20 February 2015
EMA/96594/2015 rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No. EMEA/H/C/000973

P46 044

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. INTRODUCTION

On February 7, 2012, the MAH submitted completed paediatric studies for Synflorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Synflorix and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the studies

The pharmaceutical formulation used in the study is the same as the commercially available.

II.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

- **10PN-PD-DIT-049**; Evaluation of immunological persistence following 3-dose priming with GSK Biologicals' 10-valent pneumococcal conjugate vaccine in study 111654 and safety and immunogenicity following a booster dose of the same vaccine.
- **10PN-PD-DIT-066;** Primary vaccination course with the pneumococcal vaccine GSK 1024850A, in healthy infants in Vietnam when co-administered with GSK Biologicals' Infanrix hexa™ (DTPa- HBV-IPV/Hib) vaccine.

2. Clinical studies

10PN-PD-DIT-049; Evaluation of immunological persistence following 3-dose priming with GSK Biologicals' 10-valent pneumococcal conjugate vaccine in study 111654 and safety and immunogenicity following a booster dose of the same vaccine.

- **Description**

- **Methods**

  - Objective(s)

Primary:
To assess the antibody persistence induced by the GSK Biologicals' 10-valent pneumococcal conjugate vaccine (commercial lot versus phase III clinical lot), when co-administered with DTPa- IPV/Hib 13-16 months after completion of the 3-dose primary vaccination course in study 10PNPD- DIT-048 (111654).
Secondary:
To assess the safety and reactogenicity of a booster dose of the 10Pn-PD-DiT vaccine (commercial lot), when co-administered with DTPa-IPV/Hib at 18-21 months of age in children primed at 2, 3 and 5 months of age in study 10PN-PD-DIT-048 (111654).
To assess the immunogenicity of a booster dose of the 10Pn-PD-DiT vaccine (commercial lot), when co-administered with DTPa-IPV/Hib at 18-21 months of age in children primed at 2, 3 and 5 months of age in study 10PN-PD-DIT-048 (111654).

  - Study design

Phase III, multicentre, open study with 2 parallel groups. The study was conducted in Singapore.

- Study population /Sample size

  The sample size was contingent on the number of subjects who received three doses of pneumococcal conjugate vaccine (either commercial lot or phase III clinical lot) in study 10PN-PD-DIT-048 (111654) in Singapore. Assuming that around 20% of these subjects did not enter this study, it could be considered that approximately 240 subjects among the 298 enrolled in Singapore during primary vaccination study (120 in Clin-Com group and 120 subjects in Com-Com group) received the booster dose of study vaccine.
  Considering that 120 subjects per group (240 subjects in total) were to be enrolled and included in the Total vaccinated cohort, and up to 10% of the subjects might be excluded from the ATP cohort for analysis of immunogenicity, there were 108 evaluable subjects per group (216 subjects in total) in the current study.

  Healthy male or female, between and including 18 and 21 months of age at the time of the booster vaccination, who received three doses of pneumococcal conjugate vaccine in study 10PN-PD-DIT-048 (111654) and for whom the investigator believes that their parents/ Legally acceptable representative(s) (LARs) could and would comply with the requirements of the protocol. Written informed consent was obtained from the parents/LAR(s) of the subject.

- Treatments

  The study groups were as follows:
  Clin-Com group ('ClinCom' in result tables and figures): subjects previously primed with 3 doses of the phase III clinical lot of 10Pn-PD-DiT, co-administered with HRV1 and DTPa combined 2 vaccines in study 10PN-PD-DIT-048 (111654) in Singapore and receiving a booster dose of the commercial lot of 10Pn-PD-DiT, co-administered with DTPa-IPV/Hib, at 18-21 months of age.
  Com-Com group ('ComCom' in result tables and figures): subjects previously primed with 3 doses of the commercial lot of 10Pn-PD-DiT, co-administered with HRV1 and DTPa combined2 vaccines in study 10PN-PD-DIT-048 (111654) in Singapore and receiving a booster dose of the commercial lot of 10Pn-PD-DiT, co-administered with DTPa-IPV/Hib, at 18-21 months of age.

  Note:
  1. HRV was given at at the first and second vaccination visits (Visit 1 and Visit 2) during primary vaccination course.
  2. DTPa-HBV-IPV/Hib was given at the first and third vaccination visits (Visit 1 and Visit 3) and DTPa-IPV/Hib was given at the second vaccination visit (Visit 2), during primary vaccination course.

Vaccination schedule: single-dose booster vaccination at 18-21 months of age.
Note: Local medically recommended or required vaccines (for example hepatitis A, Japanese encephalitis, measles-mumps-rubella, varicella, influenza or OPV vaccines) provided through the EPI program or through national immunization campaigns were allowed, even if concomitantly administered with the study vaccines, but had to be documented in the eCRF.

- Outcomes/endpoints

Primary Outcome:
Immunogenicity:

Evaluation of the immune responses to components of the investigational vaccine before booster vaccination in terms of:

Concentrations of antibodies against vaccine pneumococcal serotypes.
Concentrations of antibodies against protein D.

Secondary Outcomes:

Safety and reactogenicity:

Occurrence of each solicited adverse event (AE), within 4 days after booster vaccination.

Local (any, grade 3) adverse events.
General (any, grade 3, related) adverse events.

Occurrence of unsolicited AEs within 31 days after booster vaccination.
Occurrence of serious adverse events (SAEs) after booster vaccination up to study end (Visit 1 to Visit 2).

Immunogenicity:
Evaluation of the immune responses to components of the investigational vaccine, before and one month after booster vaccination in terms of:

- Concentrations of antibodies against vaccine pneumococcal serotypes.
- Concentrations of antibodies against cross-reactive pneumococcal serotypes 6A and 19A.
- Concentrations of antibodies against protein D.

Note: The opsonophagocytic activity (OPA) testing was not performed as initially planned in the study protocol.

Evaluation of the immune responses to components of the co-administered vaccine, before and one month after booster vaccination in terms of: Antibody concentrations against diphtheria, tetanus, PRP, PT, FHA and PRN, and titres against polio type 1, 2 and 3.

- Statistical Methods

Immunogenicity
The primary analysis was based on the ATP cohort for persistence for the analysis of the primary immunogenicity objective and on the ATP cohort for immunogenicity for the analysis of the secondary immunogenicity objectives. As, in any group, the percentage of vaccinated subjects with serological data excluded from this ATP cohort was less than 5%, a second analysis based on the Total vaccinated cohort was not performed to complement the ATP analysis.

Within group assessment:

- Geometric mean concentrations/titres (GMCs/GMTs), seropositivity/seroprotection rates were calculated with their 95% confidence interval (CI) for each group and each antigen, prior to and one month post-booster vaccination.
- Distribution of antibody concentrations/titres was displayed using tables and/or reverse cumulative curves for each group and each antigen, prior to and one month post-booster vaccination.

Safety:
The primary analysis was based on the Total vaccinated cohort. As, in any group, the percentage of enrolled subjects excluded from the ATP cohort for analysis of safety was less than 5%, a second analysis based on this ATP cohort was not performed to complement the Total analysis.

Within group assessment:

- Incidence of solicited and/or unsolicited local and/or general AEs during the 31-day post-booster vaccination period was calculated with exact 95% CI, according to the type of symptom, intensity and relationship to vaccination.
- Incidence of each local and each general solicited symptom reported during the 4-day post-booster vaccination period was calculated with exact 95% CI, according to the type of symptom, intensity and relationship to vaccination.
- The percentages of subjects with unsolicited symptoms reported within the 31-days post-booster vaccination period were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA), with exact 95% CI, according to the intensity and relationship to vaccination. The same tabulation was done for unsolicited symptoms resulting in a medically attended visit.
- The number and percentage of subjects who took concomitant antipyretic/medication during the 4- day post-booster vaccination period was computed with exact 95% CI.

SAEs, large swelling reactions and withdrawal(s) due to AE(s)/SAE(s) reported during the entire study period were described in detail

➢ Results

- Recruitment/ Number analysed

Number of subjects	Total	10Pn-Hx group	Hexa group
Planned	300	200	100
Enrolled	300	199	101
Completed	292	193	99
Total vaccinated cohort (TVC)	298	199	99
ATP cohort for safety	296	197	99

- Immunogenicity results
  Not applicable.

- Safety results

  The safety analysis was performed on the TVC.
  Primary Objective (Table 1): During the 31-day post-vaccination period, 8.2% overall doses in the 10Pn-Hx group were followed by at least one type of grade 3 AEs (solicited and unsolicited, local and general), whereas this was 3.0% in the Hexa group.

Table 1: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period following each dose and overall (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	10Pn-Hx	197	24	12.2	8.0	17.6	197	5	2.5	0.8	5.8	197	23	11.7	7.5	17.0
	Hexa	99	3	3.0	0.6	8.6	99	1	1.0	0.0	5.5	99	2	2.0	0.2	7.1
Dose 2	10Pn-Hx	193	18	9.3	5.6	14.3	193	7	3.6	1.5	7.3	193	15	7.8	4.4	12.5
	Hexa	99	3	3.0	0.6	8.6	99	1	1.0	0.0	5.5	99	2	2.0	0.2	7.1
Dose 3	10Pn-Hx	193	6	3.1	1.1	6.6	193	1	0.5	0.0	2.9	193	5	2.6	0.8	5.9
	Hexa	99	3	3.0	0.6	8.6	99	1	1.0	0.0	5.5	99	2	2.0	0.2	7.1
Overall/dose	10Pn-Hx	583	48	8.2	6.1	10.8	583	13	2.2	1.2	3.8	583	43	7.4	5.4	9.8
	Hexa	297	9	3.0	1.4	5.7	297	3	1.0	0.2	2.9	297	6	2.0	0.7	4.3
Overall/subject	10Pn-Hx	197	32	16.2	11.4	22.2	197	10	5.1	2.5	9.1	197	28	14.2	9.7	19.9
	Hexa	99	9	9.1	4.2	16.6	99	3	3.0	0.6	8.6	99	6	6.1	2.3	12.7

10Pn-Hx = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccines
Hexa = DTPa-HBV-IPV/Hib vaccine
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Solicited local adverse events (Table 2):
Pain was the most frequently reported solicited local symptoms during the 4-day post-vaccination period in 10Pn-Hx and Hexa groups (reported following 48.9% and 31.0% of overall doses whatever the injection site, respectively).
In the 10Pn-Hx group, grade 3 solicited local symptoms were reported following 0.9% (redness) to 6.5% (pain) of overall doses, whatever the injection site.
In the Hexa group, grade 3 solicited local symptoms were reported following 0.3% (redness) to 1.0% (pain) of overall doses.

Table 2: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

			10Pn-Hx					Hexa				
						95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	583	285	48.9	44.8	53.0	297	92	31.0	25.8	36.6
		Grade 3	583	38	6.5	4.7	8.8	297	3	1.0	0.2	2.9
		Medical advice	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2
	10Pn-PD-DiT	All	583	261	44.8	40.7	48.9	-	-	-	-	-
		Grade 3	583	35	6.0	4.2	8.3	-	-	-	-	-
		Medical advice	583	0	0.0	0.0	0.6	-	-	-	-	-
	DTPa-HBV-IPV/Hib	All	583	256	43.9	39.8	48.0	297	92	31.0	25.8	36.6
		Grade 3	583	33	5.7	3.9	7.9	297	3	1.0	0.2	2.9
		Medical advice	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2
Redness (mm)	Total	All	583	135	23.2	19.8	26.8	297	44	14.8	11.0	19.4
		>20	583	10	1.7	0.8	3.1	297	2	0.7	0.1	2.4
		>30	583	5	0.9	0.3	2.0	297	1	0.3	0.0	1.9
		Medical advice	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2
	10Pn-PD-DiT	All	583	96	16.5	13.5	19.7	-	-	-	-	-
		>20	583	10	1.7	0.8	3.1	-	-	-	-	-
		>30	583	4	0.7	0.2	1.7	-	-	-	-	-
		Medical advice	583	0	0.0	0.0	0.6	-	-	-	-	-
	DTPa-HBV-IPV/Hib	All	583	103	17.7	14.7	21.0	297	44	14.8	11.0	19.4
		>20	583	4	0.7	0.2	1.7	297	2	0.7	0.1	2.4
		>30	583	2	0.3	0.0	1.2	297	1	0.3	0.0	1.9
		Medical advice	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2
Swelling (mm)	Total	All	583	120	20.6	17.4	24.1	297	34	11.4	8.1	15.6
		>20	583	28	4.8	3.2	6.9	297	2	0.7	0.1	2.4
		>30	583	7	1.2	0.5	2.5	297	2	0.7	0.1	2.4
		Medical advice	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2
	10Pn-PD-DiT	All	583	87	14.9	12.1	18.1	-	-	-	-	-
		>20	583	21	3.6	2.2	5.5	-	-	-	-	-
		>30	583	6	1.0	0.4	2.2	-	-	-	-	-
		Medical advice	583	0	0.0	0.0	0.6	-	-	-	-	-
	DTPa-HBV-IPV/Hib	All	583	96	16.5	13.5	19.7	297	34	11.4	8.1	15.6
		>20	583	18	3.1	1.8	4.8	297	2	0.7	0.1	2.4
		>30	583	4	0.7	0.2	1.7	297	2	0.7	0.1	2.4
		Medical advice	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2

10Pn-Hx = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccines
Hexa = DTPa-HBV-IPV/Hib vaccine
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
Total : n/%= number/percentage of doses with at least one local symptom whatever the number of injections.
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Solicited general adverse events(Table 3):
Irritability was the most frequently reported solicited general symptom in both groups (58.0% of doses in the 10Pn-Hx group and 40.4% doses in the Hexa group).
In the 10Pn-Hx group, the incidence of grade 3 solicited general symptoms ranged from 0.0% to 1.9% (irritability). Out of these, all except one were considered by the investigator to be causally related to vaccination (1.7%).
In the Hexa group, the incidence of grade 3 solicited general symptoms ranged from 0.0% to 0.3%.
There was one report of grade 3 fever (axillary temperature > 39.5°C) during the 4-day post dose 3 vaccination period and was considered by the investigator to be causally related to vaccination.

Table 3: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

		10Pn-Hx					Hexa				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	583	153	26.2	22.7	30.0	297	34	11.4	8.1	15.6
	Grade 3	583	3	0.5	0.1	1.5	297	0	0.0	0.0	1.2
	Related	583	133	22.8	19.5	26.4	297	27	9.1	6.1	13.0
	Grade 3 & Related	583	2	0.3	0.0	1.2	297	0	0.0	0.0	1.2
	Medical advice	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2
Fever (Axillary) (°C)	All	583	318	54.5	50.4	58.6	297	64	21.5	17.0	26.7
	>38.0	583	119	20.4	17.2	23.9	297	11	3.7	1.9	6.5
	>38.5	583	21	3.6	2.2	5.5	297	2	0.7	0.1	2.4
	>39.0	583	2	0.3	0.0	1.2	297	1	0.3	0.0	1.9
	>39.5	583	0	0.0	0.0	0.6	297	1	0.3	0.0	1.9
	Related	583	307	52.7	48.5	56.8	297	61	20.5	16.1	25.6
	>39.5 & Related	583	0	0.0	0.0	0.6	297	1	0.3	0.0	1.9
	Medical advice	583	1	0.2	0.0	1.0	297	0	0.0	0.0	1.2
Irritability	All	583	338	58.0	53.9	62.0	297	120	40.4	34.8	46.2
	Grade 3	583	11	1.9	0.9	3.4	297	1	0.3	0.0	1.9
	Related	583	325	55.7	51.6	59.8	297	112	37.7	32.2	43.5
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	Grade 3 & Related	583	10	1.7	0.8	3.1	297	0	0.0	0.0	1.2
	Medical advice	583	0	0.0	0.0	0.6	297	1	0.3	0.0	1.9
Loss of appetite	All	583	270	46.3	42.2	50.5	297	86	29.0	23.9	34.5
	Grade 3	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2
	Related	583	236	40.5	36.5	44.6	297	73	24.6	19.8	29.9
	Grade 3 & Related	583	0	0.0	0.0	0.6	297	0	0.0	0.0	1.2
	Medical advice	583	0	0.0	0.0	0.6	297	1	0.3	0.0	1.9

10Pn-Hx = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib vaccines
Hexa = DTPa-HBV-IPV/Hib vaccine
For each dose and overall/subject:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Unsolicited adverse events:
Unsolicited adverse events were reported following 12.3% and 14.8% of administered doses in the 10Pn-Hx and Hexa groups, respectively.

Grade 3 unsolicited symptoms were reported for a maximum of 0.3% of doses in the two study groups. None of the grade 3 adverse events was assessed by the investigator to be causally related to vaccination.

Serious adverse events:
At least one SAE was reported by 15 subjects (9/199 subjects in the 10Pn-Hx group and 6/99 subjects in the Hexa group) during this study.
Among these SAEs, none was assessed by the investigator to be causally related to vaccination. No fatal SAEs were reported during the entire study period.

Assessor's comment: There was an increase in reactogenicity when Synflorix was co-administered with Infanrix hexa, which has also been reported from previous studies. No further regulatory action is required based on these results.

3. Discussion on clinical aspects
In both submitted studies Synflorix was given in accordance with the EU approved dosing schedule. The results were also in line with the previously submitted studies, and no further regulatory action is considered necessary.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

This article 46 submission is considered satisfactory and no further regulatory action is required.

- **Recommendation**

☒ **Fulfilled –**

No further action required.

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable.