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/0017/pdWS/001-002

Marketing Authorisation Holder: GlaxoSmithKline Biologicals

Rapporteur:	Poland
Finalisation procedure (day 90)	08.02.2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Poliorix
INN (or common name) of the active substance(s):	Inactivate poliovirus (IPV) types 1, 2 and 3
MAH:	GlaxoSmithKline Biologicals s.a.
Currently approved Indication(s)	Booster immunisation of healthy children in the second year of life against poliomyelitis
Pharmaco-therapeutic group (ATC Code):	J 07 BF 03
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

Presented studies do 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 5 October 2015, the MAH submitted two completed paediatric studies 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 has also been provided.

The MAH stated that the submitted paediatric studies do 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™ was used in both performed studies.
GSK Biologicals' DTPa Vaccine (Infanrix-Hib) was used in comparative study.
GSK Biologicals' DTPa vaccine Infanrix™ was applied in non-comparative study.

The pharmaceutical formulation corresponds to WHO and European regulatory requirements.
The composition of the study vaccines is presented in tables below.

Table 1 Composition of study vaccines

Vaccine	Vaccine composition	Design	Volume
GSK Biologicals' DTPa vaccine (Infanrix)	Diphtheria toxoid (DT) - min 30 International Units (IU) Tetanus toxoid (TT) - 40 IU Pertussis toxoid (PT - 25 µg Filamentous haemagglutinin (FHA) - 25 µg Pertactin (69 kilodalton membrane protein, PRN) - 8 µg adjuvants: Aluminium hydroxide - 0,5 mg; 2 - Phenoxy-ethanol - 2,5 mg; sodium chloride - 4,5 mg; water for injections - up to 0,5 ml	Suspension in neutral type I (EP) glass syringes (volune of 1 ml) as a unit with two disposable needles	0,5 ml (1 dose)
GSK Biologicals' Inactivated poliomyelitis vaccine (Poliorix)	Inactivated type I poliovirus (Mahoney): 40 IU of D-antigen in IEA units Inactivated type II poliovirus (MEF-1): 8 IU of D-antigen in IEA units Inactivated type III poliovirus (Saukett): 32 IU of D-antigen in IEA units adjuvants: 2 - Phenoxyethanol (preservative) medium 199 (M-199) formaldehyde, polysorbate 80. water for injections Minor amount of neomycin sulphate	Transparent colourless fluid without visible foreign impurities volume of 0,5 ml (1 dose) in a vial made of neutral type I (EP) glass volume of 3 ml, sealed by synthetic butyl rubber plug and aluminic breaking-in cap with protective plastic latching cover	0,5 ml (1 dose)

Treatment identifier	Vaccine name	Formulation	Presentation	Volume	Lot numbers
GSK Biologicals' DTPa vaccine (*Infanrix-Hib*)	DTPa	Diphtheria toxoid: ≥ 30 IU (25 Lf) Tetanus toxoid: ≥ 40 IU (10 Lf) Pertussis toxoid: 25 µg Filamentous haemagglutinin: 25 µg Pertactin: 8 µg Aluminium as salts: 0.5 mg 2-phenoxyethanol: ≤ 2.5 mg	The DTPa component is presented as a turbid white suspension in a pre-filled syringe.	0.5 mL†	AC14B120A
	Hib	PRP: 10 µg, conjugated to tetanus toxoid 20-40 µg	The lyophilised Hib component is presented as a white pellet in a glass vial.		AHIBC322A

†: After reconstitution
IU: International units
Lf: Limits of flocculation

IV.2 Clinical aspects

1. Introduction

The MAH submitted two final reports for:

- **IPV-020** (GSK etrack number 113586 – Eudra CT 2013-002804-15);
- **IPV-021** BST:018 (GSK etrack number 114306 – EudraCT 2012-004513-14)

2. Clinical studies

Study number 113586 IPV-020
Title: A phase IV, open-label, multicentre, non-comparative study to assess reactogenicity and safety of co-administration of GlaxoSmithKline (GSK) Biologicals' inactivated poliomyelitis vaccine Poliorix™ and DTPa-vaccine Infanrix™ in the frame of three-doses of primary immunization course in healthy children of 3, 4.5 and 6 months of age in Russian Federation.

- **Description**

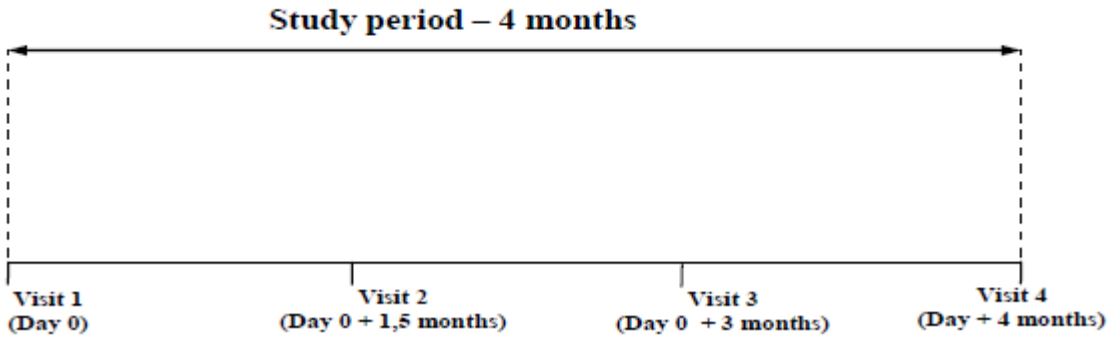
  A phase IV, open-label, multicentre, non-comparative safety study of co-administration of inactivated poliomyelitis vaccine Poliorix™ and DTPa-vaccine Infanrix™ in the frame of three-doses of primary immunization course in 400 healthy children of 3, 4.5 and 6 months of age in Russian Federation.

- **Methods**

  - Objective:
    Reactogenicity and safety assessment of co-administration of inactivated poliomyelitis vaccine Poliorix™ and DTPa-vaccine Infanrix™ in the frame of three-doses of primary immunization course in healthy children of 3, 4.5 and 6 months on age in Russian Federation according to the National Calendar oh Prophylactic Immunisation.

  - Study design

    Figure 1 Study Design



  - Study population /Sample size
    400 healthy children of 3, 4.5 and 6 months of age

  - Treatments/intervention
    All subjects received three-dose of Infanrix and Poliorix as a primary immunization at 3, 4,5 and 6 months by IM injection.

  - Outcomes/endpoints
    1. Incidence of solicited local and general adverse events (AE) reported within 4-day follow-up period (on the day of vaccination and 3 days after vaccination) following administration of each vaccine dose.

2. Incidence of unsolicited adverse events (AE), reported within 31 days following administration of each vaccine dose (the day of vaccination and 30 days after vaccination).
3. Incidence of serious adverse events reported from the date of administration of the first vaccine dose and up to Month 1 after administration of the final dose of the study vaccine.

- Statistical Methods
  Descriptive analysis: The percentage of subjects with at least one local adverse event (solicited –expected and unsolicited- unexpected), with at least one general adverse event(solicited-expected and unsolicited- unexpected) and with any adverse event during the 4-day (Day 0 to Day 3) follow-up period after vaccination was tabulated with exact 95% CI after
  each vaccine dose and overall.

➢ Results

- Recruitment/ Number analysed
  400 healthy caucasian babies were vaccinated, the mean age of the subjects included in the analysis was 3,4 ± 0,5 months. 178/400 (44.5%) subjects enrolled into the study were female and 222/400 (55.5%) were male. Full schedule of vaccination was completed by 391/400 (97.8%) subjects. The reasons for discontinuation or withdrawal were: Informed consent withdrawal 4 (1.0%); migration from the study area 3 (0.8%); lost to follow-up 2(0,5%), and other 1 (0,3%).

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

- Efficacy results
  NA

- Safety results
  In 167/400 (42.1%) / (95% CI: 37.2%, 47.1%) subjects during the study following vaccination with Poliorix, the most frequent adverse event was redness (160/400 (40.4%) subjects (95% CI : 35.5%,45.4%)
  In total over the study period unexpected adverse events starting from Day 0 till Day 3 following the vaccination, were reported for 43/400 (48.9%)/(95% CI: 38.1%, 59.8%) subjects.
  Serious adverse events were reported for 4 subjects (4/400 (1.0%)) of which none were related to the study products.
  The safety results are presented in the tables below:

Table 8 Nature of grade 3 symptoms

Visit	Symptom	Percentage / 95% CI
Total	At least one symptom	49 (12.3%) / (9.2%, 15.9%)
	Pain	7 (1.8%) / (0.7%, 3.6%)
	Redness	12 (3.0%) / (1.6%, 5.2%)
	Swelling	8 (2.0%) / (0.9%, 3.9%)
	Drowsiness	15 (3.8%) / (2.1%, 6.1%)
	Fever	1 (0.3%) / (0.0%, 1.4%)
	Irritability	20 (5.0%) / (3.1%, 7.6%)
	Loss of appetite	10 (2.5%) / (1.2%, 4.5%)
Visit 1	At least one symptom	29 (7.3%) / (4.9%, 10.2%)
	Pain	6 (1.5%) / (0.6%, 3.2%)
	Redness	3 (0.8%) / (0.2%, 2.2%)
	Swelling	3 (0.8%) / (0.2%, 2.2%)
	Drowsiness	10 (2.5%) / (1.2%, 4.5%)
	Irritability	15 (3.8%) / (2.1%, 6.1%)
	Loss of appetite	5 (1.3%) / (0.4%, 2.9%)
Visit 2	At least one symptom	12 (3.0%) / (1.6%, 5.2%)
	Pain	3 (0.8%) / (0.2%, 2.2%)
	Redness	4 (1.0%) / (0.3%, 2.5%)
	Swelling	3 (0.8%) / (0.2%, 2.2%)
	Drowsiness	2 (0.5%) / (0.1%, 1.8%)
	Fever	1 (0.3%) / (0.0%, 1.4%)
	Irritability	3 (0.8%) / (0.2%, 2.2%)
	Loss of appetite	3 (0.8%) / (0.2%, 2.2%)
Visit 3	At least one symptom	16 (4.0%) / (2.3%, 6.4%)
	Redness	6 (1.5%) / (0.6%, 3.2%)
	Swelling	4 (1.0%) / (0.3%, 2.5%)
	Drowsiness	4 (1.0%) / (0.3%, 2.5%)
	Irritability	4 (1.0%) / (0.3%, 2.5%)
	Loss of appetite	2 (0.5%) / (0.1%, 1.8%)

Table 18 Description of serious adverse events

Site number	Subject number	Description of AE	MedDRA system organs/ MedDRA term	Intensity	Start / End	Relation to study vaccine	Medically attended visit	Outcome	Code
70011	61	temperature rise to 38.5	Investigations / Body temperature increased	Mean	20111029/20111105	No	Yes	Resolved	Hospitalization or prolonging stay in clinic
70011	158	ARD, acute nasopharyngitis, obstructive bronchitis	Respiratory, thoracic and mediastinal disorders / Respiratory disorder	Mean	20120120/20120213	No	Yes	Resolved	Hospitalization or prolonging stay in clinic
70011	180	acute paraproctitis	Gastrointestinal disorders / Periproctitis	Mean	20120303/20120314	No	Yes	Resolved	Hospitalization or prolonging stay in clinic
70011	191	diarrhea	Gastrointestinal disorders / Diarrhoea	Mean	20120524/20120529	No	Yes	Resolved	Hospitalization or prolonging stay in clinic

Study number: 114306 (**IPV-021** BST: 018)
Title: An open-label study to assess the immunogenicity and reactogenicity of GlaxoSmithKline (GSK) Biologicals' IPV vaccine (Poliorix) administered as a booster dose at 18 months of age in healthy Chinese toddlers previously primed with the same vaccine in the study IPV-018 (112679).

- Description

The study was conducted in an open manner since the vaccination regimen differed between the two groups. Subjects in the Poliorix group were to receive two vaccines, Poliorix and Infanrix-Hib, whereas subjects in the control group were to receive only one vaccine, Infanrix-Hib. For each treatment group, at exact timepoint serological result were performed: the seroprotection rates with exact 95% CIs were calculated for each of the three poliovirus antigens.

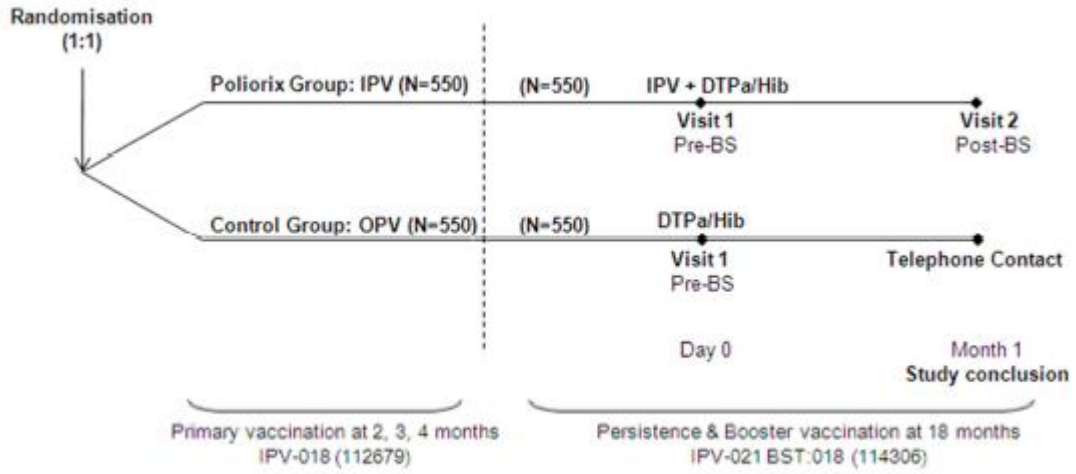
- Methods

• Objective(s)

To assess the efficacy - the immunological response to a booster dose of GSK Biologicals' IPV in terms of poliovirus type 1, 2 and 3 antibodies, and safety after the booster dose in subjects primed with three doses of the same IPV vaccine in study IPV-018.

• Study design

5.1.1. Overall study design – Description



N= Number of subjects planned to be enrolled
Pre-BS= Blood sample collected for all subjects at 18 months
Post-BS= Blood sample collected one month after booster vaccination in the *Poliorix* group

- Study population /Sample size

Healthy male and female toddlers who completed the full three-dose primary vaccination course of polio vaccine in study IPV-018 were invited to participate in this study. The subjects were between 18 and 24 months of age.

- Treatments/intervention

In accordance with the locally recommended immunisation schedule, all subjects also received a booster dose of GSK Biologicals' diphtheria-tetanus-acellular pertussis/Haemophilus influenzae type b (DTPa/Hib) vaccine (Infanrix-Hib) at Visit 1.

- Outcomes/endpoints

Primary:
- To assess the immunological response to a booster dose of GSK Biologicals' IPV in terms of poliovirus type 1, 2 and 3 antibodies, one month after the booster dose in subjects primed with three doses of the same IPV vaccine in study IPV-018.
- To assess the persistence of antibodies to poliovirus types 1, 2 and 3 antigens at 18 months of age in subjects primed with three doses of GSK Biologicals' IPV or three doses of OPV in study IPV-018.

Secondary:
- To assess the safety and reactogenicity of a booster dose of GSK Biologicals' IPV in terms of expected and unexpected, local and general symptoms and serious adverse events (SAEs), in children primed with three doses of the same IPV vaccine in study IPV-018.

- Statistical Methods

The analysis of antibody persistence was performed on the according-to-protocol (ATP) cohort for analysis of antibody persistence. The analysis of immune response to the booster dose of IPV was based on the ATP cohort for analysis of immunogenicity.
For each treatment group, at each timepoint with available serological results:
- the seroprotection rates with exact 95% confidence intervals (CIs) were calculated for each of the three poliovirus antigens
- Geometric Mean Titres (GMTs) with 95% CI were tabulated for antibodies against the three poliovirus types.

- Descriptive analysis of safety data

Results

- Recruitment/ Number analysed

Table 13 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

	Poliorix Group
Number of subjects vaccinated	470
Number of subjects completed	461
Number of subjects withdrawn	9
Number of subjects with unknown completion status	0
Reasons for withdrawal:	
Serious Adverse Event	0
Non-Serious Adverse Event	0
Protocol violation	0
Consent withdrawal (not due to an adverse event)	5
Migrated/moved from study area	2
Lost to follow-up (subjects with incomplete vaccination course)	0
Lost to follow-up (subjects with complete vaccination course)	2
Sponsor study termination	0
Others	0

Poliorix Group = Subjects who received the GSK Biologicals IPV vaccine according to 2-3-4 month schedule 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
Unknown = number of subjects who have not come for the last visit yet

- Baseline data

Table 16 Summary of demographic characteristics (ATP cohort for analysis of antibody persistence)

		Poliorix Group N = 470		Control Group N = 484		Total N = 954	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (months) at blood sampling: PRE	Mean	18.7	-	18.8	-	18.7	-
	SD	0.94	-	1.02	-	0.98	-
	Median	18.0	-	18.0	-	18.0	-
	Minimum	18	-	18	-	18	-
	Maximum	22	-	22	-	22	-
Gender	Female	234	49.8	227	46.9	461	48.3
	Male	236	50.2	257	53.1	493	51.7
Geographic Ancestry	Asian - Chinese Heritage	470	100	484	100	954	100

Poliorix Group = Subjects who received the GSK Biologicals IPV vaccine according to 2-3-4 month schedule in the primary study
Control Group = Subjects who received the Chinese OPV vaccine according to 2-3-4 month schedule 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
PRE=blood sample taken at pre-booster vaccination in subjects who have returned for this booster study

- Efficacy results

At persistence timepoint, 98.3%, 94.7% and 94.9% of the subjects in the Poliorix group and 99%, 99.6% and 96.1% of the subjects in the Control group were seroprotected against poliovirus types 1, 2 and 3, respectively.
One month after the booster dose, all the subjects in the Poliorix group were seroprotected against all poliovirus types.

Table 21 Number and percentage of subjects with an anti-Polio 1 Ab ,anti-Polio 2 Ab , and anti-Polio 3 Ab titre equal to or above the cut-off of 8 ED_{50} and GMTs for Poliorix group one month post vaccination (ATP cohort for immunogenicity)

				≥ 8 ED_{50}				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Polio 1 Ab	Poliorix Group	PRE	456	448	98.2	96.6	99.2	94.7	84.5	106.1
		POST	456	456	100	99.2	100	3420.8	3153.8	3710.5
Polio 2 Ab	Poliorix Group	PRE	456	431	94.5	92.0	96.4	84.7	72.6	98.7
		POST	456	456	100	99.2	100	1886.8	1732.7	2054.5
Polio 3 Ab	Poliorix Group	PRE	456	432	94.7	92.3	96.6	106.1	90.8	123.9
		POST	456	456	100	99.2	100	5097.0	4706.8	5519.6

Poliorix Group = Subjects who received the GSK Biologicals IPV vaccine according to 2-3-4 month schedule in the primary study
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE=Pre-booster vaccination blood sample time point
POST=Post booster vaccination blood sample time point

- Safety results

At least one symptom (expected/unexpected, local/general) was reported for 43.2% ofthe subjects. General symptoms were reported in 41.7% of the subjects and local symptoms in11.7% of the subjects.
Unexpected symptoms were reported for 4.7% of the subjects in the Poliorix group. One non-fatal SAE was reported for one subject in the Control group.
Poliorix was well tolerated when given as a booster vaccination.

Table 26 Incidence of solicited local symptoms by highest intensity reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

		Poliorix Group				
					95% CI	
Symptom	Type	N	n	%	LL	UL
Pain	All	467	49	10.5	7.9	13.6
	Grade 1	467	33	7.1	4.9	9.8
	Grade 2	467	13	2.8	1.5	4.7
	Grade 3	467	3	0.6	0.1	1.9
Redness (mm)	All	467	22	4.7	3.0	7.0
	Grade 1	467	21	4.5	2.8	6.8
	Grade 2	467	1	0.2	0.0	1.2
	Grade 3	467	0	0.0	0.0	0.8
Swelling (mm)	All	467	11	2.4	1.2	4.2
	Grade 1	467	10	2.1	1.0	3.9
	Grade 2	467	1	0.2	0.0	1.2
	Grade 3	467	0	0.0	0.0	0.8

Poliorix Group = Subjects who received the GSK Biologicals IPV vaccine according to 2-3-4 month schedule in the primary study
N = number of subjects with the documented dose
n/%= number/percentage of subjects reporting the symptom at least once when the intensity is maximum
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Grade 1 For pain: Minor reaction to touch
For Redness/Swelling: <15mm
Grade 2 For pain: Cries/protests on touch
For Redness/Swelling: ≥15mm but ≤ 30 mm
Grade 3 For pain: Cries when limb is moved/spontaneously painful
For Redness/Swelling: >30mm

Table 56 Number (%) of subjects with serious adverse events (Total cohort)

System Organ Class	All SAEs	Poliorix Group N = 470	Control Group N = 451
.	Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	1 (0.2) [1]
General disorders and administration site conditions	Pyrexia	0 (0.0) [0]	1 (0.2) [1]
.	**Fatal SAEs**	**Poliorix Group**	**Control Group**
.	Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Poliorix Group = Subjects who received the GSK Biologicals IPV vaccine according to 2-3-4 month schedule in the primary study
Control Group = Subjects who received the Chinese OPV vaccine according to 2-3-4 month schedule in the primary study

3. Discussion on clinical aspects

Both studies IPV-020 and IPV-021 were conducted according to GCP, properly designed and analysed. The primary and secondary endpoints of both studies were well selected, met and are properly documented. It was confirmed that Poliorix vaccine gives seroprotection against poliovirus type1, 2 and 3 and when combined with DTPa-vaccine Infanrix™ is effective and safe.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

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

- **Overall conclusion**

No changes in the product information are required

- **Recommendation**

No further action required.