20 February 2015
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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 049

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

I. INTRODUCTION

On November 7, 2012 the MAH submitted a completed paediatric study 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 study does 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 study

The commercially available formulation of Synflorix was used in the control group of this study.

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

- Study SPNG-007; Safety and immunogenicity study of GSK Biologicals' pneumococcal vaccine 2830930A when administered as a single dose in healthy toddlers aged 12-23 months.

2. Clinical study

Study SPNG-007; Safety and immunogenicity study of GSK Biologicals' pneumococcal vaccine 2830930A when administered as a single dose in healthy toddlers aged 12-23 months

➢ **Methods**

- Objectives

Primary:

To assess the safety and reactogenicity of GSK Biologicals' 12-valent pneumococcal polysaccharide and NTHi protein D conjugate vaccine when administered as a one-dose vaccination to toddlers aged 12-23 months primed with 3 doses of Synflorix, in terms of occurrence of grade 3 related solicited and unsolicited adverse events (AEs) and related serious adverse events (SAEs).

Secondary:

To evaluate the safety and reactogenicity of GSK Biologicals' 12-valent pneumococcal polysaccharide and NTHi protein D conjugate vaccine when administered as a one-dose vaccination to toddlers aged 12-23 months primed with 3 doses of Synflorix, in terms of occurrence of any AEs including SAEs.
To assess the immune response elicited by the GSK Biologicals' 12-valent pneumococcal polysaccharide and NTHi protein D conjugate vaccine when administered as a one-dose vaccination to toddlers aged 12-23 months primed with 3 doses of Synflorix.

- Study design

  Experimental design: Phase I, randomised, double-blind, controlled, multicentric study.
  Control: active control (10Pn-PD-DiT vaccine).
  Treatment allocation: randomised (1:1).
  Vaccination schedule: one dose between 12 to 23 months of age. Blood sampling was to be done in all subjects at each of the following timepoints:
  prior to vaccination [Pre]
  one month post-vaccination [(PI(M1)]
  Type of study: self-contained.

- Study population /Sample size

Healthy male or female toddlers aged 12 to 23 months at the time of vaccination and for whom the investigator believed that their parent(s)/Legally Acceptable Representative(s) (LARs) would comply

with the requirements of the protocol. Subjects were to be born after a gestation period of at least 36 weeks, and previously completed a three-dose vaccination course with Synflorix. Written informed consent was obtained from each subject's parent(s)/LAR(s).

- Treatments
  One dose (0.5 mL) of the 12Pn-PD-DiT-CRM vaccine was administered as an intramuscular injection in the deltoid of the non-dominant arm (or thigh if the deltoid size was not adequate) - 12Pn_T group.
  One dose (0.5 mL) of the 10Pn-PD-DiT vaccine was administered as an intramuscular injection in the deltoid of the non-dominant arm (or thigh if the deltoid size was not adequate) - 10Pn_T group.

- Outcomes/endpoints
  Primary outcome variables
  Safety
- Occurrence of each grade 3 solicited AE with relationship to vaccination within 7 days (Day 0-Day 6) after vaccination.
    - Solicited local AEs
    - Solicited general AEs
- Occurrence of grade 3 unsolicited AEs with relationship to vaccination within 31 days (Day 0-Day 30) after vaccination.
- Occurrence of SAEs with relationship to vaccination throughout the entire study (from Month 0 up to Month 1)

  Secondary outcomes variables:
  Safety and Reactogenicity
- Occurrence of each solicited AE within 7 days (Day 0-Day 6) after vaccination.
    - Solicited local AE (any).
    - Solicited general AE (any and related).
- Occurrence of any unsolicited AE within 31 days (Day 0-Day 30) after vaccination.
- Occurrence of any SAE throughout the entire study (from Month 0 up to Month 1).

Immunogenicity

- Evaluation of the immune responses to the components of the investigational vaccine, one month post-vaccination.
- Concentrations of antibodies against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- Concentrations of antibodies against protein D.

- Statistical Methods
  Analyses were performed as per protocol.
  Demography:
    - Demographic characteristics (age in months, gender, geographic ancestry) were tabulated per group.
    - The mean age (plus range and standard deviation) of the enrolled subjects was calculated.
    - The distribution of subjects enrolled among the study centres was tabulated.

  Analysis of safety:
    - The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 31-day (Day 0-Day 30) follow-up period after vaccination was tabulated for each group with exact 95% Confidence Interval (CI). The same calculations were performed for symptoms rated as grade 3 and general symptoms with causal relationship to vaccination.
    - The percentage of subjects reporting each individual solicited local and general AE during the 7-day (Day 0-Day 6) solicited follow-up period after vaccination was tabulated for each group, with exact 95% CI.

- The same tabulation was performed for grade 3 solicited AEs and for solicited AEs with causal relationship to vaccination. For redness and swelling, grade 2 or 3 AEs were also tabulated. Occurrence of fever was reported per 0.5°C cumulative increments.
- All the above tabulations for each individual solicited AE were also performed for the first 4 days after vaccination (Day 0-Day 3).
- The proportion of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 30 days after vaccination was tabulated with exact 95% CI for each group. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.
- The proportion of AEs resulting in a medically attended visit was also tabulated.
- The number and percentage of subjects who took concomitant medication/antipyretic at least once during the 7-day (Day 0-Day 6) solicited follow-up period after vaccination were tabulated for each group with exact 95% CI. The above tabulation for concomitant medication/antipyretic was also performed for the first 4 days after vaccination (Day 0-Day 3).
- SAEs, large swelling reactions and withdrawal(s) due to SAE(s) were described in detail.

Analysis of immunogenicity:

- Geometric mean concentrations (GMCs) and seropositivity rates with 95% CIs were tabulated for each group and for each serotype/antigen, prior to and one month after vaccination.
- The distribution of antibody concentrations/titres for each appropriate serotype/antigen was displayed using tables and/or reverse cumulative distribution curves.

➢ **Results**

- Recruitment/ Number analysed
  A total of 61 subjects were enrolled in this study: 31 subjects in the 12Pn_T group and 30 subjects in the 10Pn_T group.

- Baseline data
  The cohort used for the analysis of the primary objective is the Total vaccinated cohort.
  In this cohort, the mean age of subjects at the time of vaccination was 15.0 months,
  55.7% of subjects were female and 98.4% of subjects were of White Caucasian/European heritage.

- Immunogenicity results
  Prior to vaccination, for each of the 10 common vaccine pneumococcal serotypes, at least 63.3% of subjects in the 12Pn_T group and at least 41.7 % of subjects in the 10Pn_T group had antibody concentrations ≥0.2 µg/mL. For serotypes 6A and 19A, this percentage was 36.7% and 66.7%, respectively in the 12Pn_T group and 20.0% and 36.0% respectively in the 10Pn_T group.

  One month post-vaccination, for each of the 10 common vaccine pneumococcal serotypes, all subjects in both groups had antibody concentrations ≥0.2 µg/mL. For serotypes 6A and 19A, this percentage was 100% for both serotypes in the 12Pn_T group and 84.6% and 96.3%, respectively in the 10Pn_T group.

  For each of the pneumococcal serotypes, an increase was observed in antibody GMCs one month post-vaccination compared to GMCs observed prior to vaccination in both groups.

Table 41 Seropositivity rates and GMCs for ANTI-1, ANTI-4, ANTI-5, ANTI-6A, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19A, ANTI-19F and ANTI-23F antibodies (ATP cohort for immunogenicity)

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-1	12Pn_T	PRE	30	26	86.7	69.3	96.2	19	63.3	43.9	80.1	0.20	0.13	0.31
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	2.34	1.74	3.14
	10Pn_T	PRE	24	23	95.8	78.9	99.9	10	41.7	22.1	63.4	0.18	0.12	0.26
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	2.84	2.12	3.82
ANTI-4	12Pn_T	PRE	28	26	92.9	76.5	99.1	19	67.9	47.6	84.1	0.31	0.19	0.50
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	5.18	4.05	6.63
	10Pn_T	PRE	26	25	96.2	80.4	99.9	15	57.7	36.9	76.6	0.28	0.19	0.42
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	4.52	3.34	6.10
ANTI-5	12Pn_T	PRE	29	28	96.6	82.2	99.9	20	69.0	49.2	84.7	0.34	0.23	0.49
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	3.31	2.51	4.37
	10Pn_T	PRE	24	24	100	85.8	100	15	62.5	40.6	81.2	0.32	0.21	0.50
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	2.29	1.52	3.46
ANTI-6A	12Pn_T	PRE	30	26	86.7	69.3	96.2	11	36.7	19.9	56.1	0.17	0.11	0.27
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	5.97	3.91	9.11
	10Pn_T	PRE	25	17	68.0	46.5	85.1	5	20.0	6.8	40.7	0.08	0.05	0.14
		PI(M1)	26	25	96.2	80.4	99.9	22	84.6	65.1	95.6	0.75	0.43	1.31
ANTI-6B	12Pn_T	PRE	30	30	100	88.4	100	20	66.7	47.2	82.7	0.31	0.21	0.45
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	5.37	4.03	7.14
	10Pn_T	PRE	24	23	95.8	78.9	99.9	10	41.7	22.1	63.4	0.20	0.13	0.30
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	1.92	1.50	2.46
ANTI-7F	12Pn_T	PRE	30	30	100	88.4	100	26	86.7	69.3	96.2	0.80	0.57	1.13
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	3.76	2.99	4.73
	10Pn_T	PRE	24	24	100	85.8	100	23	95.8	78.9	99.9	0.65	0.45	0.94
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	3.36	2.48	4.55
ANTI-9V	12Pn_T	PRE	30	30	100	88.4	100	27	90.0	73.5	97.9	0.70	0.49	0.99
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	4.38	3.27	5.89
	10Pn_T	PRE	24	24	100	85.8	100	20	83.3	62.6	95.3	0.59	0.34	1.02
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	3.61	2.38	5.48
ANTI-14	12Pn_T	PRE	30	30	100	88.4	100	28	93.3	77.9	99.2	0.94	0.61	1.46
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	8.30	6.27	10.98
	10Pn_T	PRE	24	24	100	85.8	100	22	91.7	73.0	99.0	0.81	0.54	1.22
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	7.15	5.51	9.28
ANTI-18C	12Pn_T	PRE	30	30	100	88.4	100	25	83.3	65.3	94.4	0.67	0.43	1.03
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	11.26	8.31	15.26
	10Pn_T	PRE	24	24	100	85.8	100	19	79.2	57.8	92.9	0.55	0.35	0.88
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	11.17	7.99	15.62
ANTI-19A	12Pn_T	PRE	30	26	86.7	69.3	96.2	20	66.7	47.2	82.7	0.28	0.16	0.48
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	8.22	5.45	12.40
	10Pn_T	PRE	25	20	80.0	59.3	93.2	9	36.0	18.0	57.5	0.18	0.10	0.34
		PI(M1)	27	26	96.3	81.0	99.9	26	96.3	81.0	99.9	1.99	1.20	3.29
ANTI-19F	12Pn_T	PRE	30	29	96.7	82.8	99.9	25	83.3	65.3	94.4	1.18	0.67	2.09
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	17.34	12.09	24.87
	10Pn_T	PRE	24	24	100	85.8	100	22	91.7	73.0	99.0	0.57	0.36	0.90
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	10.89	8.03	14.76
ANTI-23F	12Pn_T	PRE	30	29	96.7	82.8	99.9	21	70.0	50.6	85.3	0.36	0.23	0.54
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	3.46	2.63	4.56
	10Pn_T	PRE	24	24	100	85.8	100	18	75.0	53.3	90.2	0.40	0.24	0.66
		PI(M1)	27	27	100	87.2	100	27	100	87.2	100	3.54	2.65	4.72

- Safety results
  Overall incidence of adverse events
  The results are presented in tables 25-27.

Table 25 Incidence and nature of symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period (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
12Pn_T	31	31	100	88.8	100	31	25	80.6	62.5	92.5	31	26	83.9	66.3	94.5
10Pn_T	29	27	93.1	77.2	99.2	29	26	89.7	72.6	97.8	29	23	79.3	60.3	92.0

Table 26 Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period (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
12Pn_T	31	4	12.9	3.6	29.8	31	1	3.2	0.1	16.7	31	3	9.7	2.0	25.8
10Pn_T	29	3	10.3	2.2	27.4	29	2	6.9	0.8	22.8	29	1	3.4	0.1	17.8

Table 27 Incidence and nature of symptoms (solicited and unsolicited), with causal relationship to vaccination, reported during the 31-day (Days 0-30) post-vaccination period (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
12Pn_T	31	30	96.8	83.3	99.9	31	20	64.5	45.4	80.8	31	26	83.9	66.3	94.5
10Pn_T	29	26	89.7	72.6	97.8	29	21	72.4	52.8	87.3	29	23	79.3	60.3	92.0

Table 28 Incidence and nature of grade 3 symptoms (solicited and unsolicited), with causal relationship to vaccination, reported during the 31-day (Days 0-30) post-vaccination period (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
12Pn_T	31	3	9.7	2.0	25.8	31	0	0.0	0.0	11.2	31	3	9.7	2.0	25.8
10Pn_T	29	3	10.3	2.2	27.4	29	2	6.9	0.8	22.8	29	1	3.4	0.1	17.8

Solicited local adverse events

The incidence of each solicited local AE during the 7-day (Day 0-Day 6) postvaccination period is shown in table 30. During the 7-day post-vaccination period:

Grade 3 solicited local AEs were reported for:

- 2 subjects (6.5%) (redness) and 3 subjects (9.7%) (swelling) out of 31 subjects in the 12Pn_T group and,
- 1 subject (3.4%) (swelling), out of 29 subjects in the 10Pn_T group.

As per protocol, all grade 3 solicited local AEs were considered to be causally related to vaccination.

Redness at injection site was the most frequently reported solicited local AE in both groups (64.5% subjects in the 12Pn_T group and 65.5% subjects in the 10Pn_T group).

Table 30 Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

		12Pn_T					10Pn_T				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	31	14	45.2	27.3	64.0	29	12	41.4	23.5	61.1
	Grade 3	31	0	0.0	0.0	11.2	29	0	0.0	0.0	11.9
	Medical advice	31	1	3.2	0.1	16.7	29	0	0.0	0.0	11.9
Redness (mm)	All	31	20	64.5	45.4	80.8	29	19	65.5	45.7	82.1
	>20.0	31	3	9.7	2.0	25.8	29	0	0.0	0.0	11.9
	>30.0	31	2	6.5	0.8	21.4	29	0	0.0	0.0	11.9
	Medical advice	31	1	3.2	0.1	16.7	29	0	0.0	0.0	11.9
Swelling (mm)	All	31	12	38.7	21.8	57.8	29	9	31.0	15.3	50.8
	>20.0	31	4	12.9	3.6	29.8	29	1	3.4	0.1	17.8
	>30.0	31	3	9.7	2.0	25.8	29	1	3.4	0.1	17.8
	Medical advice	31	1	3.2	0.1	16.7	29	0	0.0	0.0	11.9

Solicited general adverse events

The incidence of each solicited general AE during the 7-day (Day 0-Day 6) postvaccination period is shown in table 32 .

During the 7-day post-vaccination period:

- Grade 3 solicited general AEs were reported for:
  - 1 subject (3.2%) (fever) out of 31 subjects in the 12Pn_T group and,
  - 1 subject (3.4%) (irritability/fussiness) and 1 subject (3.4%) (fever) out of 29 in the 10Pn_T group.
- The grade 3 solicited general AE reported in the 12Pn_T group was not considered by the investigator to be causally related to vaccination. In the 10Pn_T group, the two reported grade 3 solicited general AEs were considered by the investigator to be causally related to vaccination.
- Irritability/fussiness was the most frequently reported solicited general AE during the 7-day post-vaccination period (48.4% subjects in the 12Pn_T group and 48.3% subjects in the 10Pn_T group).

Table 32 Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

		12Pn_T					10Pn_T				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	31	9	29.0	14.2	48.0	29	6	20.7	8.0	39.7
	Grade 3	31	0	0.0	0.0	11.2	29	0	0.0	0.0	11.9
	Related	31	8	25.8	11.9	44.6	29	5	17.2	5.8	35.8
	Grade 3 Related	31	0	0.0	0.0	11.2	29	0	0.0	0.0	11.9
	Medical advice	31	1	3.2	0.1	16.7	29	1	3.4	0.1	17.8
Irritability/fussiness	All	31	15	48.4	30.2	66.9	29	14	48.3	29.4	67.5
	Grade 3	31	0	0.0	0.0	11.2	29	1	3.4	0.1	17.8
	Related	31	14	45.2	27.3	64.0	29	13	44.8	26.4	64.3
	Grade 3 Related	31	0	0.0	0.0	11.2	29	1	3.4	0.1	17.8
	Medical advice	31	2	6.5	0.8	21.4	29	0	0.0	0.0	11.9
Loss of appetite	All	31	6	19.4	7.5	37.5	29	9	31.0	15.3	50.8
	Grade 3	31	0	0.0	0.0	11.2	29	0	0.0	0.0	11.9
	Related	31	4	12.9	3.6	29.8	29	5	17.2	5.8	35.8
	Grade 3 Related	31	0	0.0	0.0	11.2	29	0	0.0	0.0	11.9
	Medical advice	31	0	0.0	0.0	11.2	29	0	0.0	0.0	11.9
Temperature/(Rectally) (°C)	All	31	14	45.2	27.3	64.0	29	13	44.8	26.4	64.3
	>38.5	31	8	25.8	11.9	44.6	29	4	13.8	3.9	31.7
	>39.0	31	3	9.7	2.0	25.8	29	1	3.4	0.1	17.8
	>39.5	31	1	3.2	0.1	16.7	29	1	3.4	0.1	17.8
	>40.0	31	1	3.2	0.1	16.7	29	1	3.4	0.1	17.8
	Related	31	10	32.3	16.7	51.4	29	11	37.9	20.7	57.7
	>40.0 Related	31	0	0.0	0.0	11.2	29	1	3.4	0.1	17.8
	Medical advice	31	5	16.1	5.5	33.7	29	2	6.9	0.8	22.8

Unsolicited adverse events

At least one unsolicited AE was reported for 58.1% of subjects in the 12Pn_T group and 50.0% of subjects in the 10Pn_T group during the 31-day post-vaccination period. Rhinitis was the most frequently reported unsolicited AE in the 12Pn_T group [4 subjects (12.9%)] while diarrhea, bronchitis, otitis externa, rhinitis and viral infection were most frequently reported in the 10Pn_T group [2 subjects (6.7%)].

No grade 3 unsolicited AEs or grade 3 unsolicited AEs considered by the investigator to be causally related to vaccination were reported in both groups.

Serious adverse events

No fatal or non-fatal SAEs were reported during the study. No subject was withdrawn from the study due to an AE or SAE.

3. Discussion on clinical aspects

The immunogenicity data from this study generally confirm what is known from other studies using Synflorix. Likewise, the safety data do not add any new safety concerns for Synflorix, and the reactogenicity profile is similar to that seen in other studies. Therefore, it can be concluded that no further regulatory action is needed.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**
This paediatric procedure is considered fulfilled and no further regulatory action is required.

➢ **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable