

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

Infanrix-IPV+Hib

DE/W/0036/pdWS/006

Marketing Authorisation Holder:

GlaxoSmithKline Biologicals S.A.

Rapporteur:	Germany (PEI)
Finalisation procedure (day 90):	8 November 2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Infanrix-IPV+Hib
INN (or common name) of the active substance(s):	Diphtheria toxoid (D), Tetanus toxoid (T), Pertussis toxoid (PT), Filamentous haemagglutinin (FHA), Pertactin (PRN), Inactivated Polio Virus (IPV) Type 1, Inactivated Polio Virus (IPV) Type 2, Inactivated Polio Virus Type 3 and Conjugate of Haemophilus influenzae type b polysaccharide (PRP) and Tetanus toxoid (T)
MAH:	GlaxoSmithKline Biologicals S.A.
Currently approved Indication(s):	INFANRIX-IPV+Hib is indicated for active immunisation in infants from the age of 2 months against diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus influenzae type b. INFANRIX™-IPV+Hib is also indicated as a booster dose for children who have previously been immunised with DTP, polio and Hib antigens. The Hib component of the vaccine does not protect against diseases due to other serotypes of Haemophilus influenzae nor against meningitis caused by other organisms.
Pharmaco-therapeutic group (ATC Code):	J07CA06
Pharmaceutical form(s) and strength(s):	Powder and suspension for suspension for injection

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

The three studies submitted here do not add any new information to the well-known immunogenicity or safety profile of the vaccine. No further action is required.

III. INTRODUCTION

On 22 January 2016 the MAH submitted completed paediatric studies for Infanrix-IPV+Hib, 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 Infanrix-IPV+Hib and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Only the licensed products were used.

IV.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

- **DTPa-IPV-056** – A randomised, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 2-3-4 or 3-4-5 months of age in healthy infants in China
- **DTPa-IPV-057** – An open-label study to assess the immune persistence in healthy Chinese toddlers primed in infancy with three doses of GSK Biologicals' DTPa-IPV/Hib vaccine and to assess the safety and immunogenicity of a booster dose of IPV and DTPa/Hib administered at 18 to 24 months of age (**Extension study for DTPa-IPV-056**)
- **DTPa-IPV-060** – A phase III, single-group, open-label, multicentre study to assess the safety and reactogenicity of GlaxoSmithKline Biologicals' combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae type b (DTPa-IPV/Hib) vaccine Infanrix-IPV+Hib administered as a booster vaccine dose in healthy Vietnamese toddlers

2. Clinical study(ies)

Study DTPa-IPV-056

A randomised, open-label study to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered as a three-dose primary vaccination course at 2-3-4 or 3-4-5 months of age in healthy infants in China

➤ **Description**

Primary vaccination in two different schemes.

➤ **Methods**

- **Objective(s)**

Primary:

☐ To demonstrate that the immunogenicity of GSK Biologicals' DTPa-IPV/Hib vaccine administered at 2, 3 and 4 months of age (Group A) was non-inferior to that of the concomitant administration of GSK Biologicals' DTPa/Hib and IPV vaccines at the same age (Control Group), in terms of immune response to all vaccine antigens, one month after the third vaccine dose. Non-inferiority in terms of response to diphtheria, tetanus, poly-ribosyl-ribitol phosphate (PRP), poliovirus types 1, 2 and 3 was demonstrated if the 95% confidence interval (CI) on the group difference [Control Group minus Group A] in percentage of seroprotected subjects was $\leq 10\%$.

Non-inferiority in terms of response to pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) was demonstrated if the 95% CI on the group difference [Control Group minus Group A] in the percentage of subjects with a vaccine response was $\leq 10\%$.

Secondary:

☐ To assess the immunological response to the study vaccines in terms of seroprotection/seropositivity, geometric mean concentrations (GMCs) or geometric mean titres (GMTs) for all antigens and in terms of vaccine response for pertussis antigens, one month after the third vaccine dose.

☐ To assess the safety and reactogenicity of the study vaccines in terms of solicited, unsolicited, local and general symptoms and serious adverse events.

- **Study design**

An open-label, randomised (1:1:1) multicentre study in China with three parallel groups. Subjects were assigned to one of three following groups:

☐ Group A: DTPa-IPV/Hib vaccine at 2, 3, 4 months of age.

☐ Group B: DTPa-IPV/Hib vaccine at 3, 4, 5 months of age.

☐ Control Group: DTPa/Hib + IPV vaccines at 2, 3, 4 months of age.

Two blood samples were taken from an immunogenicity subset that comprised of 480 subjects (first 160 subjects in each group), one before the administration of the first vaccine dose and the other one month after the third vaccine dose.

- **Study population /Sample size**

Healthy male or female infants, between, and including, 60 and 90 days of age at the time of the first study visit were included in this study.

- Outcomes/endpoints

Immunogenicity:

Measurement of anti-tetanus, anti-diphtheria, anti-PRP and anti-poliovirus types 1, 2 and 3 antibody concentrations or titres one month after the third vaccine dose. Seroprotection was defined as antibody concentrations ≥ 0.1 IU/ml for anti-T and anti-D, ≥ 0.15 µg/ml for anti-PRP and antibody titres ≥ 8 ED₅₀ for anti-poliovirus types 1, 2, and 3. Vaccine response to PT, FHA and PRN was also evaluated. Vaccine response was defined as antibody concentration ≥ 20 EL.U/ml at postvaccination for PT and FHA antigens. For PRN antigen, vaccine response was defined as postvaccination antibody concentration ≥ 20 EL.U/ml (4-fold the assay cut-off) for initially seronegative subjects and at least a 4-fold increase in antibody concentration from pre- to post-vaccination for initially seropositive subjects.

Safety /reactogenicity:

Recording of solicited local (pain, redness, swelling) and general (fever, drowsiness, irritability/fussiness, loss of appetite) adverse events (AEs) by the parent(s) /LAR(s) during the 4-day (Day 0-3) follow-up period after each dose of study vaccine. Recording of unsolicited AEs that occurred during the 31-day (Day 0-30) follow-up period after each dose of study vaccine and Serious Adverse Events (SAEs) from Dose 1 up to study end.

- Statistical Methods

Analysis of immunogenicity: The primary analysis was based on the ATP cohort for analysis of immunogenicity. Since the percentage of subjects excluded from the ATP cohort for immunogenicity did not exceed 5%, secondary analyses based on the Total Vaccinated cohort was not performed. Inferential analysis: One month after the third vaccine dose, for each antibody for which results were available:

☐ The standardised asymptotic 95% CIs for the difference between groups (Control Group minus Group A) in seroprotection rates against diphtheria, tetanus, Hib and poliovirus types 1, 2 and 3 were computed.

☐ The standardised asymptotic 95% CIs for the difference between groups (Control Group minus Group A) in vaccine response rates against pertussis antigens PT, FHA and PRN was computed.

Descriptive analysis: For each treatment group, at each time point that a blood sample result was available:

☐ Seroprotection rates (with exact 95% CI) for diphtheria, tetanus, PRP and each of the three poliovirus antigens were calculated.

☐ Seropositivity rates (with exact 95% CI) and percentage of subjects ≥ 20 ELU/ml for PT, FHA and PRN were calculated per group.

☐ Percentage of subjects with a fourfold increase for PT, FHA and PRN antigens were calculated per group.

☐ GMC/GMT with 95% CI was tabulated for antibodies against each antigen.

☐ The distribution of antibody concentrations at post-vaccination time point for each antigen was displayed using reverse cumulative distribution curves (RCCs).

Exploratory analysis: The following exploratory comparisons between groups were performed:

☐ The standardised asymptotic 95% CIs for the group difference in seroprotection rates to diphtheria tetanus, PRP and poliovirus types 1, 2 and 3 [Control Group minus Group B and Group B minus Group A], one month after the last vaccine dose, was computed.

☐ The standardised asymptotic 95% CIs for the group difference in vaccine response to the pertussis antigens [Control Group minus Group B and Group B minus Group A], one month after the last vaccine dose, was computed.

□ The standardised asymptotic 95% CIs for the GMC ratio between groups (Control Group divided by Group A and Control Group divided by Group B) for all vaccine antigens one month after the three dose vaccination course was computed using analysis of co-variance (ANCOVA) model including the group as fixed effect and the log-transformed pre-vaccination titre as co-variable.

Exploratory group comparisons were examined as follows: the exclusion of 1 from the 95% CI on the GMC ratios or exclusion of 0 from the 95% CI on the differences in seroprotection/vaccine response rates was used to highlight potential group differences. However, these potential differences should be interpreted with caution considering that there was no adjustment for multiplicity for these comparisons and that the clinical relevance of any differences was not accounted for in the planning of the exploratory analyses.

➤ Results

• Recruitment/ Number analysed

Title	Total			Group A		Group B		Control Group	
	n	s	%	n	s	n	s	n	s
Total cohort	985			331		324		330	
Study vaccine dose not administered but subject number allocated (code 1030)	1	1		1	1	0	0	0	0
Total Vaccinated cohort	984		100	330		324		330	
ATP cohort for safety	984		100	330		324		330	
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	10	10		6	6	3	3	1	1
Essential serological data missing (code 2100)	20	21		10	11	2	2	8	8
Subject not planned to be bled for their all blood sampling visits (code 2130)	499	504		167	170	162	164	170	170
ATP cohort for immunogenicity*	455		46.2	147		157		151	

Group A = Subjects who received DTPa-IPV/Hib vaccine at 2, 3, 4 months of age

Group B = Subjects who received DTPa-IPV/Hib vaccine at 3, 4, 5 months of age

Control Group = Subjects who received DTPa/Hib + IPV vaccines at 2, 3, 4 months of age

- Baseline data
The mean age of the subjects in the ATP cohort for immunogenicity was 11.4 weeks with a standard deviation of 2.36 weeks. Male subjects constituted 55.6% of the study population. All the subjects vaccinated in the study were of Asian-Chinese heritage. The demographic profile between the three groups was comparable, with respect to mean age, gender and distribution of geographic ancestry.
- Efficacy results
Non-inferiority of Infanrix-IPV/Hib could be shown:

Table 1 Difference between groups (Control minus Group A) one month after the third dose of vaccination (ATP cohort for immunogenicity)

Antibody	Group 1	N	%	Group 2	N	%	Difference in seroprotection rate (Control- Group A)			
							Difference	95 % CI		
								%	LL	UL
Anti-D (≥ 0.1 IU/ml)	Group A	147	99.3	Control Group	147	100	Control - Group A	0.68	-1.88	3.76*
Anti-T (≥ 0.1 IU/ml)	Group A	147	100	Control Group	147	100	Control - Group A	0.00	-2.56	2.56*
Anti-PRP (≥ 0.15 μ g/ml)	Group A	147	96.6	Control Group	150	88.7	Control - Group A	-7.93	-14.44	-2.13*
Anti-poliovirus type 1 (≥ 8 ED ₅₀)	Group A	147	100	Control Group	150	100	Control - Group A	0.00	-2.51	2.56*
Anti-poliovirus type 2 (≥ 8 ED ₅₀)	Group A	147	100	Control Group	150	100	Control - Group A	0.00	-2.51	2.56*
Anti-poliovirus type 3 (≥ 8 ED ₅₀)	Group A	147	100	Control Group	150	100	Control - Group A	0.00	-2.51	2.56*

Group A = Subjects who received DTPa-IPV/Hib vaccine at 2, 3, 4 months of age; Control Group = Subjects who received DTPa/Hib + IPV vaccines at 2, 3, 4 months of age

Antibody	Control Group			Group A			Difference in vaccine response rate (Control minus Group A)		
	N	n	%	N	n	%	%	95% CI	
								LL	UL
Anti-PT	148	147	99.3	147	147	100	-0.68	-3.74	1.89*
Anti-FHA	148	144	97.3	147	147	100	-2.70	-6.75	-0.11*
Anti-PRN	148	145	98.0	147	145	98.6	-0.67	-4.60	3.04*

Table 2 Seroprotection rates and GMCs

Antibody	Group	Timing	N	$\geq 8 \text{ ED}_{50}$				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
Anti-poliovirus type 1	Group A	PRE	146	63	43.2	35.0	51.6	9.4	7.7	11.5
		POST	147	147	100	97.5	100	1143.7	952.7	1372.9
	Group B	PRE	157	62	39.5	31.8	47.6	7.1	6.2	8.2
		POST	157	157	100	97.7	100	1328.9	1137.6	1552.4
	Control Group	PRE	151	69	45.7	37.6	54.0	9.2	7.7	11.0
		POST	150	150	100	97.6	100	533.6	469.5	606.4
Anti-poliovirus type 2	Group A	PRE	146	43	29.5	22.2	37.6	6.3	5.5	7.2
		POST	147	147	100	97.5	100	416.2	344.5	502.8
	Group B	PRE	157	32	20.4	14.4	27.5	5.0	4.6	5.5
		POST	157	157	100	97.7	100	458.6	385.6	545.5
	Control Group	PRE	151	54	35.8	28.1	44.0	6.9	6.0	8.0
		POST	150	150	100	97.6	100	186.4	160.4	216.5
Anti-poliovirus type 3	Group A	PRE	146	29	19.9	13.7	27.3	5.8	5.0	6.8
		POST	147	147	100	97.5	100	1478.8	1210.6	1806.5
	Group B	PRE	157	18	11.5	6.9	17.5	4.9	4.3	5.6
		POST	157	157	100	97.7	100	1411.6	1175.3	1695.3
	Control Group	PRE	151	34	22.5	16.1	30.0	5.7	5.1	6.4
		POST	150	150	100	97.6	100	820.7	698.5	964.4

Antibody	Group	Timing	N	$\geq 0.15 \mu\text{g/ml}$				$\geq 1 \mu\text{g/ml}$				GMC		
				n	%	95% CI		n	%	95% CI		value	95% CI	
						LL	UL			LL	UL		LL	UL
Anti-PRP	Group A	PRE	146	25	17.1	11.4	24.2	18	12.3	7.5	18.8	0.127	0.104	0.154
		POST	147	142	96.6	92.2	98.9	141	95.9	91.3	98.5	5.601	4.676	6.709
	Group B	PRE	157	32	20.4	14.4	27.5	23	14.6	9.5	21.2	0.135	0.112	0.163
		POST	157	155	98.7	95.5	99.8	155	98.7	95.5	99.8	9.396	8.032	10.992
	Control Group	PRE	151	35	23.2	16.7	30.7	25	16.6	11.0	23.5	0.150	0.122	0.185
		POST	150	133	88.7	82.5	93.3	133	88.7	82.5	93.3	2.826	2.235	3.572

Antibody	Group	Timing	N	$\geq 0.1 \text{ IU/ml}$				$\geq 1 \text{ IU/ml}$				GMC		
				n	%	95% CI		n	%	95% CI		value	95% CI	
						LL	UL			LL	UL		LL	UL
Anti-D	Group A	PRE	147	3	2.0	0.4	5.8	0	0.0	0.0	2.5	0.052	0.050	0.053
		POST	147	146	99.3	96.3	100	27	18.4	12.5	25.6	0.719	0.661	0.782
	Group B	PRE	157	2	1.3	0.2	4.5	0	0.0	0.0	2.3	0.051	0.050	0.052
		POST	156	156	100	97.7	100	36	23.1	16.7	30.5	0.753	0.699	0.812
	Control Group	PRE	151	1	0.7	0.0	3.6	0	0.0	0.0	2.4	0.051	0.049	0.052
		POST	147	147	100	97.5	100	24	16.3	10.7	23.3	0.613	0.565	0.666
Anti-T	Group A	PRE	147	2	1.4	0.2	4.8	0	0.0	0.0	2.5	0.051	0.050	0.052
		POST	147	147	100	97.5	100	147	100	97.5	100	4.118	3.779	4.488
	Group B	PRE	157	4	2.5	0.7	6.4	0	0.0	0.0	2.3	0.052	0.050	0.054
		POST	156	156	100	97.7	100	155	99.4	96.5	100	4.124	3.796	4.479
	Control Group	PRE	151	0	0.0	0.0	2.4	0	0.0	0.0	2.4	0.050	0.050	0.050
		POST	147	147	100	97.5	100	147	100	97.5	100	3.618	3.339	3.921

Group A = Subjects who received DTPa-IPV/Hib vaccine at 2, 3, 4 months of age

Group B = Subjects who received DTPa-IPV/Hib vaccine at 3, 4, 5 months of age

Control Group = Subjects who received DTPa/Hib + IPV vaccines at 2, 3, 4 months of age

Table 3 Vaccine response

Antibody	Group	Pre-vaccination status	N	Vaccine response			
				n	%	95% CI	
						LL	UL
Anti-PRN	Group A	S-	141	140	99.3	96.1	100
		S+	6	5	83.3	35.9	99.6
		Total	147	145	98.6	95.2	99.8
	Group B	S-	152	152	100	97.6	100
		S+	4	4	100	39.8	100
		Total	156	156	100	97.7	100
	Control Group	S-	145	142	97.9	94.1	99.6
		S+	3	3	100	29.2	100
		Total	148	145	98.0	94.2	99.6
Antibody	Group	Pre-vaccination status	N	Vaccine response			
				n	%	95% CI	
						LL	UL
Anti-PT	Group A	S-	124	124	100	97.1	100
		S+	23	23	100	85.2	100
		Total	147	147	100	97.5	100
	Group B	S-	145	144	99.3	96.2	100
		S+	11	11	100	71.5	100
		Total	156	155	99.4	96.5	100
	Control Group	S-	132	131	99.2	95.9	100
		S+	16	16	100	79.4	100
		Total	148	147	99.3	96.3	100
Anti-FHA	Group A	S-	128	128	100	97.2	100
		S+	19	19	100	82.4	100
		Total	147	147	100	97.5	100
	Group B	S-	147	146	99.3	96.3	100
		S+	9	9	100	66.4	100
		Total	156	155	99.4	96.5	100
	Control Group	S-	125	122	97.6	93.1	99.5
		S+	23	22	95.7	78.1	99.9
		Total	148	144	97.3	93.2	99.3

Group A = Subjects who received DTPa-IPV/Hib vaccine at 2, 3, 4 months of age

Group B = Subjects who received DTPa-IPV/Hib vaccine at 3, 4, 5 months of age

Control Group = Subjects who received DTPa/Hib + IPV vaccines at 2, 3, 4 months of age

S- = initially seronegative subjects (antibody concentrations < 5 EL.U/ml for anti-PT and anti-FHA) prior to vaccination

S+ = initially seropositive subjects (antibody concentrations ≥ 5 EL.U/ml for anti-PT and anti-FHA) prior to vaccination

- **Safety results**

Any symptom: At least one symptom (solicited/unsolicited, local/general) was reported for 83.9% of subjects in Group A, 84% in Group B and 80.9% in the Control Group. General symptoms were reported more frequently than local symptoms.

Solicited local symptoms: Pain at the injection site was the most frequently reported solicited local symptom, during the 4-day (Day 0-3) follow-up period after vaccination, reported for 27.3% of subjects in Group A, 28.1% in Group B and 30.9% in Control Group. It was also the most frequently reported Grade 3 solicited local symptom, however, it was reported by a maximum of only three subjects across groups.

Solicited general symptoms: Fever was the most frequently reported solicited general symptom, reported for 65.8% of subjects in Group A, 67% of subjects in Group B and 55.5% of subjects in the Control Group. Fever was also the most frequently reported Grade 3 solicited general symptom, reported for a maximum of nine subjects (2.8%) across groups. Most of the solicited general symptoms were causally related to vaccination.

Unsolicited symptoms: At least one unsolicited symptom was reported for 29.7% of subjects in Group A, 35.2% of subjects in Group B and 33.3% of subjects in Control Group during the 31-day (Day 0-30) follow-up period after vaccination. Grade 3 unsolicited symptoms were reported for 1.5% of subjects in Group A, 0.9% of subjects in Group B and 0.3% of subjects in the Control Group. None of the Grade 3 unsolicited symptoms were assessed by the investigator to be causally related to vaccination. Unsolicited symptoms that were considered by the investigator to be causally related to vaccination were reported for 2.7% of subjects in Group A, 1.2% of subjects in Group B and 3% in the Control Group.

Serious adverse events: A total of 17 SAEs were reported for 13 subjects (six subjects in Group A, three subjects in Group B and four subjects in the Control Group). A 4-month-old subject in Group A developed acute bronchopneumonia, hypokalaemia and protein malnutrition one day after the third dose of the DTPa-IPV/Hib vaccine. The cause of death was infectious shock due to acute bronchopneumonia and congestive heart failure. These two events were not considered by the investigator as causally related to the vaccination. This subject also experienced two other non-fatal SAEs (hypokalaemia and protein-energy malnutrition). These SAEs did not resolve by the end of the study. All other non-fatal SAEs resolved before the end of the study.

Withdrawals due to AEs /SAEs: Five subjects (three in Group A and two in Group B) were withdrawn from the study due to AEs/SAEs. None of these AEs/SAEs were considered by the investigator as causally related to the vaccination.

Study DTPa-IPV-057 (Extension study for DTPa-IPV-056)

An open-label study to assess the immune persistence in healthy Chinese toddlers primed in infancy with three doses of GSK Biologicals' DTPa-IPV/Hib vaccine and to assess the safety and immunogenicity of a booster dose of IPV and DTPa/Hib administered at 18 to 24 months of age

➤ Description

A Phase IIIA, open-label, multi-centric, single-country study with three parallel groups. The groups in this study were identified according to the vaccine received in the primary study DTPa IPV 056 (112584):

☐ Group A: Subjects who received the DTPa-IPV/Hib vaccine at 2, 3, 4 months of age in the primary study.

☐ Group B: Subjects who received the DTPa-IPV/Hib vaccine at 3, 4, 5 months of age in the primary study.

☐ Control: Subjects who received the DTPa/Hib + IPV vaccines at 2, 3, 4 months of age in the primary study.

All subjects received the same vaccines as booster: DTPa/Hib (Infanrix Hib) and IPV (Poliorix) vaccines

Two blood samples were collected: one sample before the booster dose (of Infanrix Hib and Poliorix) and the second sample one month after the booster dose.

➤ Methods

- Objective(s)

Co-Primary:

☐ The persistence of antibodies to all vaccine antigens before the booster dose was assessed.

☐ The immune response to the study vaccines in terms of seroprotection to diphtheria, tetanus, Haemophilus influenzae type b and poliovirus types 1, 2 and 3, and in terms of vaccine response to the pertussis antigens, one month after booster vaccination was assessed.

☐ The immune response to the study vaccines in terms of antibody concentrations or titres for all antigens, one month after the booster dose was assessed.

Secondary:

☐ The safety and reactogenicity of the booster dose of the study vaccines in terms of solicited and unsolicited, local and general symptoms and serious adverse events were assessed.

➤ Results

- Recruitment/ Number analysed

Table 4 Number of participants in the extension study -057

Study population (ATP cohort for immunogenicity)-			
Number of subjects	Group A	Group B	Control
Planned, N	330	330	330
N (ATP cohort for immunogenicity)	266	268	273
Completed, n (%)	266 (100)	268 (100)	273 (100)
Demographics	Group A	Group B	Control
N (ATP cohort for immunogenicity)	266	268	273
Females: Males	130:136	123:145	114:159
Mean Age, months (SD)	19.5 (0.9)	19.4 (0.9)	19.5 (1.0)
Median Age, months (minimum, maximum)	20 (18, 22)	19 (18, 21)	20 (18, 22)
Asian - Chinese heritage, n (%)	266 (100)	268 (100)	273 (100)
Group A = Subjects who received DTPa-IPV/Hib vaccine at 2, 3, 4 months of age in the primary study, Group B = Subjects who received DTPa-IPV/Hib vaccine at 3, 4, 5 months of age in the primary study, Control = Subjects who received DTPa/Hib + IPV vaccines at 2, 3, 4 months of age in the primary study.			

- Efficacy results

All groups showed similar persistence seroprotection rates and GMCs prior to the booster dose of the respective vaccine and also similar GMCs and seroprotection increases after the booster dose.

Table 5 Seroprotection rates and geometric mean concentrations (GMC) by groups at pre and one month post-booster vaccination (ATP cohort for immunogenicity)

				≥ 0.1 IU/ml				≥ 1 IU/ml				GMC		
				95% CI				95% CI				95% CI		
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-Diphtheria	Group A	Pre-BST	265	235	88.7	84.2	92.2	1	0.4	0.0	2.1	0.174	0.162	0.187
		Post-BST	265	265	100	98.6	100	160	60.4	54.2	66.3	1.341	1.239	1.451
	Group B	Pre-BST	267	245	91.8	87.8	94.8	0	0.0	0.0	1.4	0.189	0.176	0.202
		Post-BST	268	268	100	98.6	100	174	64.9	58.9	70.6	1.504	1.377	1.643
	Control	Pre-BST	272	228	83.8	78.9	88.0	2	0.7	0.1	2.6	0.154	0.142	0.166
		Post-BST	270	270	100	98.6	100	150	55.6	49.4	61.6	1.227	1.134	1.326
Anti-Tetanus	Group A	Pre-BST	266	264	99.2	97.3	99.9	8	3.0	1.3	5.8	0.455	0.429	0.483
		Post-BST	266	266	100	98.6	100	266	100	98.6	100	4.862	4.614	5.124
	Group B	Pre-BST	268	266	99.3	97.3	99.9	10	3.7	1.8	6.8	0.511	0.482	0.542
		Post-BST	268	268	100	98.6	100	268	100	98.6	100	4.927	4.693	5.173
	Control	Pre-BST	271	268	98.9	96.8	99.8	6	2.2	0.8	4.8	0.380	0.357	0.403
		Post-BST	272	272	100	98.7	100	270	99.3	97.4	99.9	4.371	4.161	4.591
				≥ 5 ELU/ml				≥ 20 ELU/ml				GMC		
				95% CI				95% CI				95% CI		
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PT	Group A	Pre-BST	266	254	95.5	92.3	97.6	37	13.9	10.0	18.7	10.3	9.5	11.1
		Post-BST	266	266	100	98.6	100	266	100	98.6	100	138.5	132.0	145.3
	Group B	Pre-BST	268	258	96.3	93.2	98.2	61	22.8	17.9	28.3	12.2	11.3	13.1
		Post-BST	268	268	100	98.6	100	268	100	98.6	100	146.2	139.7	153.0
	Control	Pre-BST	273	253	92.7	88.9	95.5	43	15.8	11.6	20.6	10.3	9.5	11.2
		Post-BST	273	273	100	98.7	100	272	99.6	98.0	100	126.8	120.4	133.5
Anti-FHA	Group A	Pre-BST	266	256	96.2	93.2	98.2	54	20.3	15.6	25.6	12.7	11.8	13.6
		Post-BST	266	266	100	98.6	100	266	100	98.6	100	124.6	119.2	130.2
	Group B	Pre-BST	268	262	97.8	95.2	99.2	73	27.2	22.0	33.0	14.3	13.4	15.2
		Post-BST	268	268	100	98.6	100	268	100	98.6	100	124.0	119.2	129.0
	Control	Pre-BST	273	255	93.4	89.8	96.0	61	22.3	17.5	27.8	12.3	11.4	13.3
		Post-BST	273	273	100	98.7	100	272	99.6	98.0	100	120.8	115.3	126.6
Anti-PRN	Group A	Pre-BST	266	254	95.5	92.3	97.6	7	2.6	1.1	5.3	9.2	8.7	9.6
		Post-BST	266	266	100	98.6	100	266	100	98.6	100	57.3	55.6	59.1
	Group B	Pre-BST	268	260	97.0	94.2	98.7	10	3.7	1.8	6.8	9.7	9.2	10.2
		Post-BST	268	268	100	98.6	100	267	99.6	97.9	100	59.9	58.1	61.8
	Control	Pre-BST	273	260	95.2	92.0	97.4	5	1.8	0.6	4.2	9.0	8.5	9.5
		Post-BST	273	273	100	98.7	100	272	99.6	98.0	100	57.2	55.3	59.1

				$\geq 8 \text{ ED}_{50}$				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-Poliovirus 1	Group A	Pre-BST	266	253	95.1	91.8	97.4	72.0	62.0	83.7
		Post-BST	265	265	100	98.6	100	3512.2	3159.7	3904.1
	Group B	Pre-BST	268	262	97.8	95.2	99.2	96.3	82.8	112.0
		Post-BST	268	268	100	98.6	100	3410.9	3081.7	3775.4
	Control	Pre-BST	273	263	96.3	93.4	98.2	75.9	65.7	87.6
		Post-BST	273	273	100	98.7	100	3386.8	3078.0	3726.6
Anti-Poliovirus 2	Group A	Pre-BST	266	243	91.4	87.3	94.4	56.5	46.2	69.0
		Post-BST	265	265	100	98.6	100	1931.2	1721.7	2166.2
	Group B	Pre-BST	268	256	95.5	92.3	97.7	64.1	53.8	76.4
		Post-BST	268	268	100	98.6	100	2237.9	2001.6	2502.1
	Control	Pre-BST	273	244	89.4	85.1	92.8	41.9	35.0	50.0
		Post-BST	273	273	100	98.7	100	1886.1	1679.6	2117.9
Anti-Poliovirus 3	Group A	Pre-BST	266	249	93.6	90.0	96.2	72.6	61.1	86.3
		Post-BST	265	265	100	98.6	100	5237.8	4671.8	5872.3
	Group B	Pre-BST	268	254	94.8	91.4	97.1	79.4	65.8	95.8
		Post-BST	268	268	100	98.6	100	5438.5	4846.8	6102.4
	Control	Pre-BST	273	250	91.6	87.6	94.6	60.3	50.8	71.6
		Post-BST	273	273	100	98.7	100	5141.2	4650.1	5684.2

- Safety results

Nearly 60% of the vaccinees reported at least one reaction (systemic or local) against the booster dose. Pain, again was the most frequently reported local (27.2%) and fever the most common systemic reaction (38.5%); rates did not differ across the groups.

At least one unsolicited symptom was reported during the 31-day (Days 0-30) follow up period for 7.5% of subjects across groups. The most frequently reported unsolicited symptom was nasopharyngitis for 4.6% of the subjects across the groups. The following unsolicited symptoms of Grade 3 intensity was reported for three subjects; bronchitis, pharyngitis and upper respiratory tract infection. The unsolicited symptom, abdominal pain was reported for one subject was considered by the investigator to be causally related to vaccination. None of the Grade 3 unsolicited symptoms were assessed by the investigator as causally related to the vaccination. Two SAEs were reported for a subject during the study period. None of these SAEs were considered by the investigator to be causally related to the vaccination. No fatal events were reported during the study.

None of the subjects were withdrawn from the study due to an AE or SAE during the study period.

Rapporteur's comment:

The two studies DTPa-IPV-056 and -057 show similar GMC and seroprotection rates for all vaccines used, persistence of antibodies is also alike. Safety profiles are very similar in both studies across the vaccine groups. After the booster dose the rate of local and systemic reactions is lower than in the priming study. No safety issues.

Study DTPa-IPV-060

A phase III, single-group, open-label, multicentre study to assess the safety and reactogenicity of GlaxoSmithKline Biologicals' combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae type b (DTPa-IPV/Hib) vaccine Infanrix-IPV+Hib administered as a booster vaccine dose in healthy Vietnamese toddlers

➤ **Description**

A Phase III, open-label, single group, single country, multicentre safety study. However enrolment was completed in one centre. No blood samples were collected in this safety study. Healthy male or female subjects between, and including, 12 to 24 months of age at the time of vaccination, who were primed with three doses of a combined diphtheria tetanus pertussis (DTP) and polio vaccine in the first six months of life, and had received the last dose of the primary vaccination at least six months before the receipt of study vaccine were included in the study. Subjects with evidence of previous or intercurrent booster vaccination against diphtheria, tetanus, pertussis, poliomyelitis and/or Hib disease or vaccination were excluded from the study. Written informed consent was to be obtained from the parent(s) or legally acceptable representative(s) of the subject prior to any study procedure.

➤ **Methods**

- Endpoints

☐ Solicited local and general symptoms

☐ Occurrence of each solicited local and general symptoms during the 4-day (Day 0–3) follow-up after booster vaccination

☐ Unsolicited adverse events.

☐ Occurrence of unsolicited symptoms during the 31-day (Day 0-30) follow-up period following the booster dose of the study vaccine, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification

☐ Serious adverse events

☐ Occurrence of SAEs from the receipt of booster dose up to study end

➤ **Results**

- Recruitment/ Number analysed

Table 6 Study participants

Study population (Total vaccinated cohort)	
Number of subjects	DTPa-IPV/Hib Group
Planned, N	300
Randomised, N (Total vaccinated cohort)	300
Completed, n (%)	300 (100)
Demographics	DTPa-IPV/Hib Group
N (Total vaccinated cohort)	300
Females: Males	143:157
Mean Age, months (SD)	15.8 (2.96)
Asian - South East Asian Heritage, n (%)	300 (100)
DTPa-IPV/Hib Group = Subjects vaccinated with a booster dose of DTPa-IPV/Hib at 12-24 months of age	
N = Total number of subjects	
n/% = Number/percentage of subjects in a given category	

All subjects completed the study.

- Safety results

Table 7 Incidence of solicited local symptoms reported during the 4-day (Day 0-3) post-vaccination period (Total vaccinated cohort)

		DTPa-IPV/Hib Group				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Pain	All	300	95	31.7	26.4	37.3
	Grade 3	300	6	2.0	0.7	4.3
	Medical advice	300	0	0.0	0.0	1.2
Redness (mm)	All	300	82	27.3	22.4	32.8
	>20.0	300	1	0.3	0.0	1.8
	Medical advice	300	0	0.0	0.0	1.2
Swelling (mm)	All	300	52	17.3	13.2	22.1
	>20.0	300	1	0.3	0.0	1.8
	Medical advice	300	0	0.0	0.0	1.2

DTPa-IPV/Hib Group = Subjects vaccinated with a booster dose of DTPa-IPV/Hib at 12-24 months of age

N= number of subjects with the documented dose

n/%= number/percentage of subjects reporting the symptom at least once

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

For pain, Grade 3: Cried when limb was moved/spontaneously painful

Table 8 Incidence of solicited sytemic symptoms reported during the 4-day (Day 0-3) post-vaccination period (Total vaccinated cohort)

		DTPa-IPV/Hib Group				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Drowsiness	All	300	52	17.3	13.2	22.1
	Grade 3	300	3	1.0	0.2	2.9
	Related	300	47	15.7	11.7	20.3
	Grade 3 Related	300	3	1.0	0.2	2.9
	Medical advice	300	0	0.0	0.0	1.2
Irritability / fussiness	All	300	108	36.0	30.6	41.7
	Grade 3	300	5	1.7	0.5	3.8
	Related	300	90	30.0	24.9	35.5
	Grade 3 Related	300	5	1.7	0.5	3.8
	Medical advice	300	0	0.0	0.0	1.2
Loss of appetite	All	300	115	38.3	32.8	44.1
	Grade 3	300	5	1.7	0.5	3.8
	Related	300	90	30.0	24.9	35.5
	Grade 3 Related	300	4	1.3	0.4	3.4
	Medical advice	300	2	0.7	0.1	2.4
Temperature/(Axillary) (°C)	≥37.5	300	101	33.7	28.3	39.3
	>38.5	300	14	4.7	2.6	7.7
	>39.0	300	6	2.0	0.7	4.3
	Related	300	88	29.3	24.2	34.8
	>39.0 Related	300	6	2.0	0.7	4.3
	Medical advice	300	8	2.7	1.2	5.2
		300				

DTPa-IPV/Hib Group = Subjects vaccinated with a booster dose of DTPa-IPV/Hib at 12-24 months of age

N= number of subjects with the documented dose

n/%= number/percentage of subjects reporting the symptom at least once

Grade 3, For Irritability/Fussiness, Severe: Crying that could not be comforted/prevented normal activity

For Drowsiness, Severe: Drowsiness that prevented normal activity

For Loss of appetite, Severe = Did not eat at all

CI= Exact 95% confidence interval; LL = lower limit. UL = upper limit

☐ At least one symptom (solicited or unsolicited) was reported for 64% of subjects and at least one symptom (solicited or unsolicited) of Grade 3 intensity was reported for 5.7% of subjects during the 4-day follow-up period after administration of DTPa-IPV/Hib vaccine.

☐ Pain and loss of appetite were the most frequently reported solicited local and general symptoms; reported for 31.7% and 38.3% of subjects, respectively. Pain and fever were the most frequently reported solicited local and general symptoms of Grade 3 intensity and were reported each for 2% of subjects, respectively.

☐ Unsolicited symptoms were reported for 35.7% of subjects during the 31-day follow-up period after vaccination. At least one unsolicited symptom of Grade 3 intensity was reported for 1% of subjects and at least one unsolicited symptom, assessed by the investigator as causally related to vaccination, was reported for 0.7% of subjects.

☐ Two SAEs (pneumonia and convulsions) were reported for one subject during the entire study period. Both the SAEs were resolved and were assessed by the investigator as not causally related to the study vaccine. No fatal SAEs were reported during the entire study period.

Rapporteur's comment:

The safety profile is very similar to that already known no new safety issues are reported.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The three studies submitted here do not add any new information to the well-known immunogenicity or safety profile of the vaccine.

➤ Recommendation

No further action required