herd protection would confer additional benefit to vaccinated and unvaccinated subjects/high-risk groups regardless of vaccination schedule applied. It is evident from the updated Health Protection Agency (HPA) surveillance report (2009/2010) of the impact of PCV 7 vaccination program in the UK employing a 2+1 schedule that vaccine effectiveness did not differ by high-risk groups or by prematurity. The VE estimate was similar to the overall estimate of 83% in the total vaccinated infant cohort. However, in individual cases the 3+1 schedule with Synflorix should be recommended to all children (and in particular the high-risk children) aged 6 week to 6 months to ensure optimal protection.

The MAH agreed to perform epidemiological surveillance for the identification and monitoring of IPD and AOM in a country routinely using Synflorix in a 2+1 schedule.

**Safety discussion**

In study 046 no increase of fever reaction in relation to vaccination in the 4$^{th}$ year of life was observed, however all fever reactions after booster vaccination should be closely monitored and cumulatively reported on in future PSURs. The Company has previously made a commitment to monitor febrile reactions including febrile convulsions.

The main conclusions on safety of 10Pn-PD-DiT administered according to a 2+1 schedule derive from studies 002 and 046. Data from the analysis of the reactogenicity and safety of the head to head comparative study 011 in the initial registration file for10Pn-PD-DiT do not differ from data in the analysis of the primary vaccination study 002 with the follow-up study 046. The safety profile for 10Pn-PD-DiT in the study of primary vaccination and the follow-up study of the challenge dose in the 4$^{th}$ year of life showed no significant differences in local or systemic adverse reactions. There were no grade 3

fever reactions reported after the challenge dose of vaccine in study 046. No new or significant safety issues were observed in any of these trials.

In conclusion, an additional dose of the 10Pn-PD-DiT vaccine (4th or 5th dose) administered at 36-46 months of age in children previously vaccinated with the 10Pn-PD-DiT vaccine according to a 2-dose or a 3-dose primary vaccination within the first 6 months of age and booster vaccination at 11 months of age, was demonstrated to be safe and well tolerated.

# 2. Conclusion and Benefit-risk assessment

Data from three clinical trials were submitted in this type II variation to support the use of a 2-dose primary course followed by a booster dose in the context of routine infant immunization programme. Two of the studies **10PN-PD-DIT-002** and **10PN-PD-DIT-011** were assessed previously in the MAA procedure and resulted in a recommendation in the current SmPC posology section of Synflorix that the infant vaccination schedule consists of 4 vaccine doses, i.e. 3-dose primary course followed by a booster dose in the 2$^{nd}$ year of life (3+1 schedule). In section 5.1, data are provided supporting the wording in section 4.2, but in addition the immune response following a 2-dose primary vaccination (2+1 schedule) is compared to a 3-dose primary series in subjects less than 6 months of age with the conclusion that the 3+1 schedule is recommended to ensure optimal protection. The new study **10PN-PD-DIT-046** submitted in this type II variation is the 2-3 years follow-up of study 002 and provides data on persistence of antibodies for 2-3 years after a booster dose at 11-12 months of age and immune responses following an additional challenge dose of the 10Pn-PD-DiT vaccine to children at 36-46 months of age (long-term immune response).

In previous study 002, lower ELISA GMC values were noted for all serotypes after the 2-dose series than the 3-dose series. In particular, low antibody titres were observed for **serotypes 6B and 23F** and a significantly smaller proportion of children achieved an antibody concentration $\geq$ 0.20 µg/ml for these serotypes. As regards the functional immune response, differences between dose groups were even more pronounced. In study 011, the immune responses measured after two vaccine doses in the *post-hoc* head to head comparison with Prevenar were overall comparable, with notably higher responses observed for serotype 6B with the 10Pn-PD-DiT vaccine. Studies on IPD effectiveness of Prevenar when used in national infant vaccination programs suggest that the lower immune response observed with the 2+1 schedule have no major impact on vaccine effectiveness.

The only new data in this submission were from the follow-up study of 002, **10PN-PD-DIT 046**, and the effectiveness modelling. In study 046, it was shown that persistence of antibodies was demonstrated 24-34 months after the booster dose under both vaccination schedules, although with varying results depending on the serotype. Overall, the percentage of subjects with antibody concentrations above the ELISA and OPA antibody thresholds were higher for the majority of serotypes in the 3+1 group. The clinical consequences of the low persistence of functional immune response for the particular serotypes in both schedules are not known. It is likely that this is of more importance in premature children, certain high-risk groups and in those with an impaired immune response, such as HIV infected children. The acceptability of using the lower immunogenic 2+1 schedule in these risk groups can be questioned. The importance of maintaining an immune response at the serum antibody threshold level during the periods between vaccine doses to uphold protection against vaccine type IPD is not known. Even less is known what is required for the non-invasive mucosal infections which likely require higher antibody levels to afford protection against AOM and pneumonia. The open questions can only be answered by the large long-term effectiveness studies that the MAH has committed to

perform. According to the MAH, effectiveness data following a 2-dose primary schedule with the 10Pn-PD-DiT vaccine are currently not available. In Finland study 10PN-PD-DIT-043 is still ongoing and effectiveness results are expected from this study**.**

The challenge dose administered to children in the 4$^{th}$ year of life primed according to either a 2+1 or a 3+1 vaccination schedule was well tolerated. This dose elicited a robust immune response which was higher than in unprimed subjects, which indicate an immunological memory in primed subjects. The OPA GMTs were in the same range in both primed groups, except for serotype 19F (higher in the 3+1 group). As regards serotypes 6B and 23F the OPA GMTs were even somewhat higher in the 2+1 group. Overall the data indicate a similar induction of immunological memory after primary vaccination according to a 2+1 or 3+1 schedule. The demonstration of immunological memory is considered a key factor for long term protection.

Modelling of the direct impact of vaccination schedule on protection against IPD suggested that the 2-dose schedule is expected to provide less protection than the 3-dose schedule and effectiveness of a 2 dose primary course appeared to be greater with 10Pn-PD-DiT than with Prevenar. However, it is not possible to draw conclusions on effectiveness based on these predictions. The lack of effectiveness data on 10Pn-PD-DiT is a major shortcoming, which cannot be replaced by this modelling.

The MAH provided further data on certain issues pertaining to any available effectiveness data on 2+1 schedule from on-going study 043 in Finland, the potential consequences of a reduced primary immune response in premature children and high-risk groups, the acceptability of using the 2+1 schedules in these risk populations and missing data on the quantification of antigen specific memory B cells. In addition the SPC required modifications.

All the ´other concerns´ were satisfactorily resolved. It was clarified that there are no effectiveness data on the 2+1 schedule currently available from the still blinded Finnish studies. A preliminary post-marketing analysis of the impact of Synflorix versus PCV7 in the context of 2+1 used in a routine immunization program in Quebec was reported. The post-dose 2 data in the Synflorix cohort showed promising results, which, however, must be confirmed by data from longer-term surveillance and from the ongoing RCT studies in Finland. As regards the consequences of the lower immune responses of the 2+1 schedule in high-risk groups, it can be agreed, that in the setting of national immunisation programs with high vaccine uptake, herd protection would confer additional benefit to vaccinated and unvaccinated subjects/high-risk groups regardless of vaccination schedule applied. Moreover, from the updated HPA surveillance report (2009/2010) of the impact of PCV 7 vaccination program in the UK employing a 2+1 schedule, it is evident that vaccine effectiveness did not differ by high-risk groups or by prematurity; the VE estimate was similar to the overall estimate of 83% in the total vaccinated infant cohort. However, on an individual basis the 3+1 schedule with Synflorix should be recommended to all children (and in particular the high-risk children) aged 6 week to 6 months to ensure optimal protection. The MAH proposed a new wording in section 4.4 of the SmPC, clearly stating that vaccination in high-risk groups should be considered on an individual basis with a cross-reference to section 4.2**,** which is considered satisfactory. The data on the quantification of antigen specific memory B cells were provided as requested.

In overall conclusion, the results in study 046 are considered important suggesting that comparable long-term protection can be obtained with both vaccination schedules. Considering the lower immune responses noted during the primary vaccination course and after the booster dose with the 2+1 schedule, the MAH proposed, that the this alternative schedule should only be used as part of the routine infant immunisation program, since the benefit of herd protection can be taken advantage of. In the opinion of the CHMP, the study results justify this use of Synflorix in the 2-dose primary

schedule. Moreover, the MAH has committed to submit the surveillance data of the effectiveness of the 2+1 schedule in the routine infant immunisation program in Finland. The SmPC has been revised.

**Benefit-risk assessment**

The overall expected benefit of the 10Pn-PD-DiT in the 2+1 schedule may be somewhat lower than the 3+1 schedule. However, the results in study 046 indicate a similar induction of immunological memory after primary vaccination according to a 2+1 or 3+1 schedule, which suggest comparable long-term protection with both schedules. In addition, using the 2+1 schedule in routine infant immunization programs means that herd protection will contribute to protective efficacy so that any potential differences between the 2- and 3- primary schedules will not appear.

The clinical consequences of the lower post-primary and post-booster immune responses observed after the 2+1 vaccination schedule are unknown, but might be of importance in premature children, the established high-risk groups and children with an impaired antibody response to vaccines, such as HIV infected subjects. Recent data from the UK surveillance of the impact of PCV 7 suggest that the 2+1 schedule results in comparable efficacy in high-risk groups as in healthy infants. However, to ensure optimal protection against pneumococcal disease, it seems prudent to recommend the 3+1 schedule to these vulnerable risk groups. The SmPC has accordingly been amended with a statement in section 4.4 that vaccination in high-risk groups should be considered on an individual basis with a cross-reference to section 4.2**.**

Effectiveness data following a 2 dose primary schedule with the 10Pn-PD-DiT vaccine are currently not available. However, preliminary post-marketing data on the impact of Synflorix versus PCV7 in the context of 2+1 used in a routine immunization program in Quebec have become available. The post-dose 2 effectiveness data in the Synflorix cohort showed promising results, which, however, should be confirmed by data from longer-term surveillance and from the ongoing RCT studies in Finland.

The CHMP concluded that the benefit risk ratio for the applied variation is favourable provided that the proposed wording in the SmPC section 5.1 was modified as requested.

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.