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

Poliorix
Inactivated poliovirus (IPV) types 1, 2 and 3

PL/W/0018/pdWS/001

Marketing Authorisation Holder: GlaxoSmithKline Biologicals

Rapporteur:	Poland
Finalisation procedure (day 90):	24.01.2017

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Poliorix
INN (or common name) of the active substance(s):	Inactivated poliovirus (IPV) types 1, 2 and 3
MAH:	GlaxoSmithKline Biologicals S.A.
Currently approved Indication(s)	Poliorix is indicated for active immunisation from the age of 2 months against poliomyelitis
Pharmaco-therapeutic group (ATC Code):	J07BF03
Pharmaceutical form(s) and strength(s):	Solution for injection Vials of 0.5 ml dose of vaccine contains: 40 D antigen units of type 1 (Mahoney) 8 D antigen units of type 2 (MEF-1) 32 D antigen units of type 3 (Saukett) of the polio virus

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

The presented study does not contribute new information to the known efficacy and safety profiles of Poliorix™. Therefore, the EU SmPC does not need to be updated.

III. INTRODUCTION

On 26 September 2016, the MAH submitted one completed paediatric study for Poliorix™ , in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview from September 2016 has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Poliorix™ and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

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

GSK Biologicals' Inactivated poliomyelitis vaccine Poliorix™ , and GSK Biologicals' DTPa Vaccine (Infanrix-Hib) were used in this study.
Poliorix™ pharmaceutical formulation corresponds to WHO and European regulatory requirements.
The composition of the study vaccines is presented in table below.

Treatment identifier	Vaccine name	Formulation	Presentation	Volume
Infanrix Hib	DTPa	DT ≥ 30 IU (25 Lf), TT ≥ 40 IU (10 Lf), PT 25 µg, FHA 25 µg, PRN 8 µg, Aluminium as salts: 0.5 mg, 2-phenoxyethanol: ≤ 2.5 mg Excipients: Sodium chloride, water for injections in the DTPa component and Residues: Formaldehyde, polysorbate 80	The DTPa component is presented as a turbid white suspension in a pre-filled syringe.	0.5ml*
	Hib	PRP: 10 µg conjugated to TT: 20-40 µg Excipient: Lactose	The lyophilised Hib component is presented as a white pellet in a glass vial.	
IPV	IPV	Poliovirus: Inactivated poliovirus type 1 (Mahoney): 40 D antigen units Inactivated poliovirus type 2 (MEF-1): 8 D antigen units Inactivated poliovirus type 3 (Saukett):32 D antigen units Excipients: 2-phenoxyethanol Medium 199 including amino acids Formaldehyde Polysorbate 80 Water for injections Residues: Neomycin sulphate and polymyxin sulphate	Clear liquid solution in glass vials	0.5ml

* After reconstitution

IV.2 Clinical aspects

1. Introduction

The MAH submitted the final report for one Phase IIIA study:

- **DTPa-IPV-057 BST:056 (114386 – EudraCT number: 2012-003324-20).**

2. Clinical study(ies)

Title: 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**

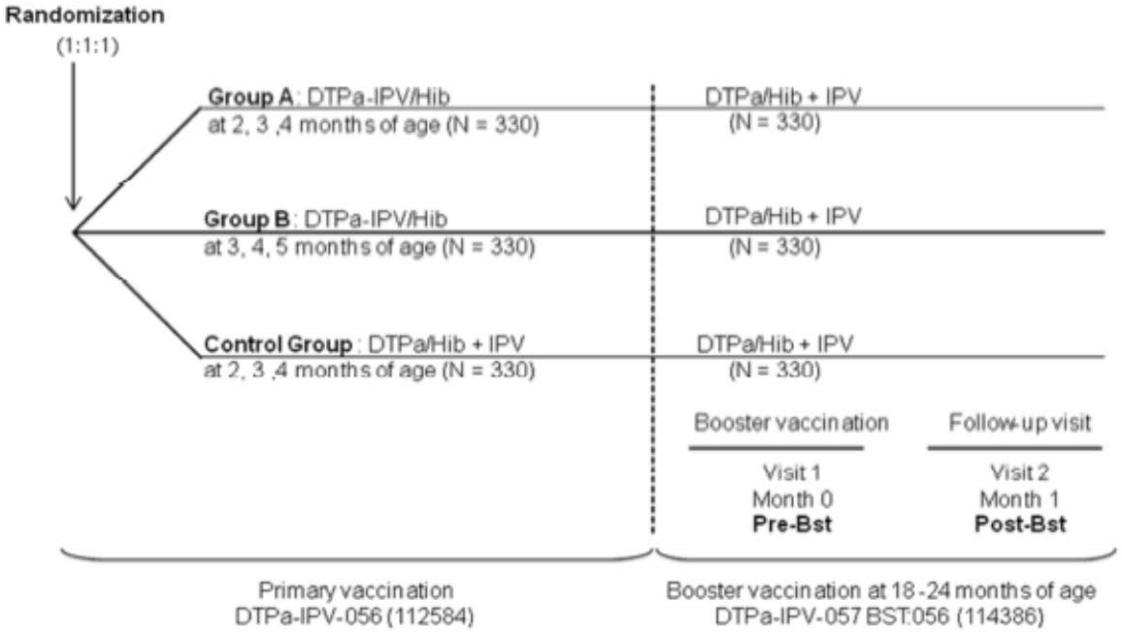
  A Phase IIIA, open-label, multi-centric, single-country study to demonstrate the efficacy and safety in booster immunisation of healthy children in the second year of life against diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus influenzae type b (Hib) diseases. The study was a multicentre study in China. GSK Biologicals' DTPa (Infanrix), Hib (Hiberix) and the combined DTPa/Hib vaccine (Infanrix Hib) vaccines are

licensed and available in China. GSK Biologicals' IPV stand-alone vaccine (Poliorix) was studied in this country in view of its submission to the regulatory authorities.
Overall this study was to be conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki, the principles of "good clinical practice" (GCP) and all applicable regulatory requirements. No study specific audits were performed for this study.

➢ Methods

- Objective:
  The purpose of this booster study was to evaluate, in subjects primed with *Infanrix-IPV+Hib* or with *Infanrix+Hib* and *Poliorix* in study DTPA-IPV (INFANRIX-IPV)-056 (112584 – EudraCT number: 2011-005868-25), the persistence, at the time of the booster vaccination, of the antibodies elicited by these vaccines. The study also evaluated the immune response of these subjects to a booster dose of *Infanrix+Hib* and *Poliorix* vaccine.

- Study design
  It was an open-label, multicentre, 3-arm parallel study with design as follow:



N = number of subjects expected to be enrolled in the booster study
Pre-Bst = before the booster dose; Post-Bst = One month after the booster dose

The first subject was enrolled in the study on 16-October-2011 and the last study visit on 16-January-2012.

- Study population /Sample size
  Approximately 990 subjects in total (330 in each group) were enrolled in this study: a male or female child between, and including, 18 and 24 months of age at the time of the booster vaccination.

- Treatments/intervention
  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.
  Dosage and administration:

Treatment Groups	Type of contact and time point	Dose	Vaccine	Route	Site	Side	Location
All groups	Visit 1 (Day 0)	1	*Infanrix Hib*	IM	Thigh	Right	U
	Visit 1 (Day 0)	1	IPV	IM	Thigh	Left	U

IM = Intramuscular; U = Upper

- Outcomes/endpoints
  The co-primary objectives:
  – 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.

  The secondary objective:
  – 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.

- Statistical Methods
  The statistical analyses were performed using the Statistical Analysis Systems (SAS) version 9.2 on SDD (SAS Drug Development software) and StatXact-8.1 procedure.
  All analyses (with calculated exact 95%CI) were performed on the according to protocol (ATP) cohort for analysis of immunogenicity and antibody persistence. Since the percentage of vaccinated subjects with serological results excluded from the ATP cohort for immunogenicity was less than 5%, a second analysis based on the Total vaccinated cohort (TVC) was not performed to complement the ATP analysis. Additionally, as exploratory comparisons of efficacy endpoints analyses of variance (ANOVA) were conducted. Four cohorts were defined for the purpose of the analysis:
  ☐ The Total vaccinated Cohort (TVC).
  ☐ ATP cohort for analysis of safety
  ☐ ATP cohort for analysis of immunogenicity
  ☐ ATP cohort for analysis of persistence.

➢ Results

- Recruitment/ Number analysed
  A total of 831 Chinese male and female children between 18 and 24 months of age were enrolled into the study, and 825 analysed in TVC, and 822 in ATP for safety.

Table 12 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

	Group A	Group B	Control	Total
Number of subjects vaccinated	272	273	280	825
Number of subjects completed	270	273	279	822
Number of subjects withdrawn	2	0	1	3
Reasons for withdrawal :				
Subject died	0	0	0	0
Serious Adverse Event	0	0	0	0
Non-Serious Adverse Event	0	0	0	0
Eligibility criteria not fulfilled (inclusion and exclusion criteria)	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawal (not due to an adverse event)	0	0	1	1
Migrated/moved from study area	1	0	0	1
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0	0
Lost to follow-up (subjects with complete vaccination course)	1	0	0	1
Sponsor study termination	0	0	0	0
Others	0	0	0	0

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
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come back for the last visit

- Baseline data
  Summary of demographic characteristics (TVC):

		Group A N = 272		Group B N = 273		Control N = 280		Total N = 825	
Characteristics	**Parameters or Categories**	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (months) at booster vaccination dose	Mean	19.5	-	19.4	-	19.5	-	19.5	-
	SD	0.9	-	0.9	-	1.0	-	0.9	-
	Median	20.0	-	19.0	-	20.0	-	20.0	-
	Minimum	18	-	18	-	18	-	18	-
	Maximum	22	-	21	-	22	-	22	-
Gender	Female	131	48.2	126	46.2	120	42.9	377	45.7
	Male	141	51.8	147	53.8	160	57.1	448	54.3
Geographic Ancestry	Asian - Chinese heritage	272	100	273	100	280	100	825	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
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Well balanced population of the healthy male and female babies fulfilled inclusion criteria for prophylactic vaccination.

- Efficacy results

  Immunogenicity results

  Vaccine response one month post-booster vaccination:

Table 27 Vaccine response for anti-PT and anti-FHA antibody concentrations one month after the booster vaccination (ATP cohort for immunogenicity)

				Booster response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
anti-PT	Group A	S-	12	12	100	73.5	100
		S+	254	254	100	98.6	100
		Total	266	266	100	98.6	100
	Group B	S-	10	10	100	69.2	100
		S+	258	258	100	98.6	100
		Total	268	268	100	98.6	100
	Control	S-	20	20	100	83.2	100
		S+	253	252	99.6	97.8	100
		Total	273	272	99.6	98.0	100
anti-FHA	Group A	S-	10	10	100	69.2	100
		S+	256	256	100	98.6	100
		Total	266	266	100	98.6	100
	Group B	S-	6	6	100	54.1	100
		S+	262	262	100	98.6	100
		Total	268	268	100	98.6	100
	Control	S-	18	18	100	81.5	100
		S+	255	254	99.6	97.8	100
		Total	273	272	99.6	98.0	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
S- = seronegative subjects (antibody concentration < 5 ELU/ml for Anti-FHA, Anti-PT) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 5 ELU/ml for Anti-FHA, Anti-PT) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Booster response to the pertussis antigen is defined as
-For PT and FHA response is defined as an antibody concentration≥20 EL.U/ml at post-booster vaccination
N = number of subjects with both pre- and post-vaccination results available
n% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 28 Vaccine response for anti-PRN antibody one month after the booster vaccination (ATP cohort for immunogenicity)

			Booster response			
					95% CI	
Group	Pre-vaccination status	N	n	%	LL	UL
Group A	S-	12	12	100	73.5	100
	S+	254	227	89.4	84.9	92.9
	Total	266	239	89.8	85.6	93.2
Group B	S-	8	8	100	63.1	100
	S+	260	222	85.4	80.5	89.4
	Total	268	230	85.8	81.1	89.8
Control	S-	13	13	100	75.3	100
	S+	260	231	88.8	84.4	92.4
	Total	273	244	89.4	85.1	92.8

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
S- = seronegative subjects (antibody concentration < 5 ELU/ml for Anti-PRN) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 5 ELU/ml for Anti-PRN) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Booster response to the pertussis antigen is defined as:
For initially seronegative subjects: post-booster antibody concentration ≥ 20 EL.U/ml (4-fold the assay cut-off).
For initially seropositive subjects: at least a 4-fold increase in antibody concentration from pre to post-booster vaccination.
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

One month after booster vaccination, at least 99.6% of subjects showed a booster response against PT and FHA antigens (Table 27) while at least 85.4% of subjects showed a booster response against PRN antigen (Table 28).
Persistence of antibodies to all vaccine antigens at 18-24 months of age, in subjects who received DTPa-IPV/Hib or DTPa/Hib+IPV vaccines:
– Antibody persistence in terms of seroprotection rates against diphtheria, tetanus, PRP, poliovirus types 1, 2 and 3 ranged from 83.1% (for anti-PRP) to 99.3% (for anti-tetanus) before the booster dose.
– Antibody persistence in terms of seropositivity rate against pertussis antigens ranged from 92.9% (for anti-PT) to 97.8% (for anti-FHA) before the booster dose.
Immune response after one month of the booster dose of DTPa/Hib+IPV vaccines:
– All the subjects reached seropositive or seroprotection antibody levels for diphtheria, tetanus, poliovirus types 1, 2, 3 and pertussis antigens. The seroprotection rates of anti-PRP antibodies ≥ 0.15 µg/ml was observed in at least 99.2% of subjects and the seroprotection rates of ≥ 1 µg/ml was observed in at least 98.9% of subjects.

- Safety results
  In total over the entire study period solicited or unsolicited adverse events were reported for 473/824 (59.3%) subjects.
  The most common adverse events were pain (27%), redness (5-7%) and swelling (3.7-5.9%) at the injection site.

Two serious adverse events were reported for one subject: bronchopneumonia and febrile convulsions, neither of which were considered by the investigator to be related to the study products, but rather to an underlying respiratory infection.
No fatal events were reported in the study.
There were no unexpected AEs.
The safety results are presented the tables below:

Table 29 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

		Group A					Group B					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	270	73	27.0	21.8	32.8	273	74	27.1	21.9	32.8	279	76	27.2	22.1	32.9
	Grade 2 or 3	270	26	9.6	6.4	13.8	273	25	9.2	6.0	13.2	279	23	8.2	5.3	12.1
	Grade 3	270	9	3.3	1.5	6.2	273	7	2.6	1.0	5.2	279	2	0.7	0.1	2.6
	Medical advice	270	0	0.0	0.0	1.4	273	0	0.0	0.0	1.3	279	0	0.0	0.0	1.3
Redness (mm)	All	270	19	7.0	4.3	10.8	273	15	5.5	3.1	8.9	279	19	6.8	4.1	10.4
	≥15	270	3	1.1	0.2	3.2	273	0	0.0	0.0	1.3	279	1	0.4	0.0	2.0
	>30	270	0	0.0	0.0	1.4	273	0	0.0	0.0	1.3	279	0	0.0	0.0	1.3
	Medical advice	270	0	0.0	0.0	1.4	273	0	0.0	0.0	1.3	279	0	0.0	0.0	1.3
Swelling (mm)	All	270	16	5.9	3.4	9.4	273	10	3.7	1.8	6.6	279	14	5.0	2.8	8.3
	≥15	270	1	0.4	0.0	2.0	273	0	0.0	0.0	1.3	279	1	0.4	0.0	2.0
	>30	270	0	0.0	0.0	1.4	273	0	0.0	0.0	1.3	279	0	0.0	0.0	1.3
	Medical advice	270	0	0.0	0.0	1.4	273	0	0.0	0.0	1.3	279	0	0.0	0.0	1.3

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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
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 2: Cries/protests on touch
Grade 3: Cries when limb is moved/spontaneously painful

		Group A					Group B					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	270	38	14.1	10.2	18.8	273	50	18.3	13.9	23.4	279	38	13.6	9.8	18.2
	Grade 2 or 3	270	6	2.2	0.8	4.8	273	8	2.9	1.3	5.7	279	5	1.8	0.6	4.1
	Grade 3	270	1	0.4	0.0	2.0	273	1	0.4	0.0	2.0	279	0	0.0	0.0	1.3
	Related	270	34	12.6	8.9	17.2	273	47	17.2	12.9	22.2	279	37	13.3	9.5	17.8
	Medical advice	270	1	0.4	0.0	2.0	273	0	0.0	0.0	1.3	279	2	0.7	0.1	2.6
Irritability / fussiness	All	270	78	28.9	23.6	34.7	273	81	29.7	24.3	35.5	279	72	25.8	20.8	31.4
	Grade 2 or 3	270	20	7.4	4.6	11.2	273	16	5.9	3.4	9.3	279	11	3.9	2.0	6.9
	Grade 3	270	2	0.7	0.1	2.7	273	2	0.7	0.1	2.6	279	0	0.0	0.0	1.3
	Related	270	75	27.8	22.5	33.5	273	76	27.8	22.6	33.6	279	70	25.1	20.1	30.6
	Medical advice	270	4	1.5	0.4	3.7	273	1	0.4	0.0	2.0	279	2	0.7	0.1	2.6
Loss of appetite	All	270	67	24.8	19.8	30.4	273	73	26.7	21.6	32.4	279	69	24.7	19.8	30.2
	Grade 2 or 3	270	15	5.6	3.1	9.0	273	15	5.5	3.1	8.9	279	13	4.7	2.5	7.8
	Grade 3	270	2	0.7	0.1	2.7	273	2	0.7	0.1	2.6	279	0	0.0	0.0	1.3
	Related	270	63	23.3	18.4	28.8	273	68	24.9	19.9	30.5	279	65	23.3	18.5	28.7
	Medical advice	270	3	1.1	0.2	3.2	273	2	0.7	0.1	2.6	279	3	1.1	0.2	3.1
Temperature/(Axillary) (°C)	All	270	102	37.8	32.0	43.9	273	105	38.5	32.7	44.5	279	91	32.6	27.1	38.5
	≥37.0	270	102	37.8	32.0	43.9	273	105	38.5	32.7	44.5	279	91	32.6	27.1	38.5
	>37.5	270	56	20.7	16.1	26.1	273	55	20.1	15.6	25.4	279	38	13.6	9.8	18.2
	>38.0	270	29	10.7	7.3	15.1	273	29	10.6	7.2	14.9	279	18	6.5	3.9	10.0
	>38.5	270	11	4.1	2.1	7.2	273	12	4.4	2.3	7.6	279	8	2.9	1.2	5.6
	>39.0	270	3	1.1	0.2	3.2	273	2	0.7	0.1	2.6	279	2	0.7	0.1	2.6
	Related	270	95	35.2	29.5	41.2	273	102	37.4	31.6	43.4	279	90	32.3	26.8	38.1
	>39.0 Related	270	2	0.7	0.1	2.7	273	1	0.4	0.0	2.0	279	2	0.7	0.1	2.6
	Medical advice	270	4	1.5	0.4	3.7	273	13	4.8	2.6	8.0	279	4	1.4	0.4	3.6

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
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
Grade 2 For Drowsiness: Drowsiness that interferes with normal activity
For Irritability: Crying more than usual/ interferes with normal activity
For Loss of appetite: Eating less than usual/ interferes with normal activity
Grade 3 For Drowsiness: Drowsiness that prevents normal activity
For Irritability: Crying that cannot be comforted/ prevents normal activity
For Loss of appetite: Not eating at all

3. Discussion on clinical aspects

Presented study was conducted according to GCP, properly designed and analysed.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

The results of the study are supportive in terms of efficacy and safety, and do not alter the risk/benefit profile of Poliorix™ in target paediatric population patients.

- **Overall conclusion**

No changes in the product information are required

- **Recommendation**

No further action required