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Committee for Medicinal Products for Human Use (CHMP)

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No. EMEA/H/C/000973

P46 012.1

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

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

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I. EXECUTIVE SUMMARY

Scope of the FUM

Study 10PN-PD-DIT-042 EXT014

- Immune memory induced by a dose of 10Pn-PD-DiT given at 40-43 months of age in children primed (Study 10PN-PD-DIT-010) and boosted (Study 10PNPD-DIT-014) with 10Pn-PD-DiT.
- Impact of the 10Pn-PD-DiT vaccine on nasopharyngeal carriage of *S. pneumoniae*, *H. influenzae* and other bacterial pathogens.

Please note that the clinical study report of 10PN-PD-DIT-042 has already been submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, and an assessment report was issued in 2011-12-21 in procedure P046 012 for Synflorix.

II. SCIENTIFIC DISCUSSION

In response to this FUM the MAH has submitted an overview of study 10PN-PD-DIT-042. In the overview the results are discussed taking into account carriage results from study 10PN-PD-DIT-014, the POET trial, studies with other PCVs, postmarketing surveillance studies, as well as immunological memory demonstrated in study 10PN-PD-DIT-046. This is summarized below.

- **Clinical aspects**

Background

Study 10PN-PD-DIT-042 is a follow-up of studies 10PN-PD-DIT-014 and 10PN-PD-DIT-010. Study 10PN-PD-DIT-010 evaluated the effect of prophylactic use of antipyretics on febrile reactions during primary vaccination with Synflorix coadministered with Infanrix hexa (combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b conjugate vaccine: DTPa-HBV-IPV/Hib).
Study10PN-PD-DIT-014 was the booster vaccination phase of 10PN-PD-DIT-010 and also evaluated as the primary objective the percentage reduction in febrile reactions when antipyretics were used prophylactically after booster vaccination with Synflorix coadministered with Infanrix hexa in children at 12-15 months of age.

Methods

For clarity of this report the methods section below is copied from the AR for P046 012.

- Objectives

  Primary:
  - To demonstrate the immunological memory induced following primary vaccination in study 10PN-PD-DIT-010 (107017) and booster vaccination in study 10PN-PD-DIT-014 (107137) with the 10Pn-PD-DiT vaccine, through evaluation of early antibody responses after an additional dose of 10Pn-PD-DiT at 40-48 months of age, compared to the unprimed group.

  Criteria for immunological memory:
  The immunological memory was demonstrated if the lower limit of the 95% CI around the GMC ratios (pooled primed groups over unprimed group) was higher than 1 for all 10 vaccine serotypes.

  Secondary:
  - To assess the antibody persistence 25-36 months following the last 10Pn-PD-DiT vaccine dose administered at 12-15 months of age in study 10PN-PD-DIT-014 (107137).
  - To assess long-term effects of the 10Pn-PD-DiT vaccine on nasopharyngeal carriage 16-32 months and 25-36 months following the last vaccine dose administered at 12-15 months of age in study 10PN-PD-DIT-014 (107137).
  - To assess the antibody persistence 25-36 months following vaccination with GSK Biologicals' MenACWY-TT conjugate vaccine in study 10PN-PD-DIT-014 (107137).
  - To assess the immunogenicity of the 10Pn-PD-DiT vaccine when given as a 2-dose catch-up vaccination course to the unprimed children that participated in study 10PN-PD-DIT-014 (107137) in their fourth year of life.

- To assess the safety and reactogenicity of the 10Pn-PD-DiT vaccine when given as a 2-dose catchup vaccination course to the unprimed children that participated in study 10PN-PD-DIT-014 (107137) in their fourth year of life.
- To assess the safety and reactogenicity of an additional booster dose of the 10Pn-PD-DiT vaccine administered at 40-48 months of age in children previously vaccinated with the 10Pn-PD-DiT vaccine at 12-15 months of age in study 10PN-PD-DIT-014 (107137).

- Study design

Open, controlled, multi-centre, long-term follow-up study with three parallel groups:

- AP-AP group*: subjects primed and boosted with 10Pn-PD-DiT co-administered with DTPa-HBV-IPV/Hib with prophylactic antipyretic treatment receiving an additional dose of 10Pn-PD-DiT vaccine.
- NAP-pre group*: subjects primed and boosted with 10Pn-PD-DiT co-administered with DTPa-HBV-IPV/Hib without prophylactic antipyretic treatment receiving an additional dose of 10Pn-PD-DiT vaccine.
- Unprimed group (referred to as 'Unprim' in result tables and figures): age-matched subjects not previously vaccinated with any pneumococcal vaccine receiving two doses of 10Pn-PD-DiT vaccine.

*pooled AP-AP and NAP-pre groups are referred to as "Prim" in result tables and figures.

- Study population /Sample size
  - Male or female between, and including 31 and 44 months of age at the time of the enrolment.
  - For the AP-AP and NAP-pre groups, subjects who received a booster dose of 10Pn-PD-DiT in study 10PN-PD-DIT-014 prior to amendment 3. For the unprimed group, subjects who received a dose of MenACWY-TT in study 10PN-PD-DIT-014.
  - Written informed consent obtained from the parent or guardian of the subject.
  - Free of any known or suspected health problems as established by medical history and clinical examination before entering into the study.

  The sample size of the primed groups (AP-AP and NAP-pre) was contingent on the number of subjects who received a full vaccination course (i.e. a 3-dose primary vaccination in study 10PN-PD-DIT-010 and a booster vaccination in study 10PN-PD-DIT-014 with the 10Pn-PD-DiT vaccine before implementation of Amendment 3. The sample size of the unprimed group depended on the number of subjects who received one dose of MenACWY-TT in study 10PN-PD-DIT-014.

- Treatments

  Vaccination schedule /site: The additional dose of 10Pn-PD-DiT vaccine was given at 40-48 months of age. Catch-up vaccination started at 40-48 months of age with an interval of at least 2 months (56-118 days) between doses. The 10Pn-PD-DiT vaccine was administered intramuscularly in the deltoid.

- Outcomes/endpoints

  <u>Serology</u>

  Pneumococcal serotype specific total IgG antibodies (antibodies to 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) were each measured by 22F-inhibition ELISA (enzyme-linked immunosorbent assay).. The cut-off of the assay was 0.05 µg/mL.

  S. pneumoniae opsonophagocytic activity (OPA) was measured by a killing-assay The cut-off of the assay was an opsonic titre of 8.

  Anti-PD antibodies were determined using an ELISA assay The cut-off of the assay was 100 EL.U/mL.

  The antibody concentrations (22F-inhibition ELISA) and OPA against the cross-reactive pneumococcal serotypes 6A and 19A were also determined (cut-off of 0.05 µg/mL for ELISA and 8 for OPA).

  Functional anti-meningococcal serogroup activity (rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY) was determined by a serum bactericidal test according to the Centres for Disease Control and Prevention (CDC) The cut-off of the assay was a dilution of 1:8.

  <u>Memory B-cell detection</u>

  Whole blood (5.0 mL) was collected from a subset of subjects from each group at Visit 2 and Visit 3 for memory B-cell detection analysis for selected serotypes.

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

Nasopharyngeal swabs
Nasopharyngeal swabs were collected at Visit 1 in all groups and before administration of the additional dose or first dose of the 10Pn-PD-DiT vaccine, as applicable.
The occurrence of *S. pneumoniae* and *H. influenzae* in the nasopharynx, at 31-44 months of age and prior to the single/first dose of investigational vaccine at 40-48 months of age was measured:

- Occurrence of *S. pneumoniae* serotypes (vaccine, cross-reactive or other serotypes) and/or *H. influenzae* in the nasopharynx.
- Acquisition of new *S. pneumoniae* and/or *H. influenzae* strains in the nasopharynx.

Safety /reactogenicity:
Occurrence of each solicited adverse event within 4 days after each vaccination.
Local (any, grade 3) adverse events.
General (any, grade 3, related) adverse events.
Occurrence of unsolicited adverse events within 31 days after each vaccination.
Occurrence of serious adverse events during the entire study period.

- Statistical Methods
  Immunogenicity:
  The primary analysis was based on the ATP cohort for analysis of antibody persistence or on the ATP cohort for analysis of immunogenicity according to the objective. A second analysis based on the Total vaccinated cohort was also performed to complement the ATP analysis of immunogenicity. Immunogenicity was analysed according to the pooled primed group, each of the primed groups (AP-AP group and NAP-pre group) and the Unprimed group.
  Confirmatory Inferential analysis
  95% CIs for the ELISA GMCs ratio (GMCs from the pooled primed groups over GMCs from the unprimed group), 7 to 10 days following vaccination at Month 9 with 10Pn-PD-DiT, were computed for each of the 10 vaccine pneumococcal serotypes, using an ANOVA model on the logarithm10 transformation of the concentrations (pooled variance). The primary objective was reached if the lower limit of the 95% CI on these ELISA GMC ratios was above 1 for all 10 vaccine pneumococcal serotypes.

Summary of Results
Immunological memory
Anamnestic response to an additional vaccine dose was demonstrated in children 40-48 months of age who had been primed and boosted in studies 10PN-PD-DIT-010 and 10PN-PD-DIT-014. The primary objective was reached as the LL of the 95% CI around the GMC ratios (pooled primed group over unprimed group) was higher than the value '1' for all 10 vaccine serotypes (LL ranging from 2.38 for serotype 4 to 27.59 for serotype 23F) (Table 3).

Table 3 Ratios of post-vaccination ELISA GMCs 7-10 days following vaccination (pooled primed group over unprimed group) (ATP cohort for immunogenicity)

The results of the immune responses (% of responders and GMC/Ts) measured following the additional dose in the individual primed groups and the pooled primed group were provided in P046 012 and will not be reproduced here.

					GMC ratio (Prim / Unprim)		
	Prim		Unprim			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
ANTI-1	215	7.63	204	1.24	6.17	5.03	7.58
ANTI-4	215	12.95	204	4.52	2.86	2.38	3.45
ANTI-5	215	9.76	202	0.72	13.47	10.96	16.55
ANTI-6B	215	7.67	203	0.27	28.81	22.54	36.81
ANTI-7F	215	6.51	204	1.37	4.75	3.90	5.78
ANTI-9V	213	9.75	202	0.69	14.10	11.21	17.75
ANTI-14	214	23.07	204	1.01	22.92	17.51	30.00
ANTI-18C	214	32.54	204	3.25	10.01	7.95	12.61
ANTI-19F	214	39.84	204	4.31	9.25	7.29	11.74
ANTI-23F	215	9.24	204	0.25	36.52	27.59	48.34

The results of the immune responses (% of responders and GMC/Ts) measured following the additional dose in the individual primed groups and the pooled primed group were provided in P046 012 and will not be reproduced here.

> Assessor's comment from P046 012:
> The additional dose given at 40-48 months of age resulted in substantial immune responses both measured by ELISA and OPA. The resulting antibody levels were clearly higher than the responses to a single dose in previously unvaccinated subjects. The responses to a single booster dose were also higher than the response to two catch-up doses for most serotypes. It is recognised that the pre-additional dose titres were higher in the primed group, than in the unprimed group, but the rapid responses resulting in high antibody titres are indicative of immunological memory.
> The immune responses to two catch-up doses are considered satisfactory, and supporting the current SPC recommendations. The OPA titres appear to decrease following the second catch-up dose, which could be explained by IgM levels in the early response, that are highly effective opsonising antibodies. They are then replaced by IgG, which ensure a longer lasting protection. As expected the same apparent decrease in response was not seen for the IgG results.

Seven days after vaccination at least 99.5% of subjects in the primed groups had antibody concentrations ≥0.20 µg/mL. In the unprimed group, the percentage of subjects with antibody concentrations ≥0.20 µg/mL 7 days after a first dose of Synflorix was at least 51.0% for serotypes 6B and 23F, 79.9% to 87.6% for serotypes 5, 9V and 14 and at least 96.6% for serotypes 1, 4, 7F, 18C and 19F. In the pooled primed groups, a 9.6- to 64.8-fold increase in antibody GMC was observed after vaccination compared to prior to vaccination.

In the individual primed groups, at least 99.1% of subjects in the AP-AP group and 100% of subjects in the NAP-pre group had antibody concentrations ≥0.20 µg/mL after the additional dose. For each vaccine serotype, the ELISA GMC increased by between 9.8- and 72.1-fold in the AP-AP group, and between 9.3- and 59.9-fold in the NAP-pre group.

Although both primed groups showed an immune response indicative of immunological memory following an additional dose of Synflorix, the observed ELISA GMC in the group that had received prophylactic use of antipyretics in study 10PN-PD-DIT-010 tended to be lower for each vaccine serotype than the group that did not receive prophylactic antipyretics.

The demonstration of immunological memory measured through the additional dose of Synflorix was confirmed by the assessment of functional responses. At least 99.5% of primed subjects had OPA titres ≥8 after the additional dose in the primed group while the percentages were lower in the unprimed group after a single dose (at least 95.8% except for serotypes 5 [88.5%] and 6B [90.2%]). An 18.0- to 1506.8-fold increase in OPA GMTs was observed in the primed groups compared to the pre-vaccination timepoint. At least 97.9% of subjects in the AP-AP group and 100% of subjects in the NAP-pre group had OPA titres above the threshold after the additional dose.

For each vaccine serotype, the OPA GMT increased by between 16.7- and 2029.6-fold in the AP-AP group, and between 19.4- and 1097.5-fold in the NAP-pre group. Postvaccination OPA GMTs in the AP-

AP group were high, and although the observed GMT was lower than the NAP-pre group for some serotypes, the 95% CI overlapped in all cases.

Immunological memory was also demonstrated for the immune responses against Protein D (PD) following the additional dose of Synflorix. After vaccination, 99.5% of subjects in the primed group had anti-PD antibody concentrations ≥100 EL.U/mL. In the AP-AP and NAP-pre groups, the percentages were 99.1% and 100% of subjects, respectively.

Persistence of antibodies and OPA prior to the additional dose
The analysis of persistence 2-3 years after completion of the primary vaccination course in study 10PN-PD-DIT-010 was performed on the ATP cohort for antibody persistence.

Prior to the additional Synflorix dose, for each vaccine serotype at least 93.4% of subjects in the pooled primed group had antibody concentrations above or equal to the assay cut-off of 0.05 µg/mL. The percentage of subjects in the pooled primed group with antibody concentrations ≥0.20 µg/mL prior to the additional dose was 51.4% for serotype 1 and 41.1% for serotype 4, ranged from 70.0% to 80.6% for serotypes 5, 6B, 7F, 9V, 18C and 23F and was at least 88.8% for serotypes 14 and 19F. The percentage of subjects in the AP-AP group with antibody concentrations ≥0.20 µg/mL prior to the additional dose was 42.7% for serotype 1 and 32.7% for serotype 4, ranged from 63.9% to 74.5% for serotypes 5, 6B, 7F, 9V, 18C and 23F and was at least 84.4% for serotypes 14 and 19F. In the NAP-pre group, the percentages were 60.4% for serotype 1 and 50.0% for serotype 4, ranged from 75.2% to 84.0% for serotypes 5, 6B, 7F, 9V and 23F and at least 91.5% for serotypes 14, 18C and 19F.

For most vaccine serotypes, a decline in antibody GMCs was observed between 12 months and 25-36 months post-booster vaccination in the pooled primed group.

The percentage of subjects in the pooled primed group with OPA titres ≥8 prior to the additional dose was at least 28.5% for serotypes 1, 4, 5 and 18C, at least 73.6% for serotypes 6B, 19F and 23F and at least 87.0% for serotypes 7F, 9V and 14. As observed with ELISA GMCs, the OPA GMTs decreased between 12 months and 25-36 months post-booster vaccination. The percentage of subjects with OPA titres ≥8 prior to the additional dose was at least 21.6% in the AP-AP group and at least 35.7% in the NAP-pre group for serotypes 1, 4, 5 and 18C, at least 64.5% in the AP-AP group and at least 74.7% in the NAP-pre group for serotypes 6B, 19F and 23F and at least 84.4% in the APAP group and at least 89.9% in the NAP-pre group for serotypes 7F, 9V and 14.

The percentage of subjects with antibodies against PD (≥100 EL.U/mL) prior to the additional dose vaccine was 92.4% in the pooled primed group. The percentage of subjects above the threshold prior to the additional dose was 85.0% in the AP-AP group and 100% in the NAP-pre group.

2-dose catch-up vaccination
After two catch-up doses at 40-48 months of age and 42-50 months of age, respectively, the percentage of subjects in the unprimed group with antibody concentrations ≥0.20 µg/mL was at least 99.5% except for serotypes 6B (92.3%) and 23F (94.3%). ELISA antibody GMCs were higher than prior to vaccination. Using OPA, the percentage of subjects with titres ≥8 was at least 90.4%. OPA GMTs after the second dose were also higher than prior to vaccination. For anti-PD responses, the percentage of subjects above the cut-off was 83.8% after the first dose and 98.6% after the second dose.

MAH discussion and conclusion:
The primary objective of study 10PN-PD-DIT-042, which was to demonstrate induction of immunological memory at 40-48 months of age by administration of an additional dose of Synflorix, was met. The study results confirm the previous demonstration of an anamnestic response after primary vaccination with Synflorix in study 10PN-PD-DIT-046 in which children primed in a 2+1 or 3+1 schedule received a single dose of Synflorix during the 4th year of life (Silfverdal, 2011). Study 10PN-PD-DIT-046 also showed that catch-up vaccination with two doses of Synflorix in 4th year of life induced robust increases in antibody GMCs and OPA GMTs for each vaccine pneumococcal serotype compared to pre-vaccination levels.

Evaluation of antibody titres 7-10 days post-dose 1 of the catch-up schedule was done for comparison with the Primed group and these data are not useful in evaluating the response to the 2-dose catch-up regimen. However, it is noteworthy that a decrease in OPA GMTs was observed for some serotypes after the second catch-up dose compared to the first dose in the unprimed group subjects in study

10PN-PD-DIT-046 (refer to the Type II variation EMEA/H/C/000973/II/0020) and in the present study 10PNPD-DIT-042. The difference in magnitude of the serotype-specific OPA responses observed 7 days after the first dose and 1 month after the second dose likely reflects the kinetics of antibody production, which is characterised by an initial high level of IgM production, with highly effective opsonising capacity, while at 30 days post-vaccination opsonisation would be mainly mediated by IgG. However, the absence of specific information on the kinetics of OPA responses does not allow firm conclusions to be drawn.

Regardless of whether subjects had received antipyretics in studies 10PN-PD-DIT-010 and 10PN-PD-DIT-014, all primed subjects demonstrated anamnestic response indicative of immunological memory following an additional dose of Synflorix at 40-48 months of age. Robust increases in antibody GMCs and OPA GMTs (with similar fold increase in ELISA antibody GMCs and OPA GMTs pre to post vaccination) were observed for each vaccine pneumococcal serotype compared to age-matched unprimed subjects. Consistent with observations made in studies 10PN-PD-DIT-010 and 10PN-PD-DIT-014, the observed ELISA GMCs tended to be lower in the group that had received prophylactic antipyretics compared to the group that did not receive prophylactic antipyretics. This trend was present but less marked for OPA titres after the additional Synflorix dose in 10PN-PD-DIT-042, possibly indicating that the effects of anti-pyretic administration during priming on the magnitude of long-term OPA immune memory responses are not as marked as on ELISA responses. In view of the robust immune memory responses observed in both the AP-AP and NAP-pre groups, the clinical relevance of differences in the magnitude of the post-vaccination response is not known.

Assessor's comment: The immune responses were assessed previously with the following conclusion: *The immune responses in the primed group were clearly superior to the responses to a single dose in unprimed children. The primed group had higher antibody titres before the challenge vaccination compared to the unprimed group, but the magnitude of the responses were clearly indicative of immunological memory. The response to the challenge dose were also higher in the primed group compared to the second dose in the catch-up group.* This conclusion remains, and the conclusions of the MAH regarding persistence of antibody responses and catch-up vaccinations are also agreed. Therefore this part of the FUM is considered fulfilled.

Nasopharyngeal carriage

The primary analysis was performed on the pooled primed group versus the unprimed control group. However, in view of the impact of prophylactic paracetamol on the immune responses observed in each study (10PN-PD-DIT-010, 10PN-PD-DIT-014 and the follow-up study 10PN-PD-DIT-042 as explained above), an additional analysis was done for each of the primed groups (AP-AP group and NAP-pre group) versus the unprimed group.

Nasopharyngeal carriage of *Streptococcus pneumoniae*

The occurrence of *S. pneumoniae* in nasopharyngeal swabs and vaccine efficacy in preventing carriage of *S. pneumoniae* in pooled primed group as well as in the NAP and AP subgroups versus the unprimed group is presented in Table 4 and in Figure 2 to Figure 5. Results from studies 10PN-PD-DIT-014 and 10PN-PD-DIT-042 are presented per visit (e.g. Visit 1 and 2 in study 10PN-PD-DIT-042) and across all visits for both studies, for any serotype, vaccine serotypes, cross-reactive serotypes, and non-vaccine and non-cross-reactive serotypes respectively.

The primary analysis showed a positive impact of vaccination with Synflorix in reducing carriage of any pneumococcal serotype at Visit 1 and Visit 2 in study 10PN-PD-DIT-042 (i.e. at 31-44 months of age and 40-48 months of age, respectively) and across all visits in studies 10PN-PD-DIT-014 and 10PN-PD-DIT-042.

Statistically significant VE against carriage of pneumococcal vaccine serotypes was observed at Visit 1 and Visit 2. The impact on carriage of vaccine serotypes across all visits was also statistically significant. No significant impact was observed on carriage of cross-reactive serotypes 6A or 19A, although a positive trend was observed at Visit 2 and across all visits. The difference in carriage of non-vaccine and non-cross-reactive serotypes* between Primed and Unprimed groups was not statistically significant at Visit 2 .

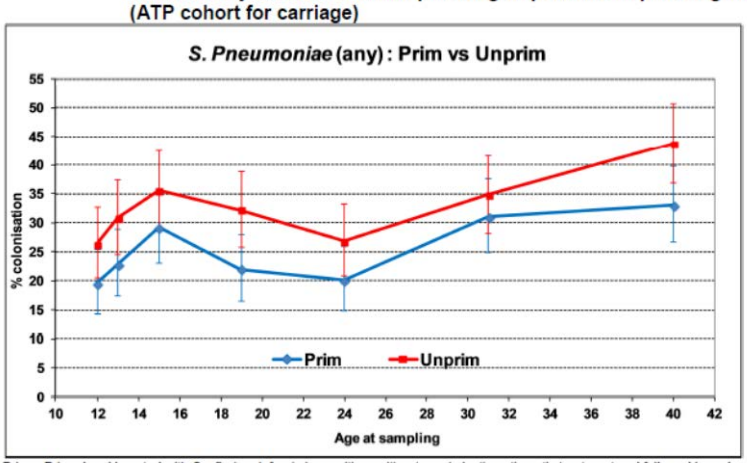
* the most prevalent non-vaccine and non-cross reactive serotypes detected in carriage samples were serotypes 3, 10A, 11A, 15B, 15C, 17F, 22F and 35F (individual serotype data shown in the clinical study report). In addition, serotypes 8, 10B, 15A, 16F, 24F, 25A, 28F, 29, 31, 33F, 35A, 35B, 35C, 37 and 38 were also detected during the study.

Serotypes 6B, 19F and 23F were the most frequently isolated serotypes in both groups. There was a trend for lower carriage prevalence of serotypes 6B, 19F and 23F in the Primed versus the Unprimed group: At each visit, the carriage prevalence of serotype 6B ranged between 0.9% and 2.3% in the Primed group, and between 2.4% and 5.3% in the Unprimed group. Carriage prevalence of serotype 19F ranged between 1.4% and 4.7% in the Primed group and between 2.9% and 6.7% in the Unprimed group. Carriage prevalence of serotype 23F ranged between 0.5% and 3.2% in the Primed group and between 2.4% and 4.8% in the Unprimed group. Statistically significant VE against carriage of pneumococcal vaccine serotypes was observed in the Primed group overall visits for serotypes 6B (52.7% [14.8-74.7]), 14 (68.6% [34.4-86.3]), 19F (40.0% [2.7-63.6]) and 23F (46.0% [4.2- 70.4]). Similar trends were observed in the AP-AP and NAP-pre groups (see the clinical study report for details). The analyses of the NAP and AP-AP groups confirmed the primary analysis. Both groups showed statistically significant VE against carriage of pneumococcal vaccine serotypes at Visit 2 (and also at Visit 1 in the NAP group) despite a lower immune response in the AP-AP group subsequent to the prophylactic administration of paracetamol. In line with study 10PN-PD-DIT-014, the percentage of nasopharyngeal swabs positive for *S. pneumoniae* (any serotype, vaccine serotypes) in both the NAP and AP-AP groups tended to be lower than in the unprimed group. The percentage of nasopharyngeal swabs positive for *S. pneumoniae* (any serotype, vaccine serotypes) for the subjects in the NAP group was comparable to that measured in subjects in the AP-AP group.

Table 4. Carriage of *S. pneumoniae* in nasopharyngeal swabs and vaccine efficacy per visit and overall (Total vaccinated cohort)

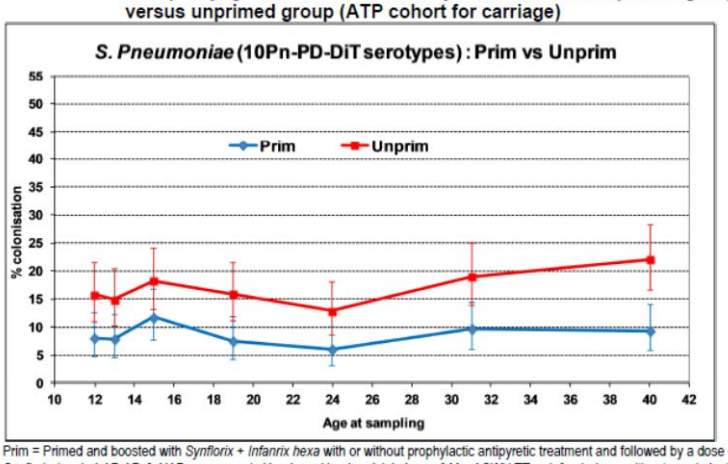
	Unprimed group		Pooled primed groups			NAP subgroup			AP-AP subgroup		
	Carriage		Carriage		VE	Carriage		VE	Carriage		VE
	N	% [95% CI]	N	% [95% CI]	% [95% CI]	N	% [95% CI]	% [95% CI]	N	% [95% CI]	% [95% CI]
Any pneumococcal serotype											
12-15 mo	209	26.3 [20.5; 32.8]	210	19.5 [14.4; 25.5]	25.8 [-13.2; 51.7]	102	18.6 [11.6; 27.6]	29.2[-21.1;60.3]	108	20.4 [13.2;29.2]	22.6 [-29.0;55.1]
13-16 mo	208	30.8 [24.6; 37.5]	215	22.8 [17.4; 29.0]	25.9 [-9.2; 50.0]	105	21.9 [14.4; 31.0]	28.8[-16.3;57.8]	110	23.6 [16.1;32.7]	23.2 [-22.9;53.3]
15-18 mo	208	35.6 [29.1; 42.5]	212	29.2 [23.2; 35.9]	17.8 [-16.8; 42.3]	104	32.7 [23.8; 42.6]	8.1 [-39.7;40.7]	108	25.9 [18.0;35.2]	27.1 [-14.0; 54.6]
19-22 mo	208	32.2 [25.9; 39.0]	214	22.0 [16.6; 28.1]	31.8 [-0.5; 54.1]	104	21.2 [13.8; 30.3]	34.3 [-7.7;61.4]	110	22.7 [15.3;31.7]	29.4 [-13.2; 57.3]
24-27 mo	209	26.8 [20.9; 33.3]	214	20.1 [14.9; 26.1]	25.0 [-13.6; 50.8]	105	18.1 [11.3; 26.8]	32.5[-15.4;62.1]	109	22.0 [14.6;31.0]	17.8 [-34.8; 51.3]
31-44 mo	210	34.8 [28.3; 41.6]	216	31.0 [24.9; 37.6]	10.8 [-26.1; 36.9]	106	29.2 [20.8; 38.9]	15.9[-29.7;46.6]	110	32.7 [24.1;42.3]	5.9 [-42.2; 38.7]
40-48 mo	208	43.8 [36.9; 50.8]	212	33.0 [26.7; 39.8]	24.5 [-4.2; 45.5]	105	34.3 [25.3; 44.2]	21.6[-16.5;48.3]	107	31.8 [23.1;41.5]	27.4 [-8.8; 52.5]
Across all visits	210	75.7 [69.3; 81.4]	216	72.7 [66.2; 78.5]	4.0 [-20.4; 23.5]	106	75.5[66.2; 83.3]	0.3[-31.2;24.8]	110	70.0 [60.5;78.4]	7.5 [-22.1; 30.5]
Pneumococcal vaccine serotype											
12-15 mo	209	15.8 [11.1; 21.5]	210	8.1 [4.8; 12.6]	48.7 [5.3; 73.2]	102	5.9[2.2;12.4]	62.7[10.0;87.2]	108	10.2 [5.2;17.5]	35.5 [-30.8;70.6]
13-16 mo	208	14.9 [10.4; 20.5]	215	7.9 [4.7; 12.4]	46.9 [1.1; 72.5]	105	5.7[5.7;2.1]	61.7[61.7;6.7]	110	10.0 [5.1;17.2]	32.9 [-37.2;69.6]
15-18 mo	208	18.3 [13.3; 24.2]	212	11.8 [7.8; 16.9]	35.5 [-9.8 ; 62.7]	104	12.5[12.5;6.8]	31.6[-31.3;66.6]	108	11.1 [5.9;18.6]	39.2 [-18.9;71.1]
19-22 mo	208	15.9 [11.2; 21.6]	214	7.5 [4.3;] 11.9	52.9 [11.9; 75.8]	104	5.8[2.1;12.1]	63.6[12.1;87.5]	110	9.1 [4.4;16.1]	42.7 [-19.0;74.8]
24-27 mo	209	12.9 [8.7; 18.2]	214	6.1 [3.3; 10.2]	53.0 [5.7; 77.7]	105	3.8[1.0;9.5]	70.5[15.4;92.5]	109	8.3 [3.8;15.1]	36.1 [-4.0;73.6]
31-44 mo	210	19.0 [14.0; 25.0]	216	9.7 [6.1; 14.5]	49.0 [11.3; 71.4]	106	8.5[4.0;15.5]	55.4[6.7;81.0]	110	10.9 [5.8;18.3]	42.7 [-11.4;72.6]
40-48 mo	208	22.1 [16.7; 28.4]	212	9.4 [5.9; 14.2]	57.3 [26.4; 76.1]	105	11.4[6.0;19.1]	48.3[0.9;75.1]	107	7.5[3.314.2]	66.2 [27.7;86.2]
Across all visits	210	56.7 [49.7; 63.5]	216	38.4 [31.9; 45.3]	32.2 [9.5; 49.4]	106	40.6[31.1;50.5]	28.4[-2.3;50.7]	110	36.4[27.4;46.1]	35.8 [7.5;56.3]
Cross-reactive pneumococcal serotypes 6A or 19A											
12-15 mo	209	2.4 [0.8; 5.5]	210	1.9 [0.5; 4.8]	20.4 [-269.9; 84.2]	102	3.9[1.1;9.7]	-36.6[-476;71.6]	108	2.8[0.6;7.9]	3.2[-353.1;84.3]
13-16 mo	208	3.4 [1.4; 6.8]	215	1.4 [0.3; 4.0]	58.5 [-81.6; 93.1]	105	3.8[1.0;9.5]	39.0[-97.3;85.5]	110	7.3[3.2;13.8]	-16.4[-202.9;58.2]
15-18 mo	208	4.3 [2.0; 8.1]	212	3.8 [1.6; 7.3]	12.8 [-154.7; 70.7]	104	6.7[2.7;13.4]	0.0[-164.8;65.8]	108	7.4[3.3;14.1]	-10.1[-181.1;60.0]
19-22 mo	208	3.4 [1.4; 6.8]	214	2.3 [0.8; 5.4]	30.6 [-154.1; 82.6]	104	1.9[0.2;6.8]	71.4[-24.4;96.8]	110	6.4[2.6;12.7]	5.5[-150.3;67.7]
24-27 mo	209	3.3 [1.4; 6.8]	214	2.3 [0.8; 5.4]	30.2 [-155.3; 82.5]	105	2.9[0.6;8.1]	50.2[84.4;91.0]	109	6.4[2.6;12.8]	-11.9[-208.1;62.7]
31-44 mo	210	2.9 [1.1; 6.1]	216	4.6 [2.2; 8.3]	-62.0 [-442.5 ; 46.6]	106	6.6[2.7;13.1]	-54.1[-365.0;51.2]	110	5.5[2.0;11.5]	-27.3[-300.4;62.7]
40-48 mo	208	5.3 [2.7; 9.3]	212	3.8 [1.6; 7.3]	28.6 [-94.8; 75.1]	105	9.5[4.7;16.8]	-4.3[-135.7;56.7]	107	7.5[3.3;14.2]	18.2[-95.8;69.0]
Across all visits	210	18.6 [13.6; 24.5]	216	16.2 [11.6; 21.8]	12.7 [-41.4; 46.3]	106	25.5[17.5;34.9]	13.7[-37.6;47.2]	110	26.4[18.4;35.6]	10.7[-40.9;44.6]
Non-vaccine and non-cross reactive serotype											
12-15 mo	209	8.6 [5.2; 13.3]	210	8.1 [4.8; 12.6]	6.0 [-93.3; 54.5]	102	8.8[4.1;16.1]	-2.5[-140.2;59.5]	108	7.4[3.3;14.1]	14.0[-107.9;67.6]
13-16 mo	208	10.6 [6.7; 15.6]	215	10.7 [6.9; 15.6]	-1.1 [-90.3; 46.1]	105	13.3[7.5;21.4]	-26.1[-157.7;40.4]	110	8.2[3.8;15.0]	22.6[-74.8;68.6]
15-18 mo	208	11.1 [7.1; 16.1]	212	10.8 [7.0; 15.8]	1.9 [-83.0; 47.4]	104	14.4[8.3;22.7]	-30.4[-161.0;36.7]	108	7.4[3.3;14.1]	33.0[-55.1;74.1]
19-22 mo	208	10.1 [6.4; 15.0]	214	10.7 [6.9; 15.7]	-6.5 [-102.2; 43.7]	104	13.5[7.6;21.6]	-33.3[-174.9;37.3]	110	8.2[3.8;15.0]	19.0[-84.6;67.3]
24-27 mo	209	8.1 [4.8; 12.7]	214	9.3 [5.8; 14.1]	-14.9 [-133.5 42.8]	105	11.4[6.0;19.1]	-40.5[-212.2;38.8]	109	7.3[3.2;14.0]	9.8[-120.6;66.3]
31-44 mo	210	11.9 [7.9; 17.1]	216	15.7 [11.2; 21.3]	-32.2 [-131.2; 23.4]	106	15.1[8.9;23.4]	-26.8[-147.0;36.7]	110	16.4[10.0;24.6]	-37.5[-162.3;29.3]
40-48 mo	208	13.0 [8.7; 18.3]	212	16.5 [11.8; 22.2]	-27.2 [-118.5; 25.2]	105	14.3[8.2;22.5]	-10.1[-114.4;45.6]	107	18.7[11.8;27.4]	-44.0[-166.5;23.4]
Across all visits	210	43.3 [36.5; 50.3]	216	46.8 [40.0; 53.6]	-7.9 [-44.9; 19.5]	106	48.1[38.3;58.0]	-11.0[-58.1;22.8]	110	45.5[35.9;55.2]	-4.9[-49.7;27.2]

Figure 2 Occurrence of *S. pneumoniae* (any) in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)



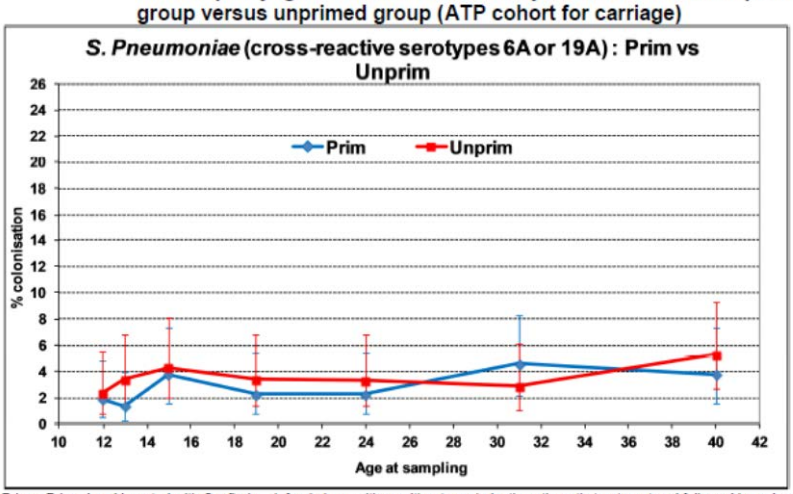
Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups); Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*

Figure 3 Occurrence of *S. pneumoniae* (Synflorix serotypes) in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)



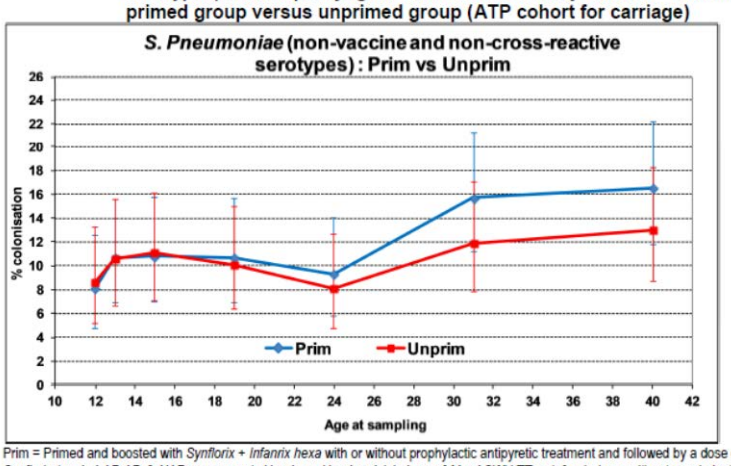
Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups); Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*

Figure 4 Occurrence of *S. pneumoniae* (cross-reactive serotypes 6A or 19A) in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)



Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups); Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*

Figure 5 Occurrence of *S. pneumoniae* (non-vaccine and non-cross-reactive serotypes) in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)



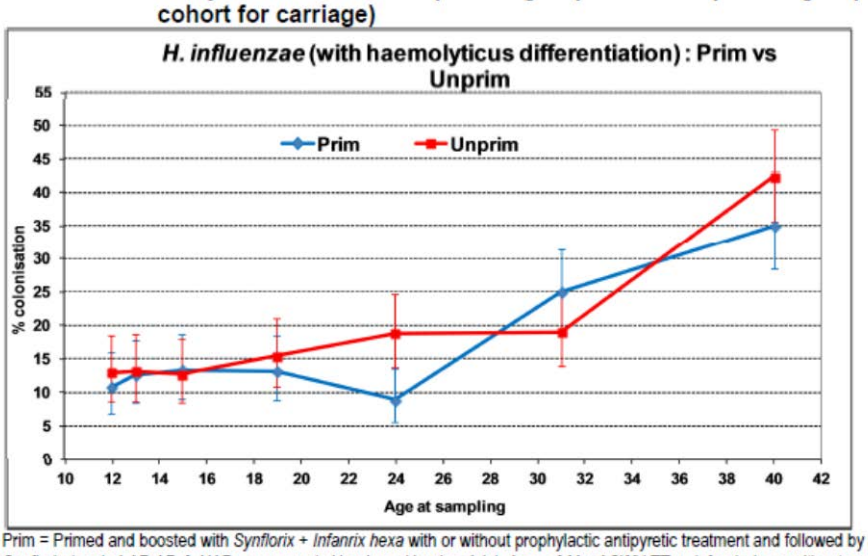
Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups); Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*

Assessor's comment: These data were presented and assessed in P046 012 and it was concluded that vaccination with Synflorix reduces nasopharyngeal carriage of vaccine serotypes, as shown above. The overall pneumococcal carriage is slightly reduced, but not statistically significant, and the carriage of non-vaccine, non-crossreactive serotypes was slighlty increased in primed vs unprimed groups (not statistically significant). This indicates that serotype replacement is occurring in a clinical trial setting, where the effects of herd immunity are not seen. It is possible that such effects could be greater when a large proportion of the population is vaccinated, but no conclusions can be drawn from these data.

Nasopharyngeal carriage of *Haemophilus influenzae* and nontypeable *Haemophilus influenzae*

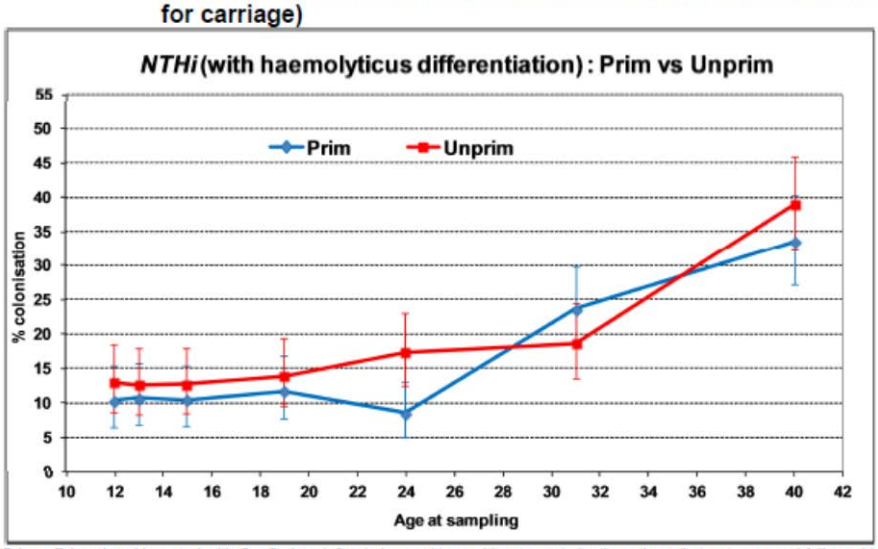
Figure 6 and Figure 7 present the occurrence in nasopharyngeal swabs of *H. influenzae* and NTHi and VE in the pooled primed as well as NAP and AP-AP subgroups versus the unprimed group. No consistent trend towards reduction of carriage of *H. influenzae* was observed in the primary analysis. Across all visits, no consistent impact could be observed on carriage of *H. influenzae*. Similarly, no consistent trends in carriage of NTHi were observed. The results from the NAP and AP-AP groups were similar to those of the primary analysis.

Figure 6 Occurrence of *H. influenzae*** in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)



Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups); Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*; ** Data presented only include results from samples confirmed as positive for *Hi* after differentiation from *H. haemolyticus*

Figure 7 Occurrence of NTHi** in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)



Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups); Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*; ** Data presented only include results from samples confirmed as positive for *NTHi* after differentiation from *H. haemolyticus*

Assessor's comment: The conclusion of the MAH that no effects in carriage of *H.influenzae* are seen, is endorsed.

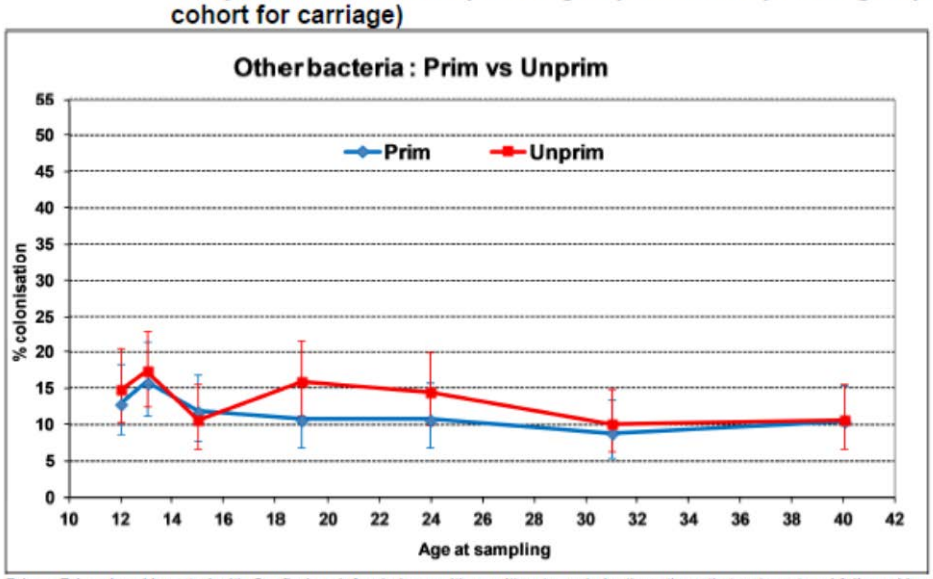
<u>Nasopharyngeal carriage of other bacterial pathogens</u>

Figure 8 to Figure 10 present the occurrence of other bacterial pathogens in nasopharyngeal swabs and VE in the pooled primed group as well as the NAP and APAP subgroups versus the unprimed group, per visit and overall. Figure 9 and 10 also shows the results for *M. catarrhalis*, and *S. aureus*, respectively. The occurrence of group A streptococci was also determined but not shown in this AR.

Carriage prevalence of *M. catarrhalis* and *S. aureus* appeared to be similar in each group. At Visit 1 and Visit 2 in study 10PN-PD-DIT-042, *M. catarrhalis* carriage prevalence was respectively 35.2 % and 47.6% in the unprimed group and respectively 44.4% and 43.9% in the pooled primed group. For *S. aureus* carriage prevalence was respectively 22.4% and 12.5% in the unprimed group and respectively 21.3% and 18.9% in the pooled primed group at Visit 1 and Visit 2. The carriage prevalence of Group

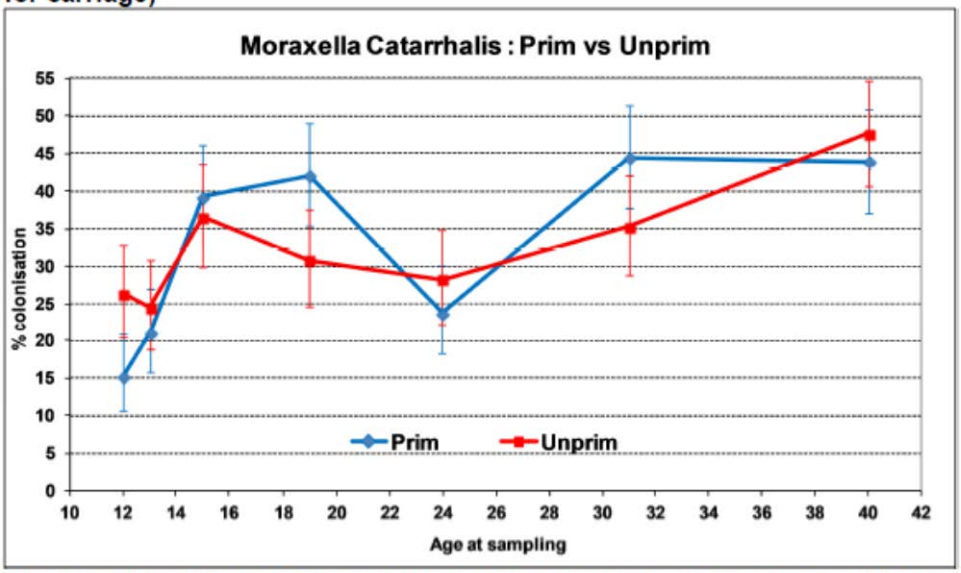
A *Streptococcus* in the pooled primed group and the unprimed group was low compared to that measured for other bacteria. Across all time-points in studies 10PN-PD-DIT-014 and 10PN-PD-DIT-042, no consistent trend on the carriage of any other bacterial pathogens between the pooled primed group and the unprimed group was observed. The analyses of the NAP and AP-AP subgroups are similar to those described for the pooled primed group.

Figure 8 **Occurrence of all other bacteria in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)**



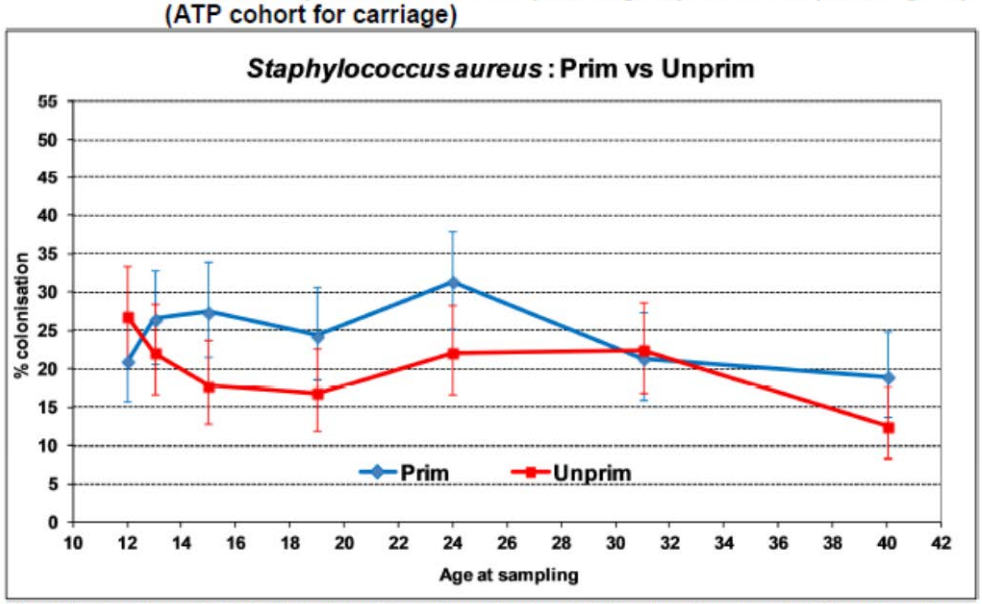
Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups); Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*

Figure 9 **Occurrence of *Moraxella catarrhalis* in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)**



Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups); Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*

Figure 10 Occurrence of *Staphylococcus aureus* in nasopharyngeal swabs across study months – Pooled primed group versus unprimed group (ATP cohort for carriage)



Prim = Primed and boosted with *Synflorix* + *Infanrix hexa* with or without prophylactic antipyretic treatment and followed by a dose of *Synflorix* (pooled AP-AP & NAP-pre groups)
Unprim = Unprimed / 1 dose of MenACWY-TT + *Infanrix hexa* without prophylactic antipyretic treatment and followed by 2 doses catch-up vaccination with *Synflorix*

Assessor's comment: Please note that the "occurrence of all other bacterial species" does not include *M. catarrhalis, S. aureus* or group A streptococcus. There was no consistent trend of replacement of other bacterial species in this study.

MAH discussion of carriage results (summarised)
The results presented here confirm the impact of Synflorix in reducing carriage of pneumococcal vaccine types that was observed in study 10PN-PD-DIT-014 up to 1 year post booster. While Synflorix showed a trend for a positive impact on the carriage of cross-reactive serotypes 6A and 19A measured in study 10PN-PD-DIT-014, this was not sustained over the additional 2-year follow-up period in study 10PN-PDDIT-042. The trend towards an increase of carriage of non-vaccine and non-cross reactive types observed in study 10PN-PD-DIT-014 was sustained in study 10PN-PD-DIT 042.

The impact of Synflorix on *S. pneumoniae* carriage in study 10PN-PD-DIT-042 is consistent with observations made with other pneumococcal conjugate vaccines (PCVs). Overall, PCVs have been observed to reduce the prevalence of nasopharyngeal carriage of vaccine serotypes by 40% to 50% (O'Brien, 2008). The effect has been observed after the primary vaccination series, as well as up to 24 months post-booster vaccination. Increases in carriage of non-vaccine, non-cross-reactive serotypes have also been observed following implementation of PCV vaccination programmes.

The current results are supported by a post-marketing study before and after introduction of Synflorix in Kenya. Synflorix was introduced into routine infant immunisation in a 3+0 schedule (6, 10, 14 weeks of age) and a two-dose catch-up for under 5-year-old children was implemented in Kilifi. Statistically significant declines in carriage of vaccine serotypes were observed in 500 randomly selected residents after Synflorix introduction (Hammitt, 2012). The prevalence of *S. pneumoniae* vaccine serotype carriage decreased in children <1 year of age from 44% prior to the vaccination programme to 10% after vaccination ($p < 0.001$), and in children 1-4 years, from 29% to 16% ($p=0.01$).

To date there are few reports that assess the impact of PCVs against pneumococcal carriage beyond 24 months of age. Madhi et al. (2007) investigated the long-term effect of a 9-valent PCV on vaccine-serotype carriage in HIV uninfected and HIV-infected South African children after a primary series of 3 doses. They found no effect on carriage of vaccine serotypes by 5.3 years of age, and concluded that the levels of antibodies after 3 doses are likely to be lower than the threshold necessary to prevent colonisation. An observational study in the United Kingdom found no effect of PCV7 on carriage of pneumococcus in children 2-5 years of age who had received a 3-dose primary series and 23-valent

polysaccharide vaccine booster at 13 months of age (Lakshman, 2003). In a US study, nasopharyngeal carriage in American Indians vaccinated with a 3-dose primary series of PCV7 and a fourth PCV7 dose at 12–15 months of age, was evaluated after a median of 27 months (range 12–48 months) after the last dose. The rate of vaccine-type pneumococcal carriage was lower among vaccine recipients (10.7%) than among controls (17.7%). It was also observed that the prevalence of non-vaccine type carriage was higher among vaccine recipients (39.3%) than among controls (29.9%). Similarly, a Finnish study reported a reduction in vaccine-type carriage 3–4 years after a 4-dose vaccination series with PCV7 (O'Brien, 2008). Taken together the available results of studies that assessed long term carriage follow-up suggest that the use of a booster dose of PCV following the primary series may provide a higher immune response and therefore, longer duration of protection against vaccine-type carriage.

There was no evidence of a statistically significant negative impact of vaccination on carriage of non-vaccine, non-cross-reactive pneumococcal serotypes in study 10PN-PD-DIT-042. In view of the small sample size in study 10PN-PD-DIT-042, and the lack of power for carriage endpoints, no conclusions can be drawn. As the consequences of serotype replacement depend on many factors including vaccine coverage, it is not possible to draw conclusions on the clinical consequences of potential serotype replacement from this type of data.

In the primary analysis of carriage of *H. influenzae* and NTHi in study 10PN-PD-DIT-042, no consistent impact of Synflorix on carriage was observed. Previous studies on the impact of Synflorix on carriage of *H. influenzae* and NTHi have provided mixed results. In the POET trial conducted with PCV11-PD, an impact on *H. influenzae* carriage was observed 3 months after the booster dose (e.g. VE of 42.6%), whereas only a positive trend could be demonstrated against carriage of NTHi. The reduction in nasopharyngeal carriage rates started to wane during further follow-up period until 24-27 months of age (Prymula, 2010). These results were not reproduced in study 10PN-PD-DIT-014 across all visits, although a significant positive impact on the carriage of *H. influenzae* and NTHi was observed 12 months after the booster dose. Important differences in the design of these two studies (for example, differences in study duration, absence of a randomised age-matched control in studies 10PN-PD-DIT-014 and 10PN-PD-DIT-042, and lack of power to evaluate the carriage endpoint in these), make it difficult to directly compare these carriage results . A significant decline in *H. influenzae* carriage was detected before and after Synflorix introduction in Kenya in children <10 years of age after Synflorix introduction (Hammitt, 2012).

Conclusions:
An additional dose of Synflorix induced immunological memory, with results consistent with a previous study (10PN-PD-DIT-046, Silfverdal, 2011). Regardless of whether subjects had received antipyretics in study 10PN-PD-DIT-010, all primed subjects demonstrated induction of immunological memory. An impact of antipyretics on the magnitude of the immune responses was observed, but there was no apparent impact on carriage and the clinical relevance of the reduced magnitude of the immune response remains unknown.
Although this study was not specifically powered to detect a difference in carriage rates, the results provide evidence of an impact of Synflorix against vaccine-serotype nasopharyngeal carriage that is sustained until the fourth year of life. Furthermore, study 10PN-PD-DIT-042 provides the first evidence of the persistence of this effect up to 36 months after vaccination. There was no statistically significant impact of Synflorix on carriage of non-vaccine, non-cross-reactive serotypes, although replacement with non-vaccine serotypes could not be ruled out and the limitations of study 10PN-PD-DIT-042 in terms of sample size and power considerations do not allow conclusions to be drawn. There was no apparent impact of Synflorix on carriage of *H. influenzae* and NTHi in study 10PN-PD-DIT-042. No consistent impact on carriage of other bacterial pathogens was observed over 36 months of follow-up.
Synflorix given to children 40-48 months as a 2-dose catch-up vaccination was immunogenic and well tolerated. The Company does not plan to submit a variation for this study and considers that the benefit risk profile for Synflorix remains positive in view of these data.

Safety results

Solicited local adverse events

During the 4-day post-vaccination period, pain was the most frequently reported solicited local AE in the primed groups (67.0% in the AP-AP group and 62.0% in the NAP-pre group) and in the Unprimed group (60.9% overall/dose). Grade 3 solicited local AEs were reported by 6.3% (pain) to 11.6% (redness) of subjects and 4.6% (pain) to

11.1% (redness) of subjects in the AP-AP and NAP-pre groups, respectively, and following 3.8% (swelling) to 7.9% (redness) of doses in the Unprimed group.
Solicited local AEs were reported in the Unprimed group by 35.0%-67.3% of subjects and by 29.3%-54.5% of subjects after the first and second dose of 10Pn-PD-DiT vaccine, respectively.

Solicited general adverse events
During the 4-day post-vaccination period, drowsiness was the most frequently reported solicited general AE in the primed groups (36.6% of subjects in the AP-AP group and 31.5% of subjects in the NAP-pre group) and in the Unprimed group (31.2% overall/dose). Grade 3 solicited general AEs were reported by maximum 0.9% of subjects in the AP-AP and NAP-pre groups and following maximum 1.3% of doses (overall/dose) in the Unprimed group.
Solicited general AEs were reported in the Unprimed group by 10.3%-35.4% of subjects and by 4.1%-27.0% of subjects after the first and second dose of 10Pn-PD-DiT vaccine, respectively.

Unsolicited adverse events
In the 31-day follow-up period after vaccination, 21.4%, 26.9% and 32.7% of subjects in the AP-AP, NAP-pre and Unprimed group, respectively, reported at least one unsolicited AE. In the Unprimed group, 19.1% of doses were followed by at least one unsolicited AE. Grade 3 unsolicited AEs were reported by maximum 0.9% of subjects per group. No grade 3 unsolicited AEs were assessed by the investigator to be causally related to vaccination.

Serious adverse events
No SAEs were reported during the entire study period. Withdrawals due to adverse events /serious adverse events No subjects withdrew due to AEs/SAEs in the study.

Assessor's comment: No new safety signals were detected in this study. The safety profile is in agreement with previous studies.

III. CONCLUSION AND RECOMMENDATION

The data provided in this FUM support that immunological memory lasting at least until 40-48 months of age is induced by 3-dose priming +a single booster dose at 12 months of age. The responses to a single booster dose given at 40-48 months of age in the primed group were clearly superior to the responses to a single dose in unprimed children of the same age. The primed group had higher antibody titres before the challenge vaccination compared to the unprimed group, but the magnitude of the responses was clearly indicative of immunological memory. The responses to the challenge dose were also higher in the primed group compared to the second dose in the catch-up group.

There was a statistically significant decrease in nasopharyngeal carriage of pneumococcal vaccine serotypes over the study period in the primed group compared to the unprimed group (unvaccinated in this part of the study). The overall reduction in pneumococcal carriage was less pronounced, and there was a slight non-significant increase in non-vaccine serotypes. There was no impact of vaccination with Synflorix on the carriage rate of *H. influenzae* or NTHi. There was no consistent change in carriage of other bacterial species in this study.

The safety data did not indicate any new safety signals.

In conclusion, this FUM is considered fulfilled and no further action is required.

IV. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RAPPORTEUR

None.