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November 2012

Mutual Recognition Procedure

Type II group of variations
Final Variation Assessment Report

Boostrix Polio
Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content)

DE/H/0466/003-004/II/125/G

Marketing Autorisation Holder:
GlaxoSmithKline GmbH & Co. KG

Date: 25.11.2016

Deadline for Comments by CMS	21.11.16

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ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	Boostrix Polio, IPV-Boostrix, BOOSTRIXTETRA, PolioBoostrix, Boostrix IPV, BOOSTRIX POLIO
Name of the active substance (INN, common name):	Diphtheria toxoid, Tetanus toxoid, Bordetella pertussis antigens Pertussis toxoid Filamentous haemagglutinin Pertactin, Inactivated poliovirus type 1 (Mahoney strain) type 2 (MEF-1 strain) type 3 (Saukett strain).
Pharmaceutical form(s) and strength(s)	Suspension for injection

Procedure number	DE/H/0466/003-004/II/125/G
Member States concerned	AT, BE,BG, CY, CZ, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK

RMS contact person	**Name(s):** [redacted] Tel: [redacted] Email: [redacted]
Names of the assessors	**Clinical:** **Name(s):** [redacted] Tel: [redacted] Email [redacted]

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Nature of change/s requested	Other, eCTD seq. 165

I. RECOMMENDATION

Based on the review of the data on immunogenicity, the RMS considers that the variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for Boostrix Polio, in the active immunization against diphtheria, tetanus, pertussis and polio in persons from the age of four years onwards as a booster following primary immunization, for the following proposed changes:

<is approvable. >

Executive Summary

I.1 Scope of the variation

The proposed changes are mainly supported by the data of the study dTpa-IPV-009 impacting the following sections of the dTpa-IPV SmPC:

- *Sections 4.1 Indication; 4.2 Posology → to broaden the age indication from 4 years to 3 years.*
- *Section 4.5 Interactions with other medicinal products → to add the data observed in study dTpa-IPV-009 for the co-administration with MMR vaccines. (Further co-administration data with Priorix Tetra [MMRV] are available from study dTpa-IPV-010. As this concerns a vaccine closely related to Priorix [MMR], the data from this study are included in the same variation as additional supportive data and a wording regarding the co-administration with MMR and MMRV vaccines is proposed.)*
- *Section 4.8 Undesirable Effects → Consequentially an update will be proposed to revise the frequency of Fever, irritability, fatigue, loss of appetite and gastrointestinal disorders (including diarrhoea and vomiting) when co-administered with MMR.*
- *Section 5.1 Pharmacodynamic properties → to add the immune response in children from 3Y observed in study dTpa-IPV-009. (The Company furthermore proposes to revise section 5.1 of the SmPC using a harmonised and more stringent definition of the booster immune response to pertussis and takes the opportunity to also include the immunogenicity data from two studies (dTpa-IPV-006 and HPV-042) that were already submitted as part of labelling variations DE/H/0466/003-004/II/45 and DE/H/0466/003-004/II/46, respectively.)*

In order to streamline the procedure and to facilitate the review, the Company would like to submit the proposed changes as a grouping of variations (1 Type II (C.I.6) and 2 Type II (C.I.4) variations). This proposal has been endorsed by the RMS (PEI) on August 10th, 2016 (see e-mail attached).

The proposed change to the indication is aligned to the intended paediatric indication stated in the Boostrix Polio paediatric investigation plan (PIP) which is now completed and for which a positive opinion of the Paediatric Committee on the compliance with the PIP (EMEA-C-000500-PIP01-08-M03) has been issued on May 27th, 2016. The Boostrix Polio article 46 studies dTpa-IPV-009 and dTpa-IPV-010 are both included in this variation dossier.

II. SCIENTIFIC DISCUSSION

II.1 < Clinical aspects>

The applicant has supplied 7 studies in total pertinent to these changes:

Main study : **dTpa- IPV-009**

Supportive studies were partly already supplied and discussed in other procedures:

- dTpa - IPV-001
- dTpa - IPV-002
- dTpa - IPV-003
- dTpa- IPV-006
- dTpa - IPV-010
- HPV-042

Methods to analyse immunogenicity were streamlined and re-calculations for the older studies have been made to allow for a better comparison of results.

Table 1 Laboratory assays (source: Table 2, Overview) A4

Marker	Assay method	Test Kit/ Manufacturer	Assay cut-off	Assay unit	Correlate of protection
Anti-diphtheria	ELISA / Vero cell[1]	[redacted]	[redacted]	IU/ml	≥0.1 / ≥0.01[1]
Anti-tetanus	ELISA				≥0.1
Anti-PT				EL.U/ml	No
Anti-FHA					No
Anti-PRN					No
Anti-poliovirus type 1	Neutralisation			dilution titre[2] (ED_{50})	8
Anti-poliovirus type 2					8
Anti-poliovirus type 3					8
Anti-measles IgG	ELISA	[redacted] (previously [redacted])		mIU/ml	No
Anti-mumps IgG				U/ml	No
Anti-rubella IgG				IU/ml	No
Anti-varicella IgG				mIU/ml	No

A4

A4

ELISA = enzyme-linked immunosorbent assay; IU/ml = international units per milliliter; EL.U/ml = ELISA units per milliliter

[1] Studies dTpa-IPV-001, dTpa-IPV-002, dTpa-IPV-003 and dTpa-IPV-006: Vero cell testing was to be performed on subjects who had test seronegative for anti-diphtheria (< 0.1 IU/ml) by ELISA one month post-vaccination.

[2] Expressed as the reciprocal of the titre which results in 50% neutralisation (ED_{50}). ED_{50} titres can be converted into IU/ml units after multiplication of the titres by 0.035 for poliovirus type 1, 0.085 for poliovirus type 2 and 0.025 for poliovirus type 3. These conversion factors were obtained using methodology described in the WHO/EPI/GEN/93.9, based on assay calibration against the third International Reference Standard anti-poliovirus serum (NIBSC code 82/585, WHO/BS.60.2038).

Booster response was defined as follows for all pertussis antigens (PT, FHA, PRN):

For initially seronegative subjects (pre-vaccination concentration below cut-off: <5 EL.U/ml): antibody concentrations at least **four times** the cut-off (postvaccination concentration ≥ 20 EL.U/ml).

For initially seropositive subjects with pre-vaccination concentration ≥ 5 EL.U/ml and < 20 EL.U/ml: an increase in antibody concentrations of at least **four times** the pre-vaccination concentration.

For initially seropositive subjects with pre-vaccination concentration ≥ 20 EL.U/ml: an increase in antibody concentrations of at least **two times** the pre-vaccination concentration.

The booster response was defined as follows for diphtheria and tetanus toxoid antigens:

For initially seronegative subjects (pre-vaccination concentration below cut-off: <0.1 IU/ml): antibody concentrations at least **four times** the assay cut-off (postvaccination concentration ≥0.4 IU/ml).

For initially seropositive subjects (pre-vaccination concentration ≥ 0.1 IU/ml): an increase in antibody concentrations of at least **four times** the pre-vaccination concentration.

The booster response was defined as follows for the poliovirus antigens:

For initially seronegative subjects (pre-vaccination antibody titre below cut-off: < 8): antibody titre ≥ 32.

For initially seropositive subjects (pre-vaccination antibody titres ≥ 8): an increase in antibody titres of at least **four times** the pre-vaccination titre.

Statistical methods:

The analysis of immunogenicity was performed on the according-to-protocol (ATP) cohort for immunogenicity (primary analysis) for all objectives. The exception to this was the co-primary objective of study dTpa-IPV-009, where the demonstration of non inferiority of Boostrix Polio versus Infanrix in study APV-039 was performed on the Total Vaccinated cohort (TVC), as the ATP cohorts would be different and may also be defined differently in the 2 studies.

In studies dTpa-IPV-001, dTpa-IPV-010 and HPV-042, the percentage of subjects excluded from the ATP cohort for immunogenicity was more than 5%. A secondary analysis of immunogenicity was performed on the TVC (on the Total cohort in study dTpa-IPV-001); the results are described in the respective CSRs located in Module 5. These results were consistent with those observed with the ATP cohort for Immunogenicity

In all studies and for each group, seroprotection/seropositivity rates, seroconversion rates, geometric mean antibody concentration/titre (GMC/GMT) and booster responses with their 95% confidence intervals (CI) were calculated using standard methods

Between group assessment

Inferential analyses in study dTpa-IPV-009:

- The standardised asymptotic 95% CIs on the group difference in booster response to the diphtheria and tetanus antigens [Control Group minus Boostrix Polio Group], one month after booster vaccination, were computed.
- The 95% CIs for the GMT ratio between groups [Control Group over Boostrix Polio Group] for the poliovirus types 1, 2 and 3 antigens, one month after booster vaccination, were computed using analysis of co-variance (ANCOVA) model including the group as fixed effect and the log-transformed pre-booster titre as covariable.
- The 95% CIs for the GMC ratio between groups [Infanrix Group in APV-039 divided by Boostrix Polio Group in this study] for anti-PT, anti-FHA and anti-PRN antigens were computed using an ANOVA model on the logarithm10 transformation of the concentrations. The GMC ratio between groups and their 95% CIs for anti-PT, anti-FHA and anti-PRN antigens was tabulated on the TVC instead of ATP cohort for immunogenicity, as the ATP cohorts would be different and may also be defined differently in the 2 studies.

Main study:

Study dTpa - IPV-009

Methods

An open-label, randomised [2:1] multicentre phase III study in children of 3-4 years. Concomitant use of MMR (Priorix). Non-inferiority comparison of Boostrix Polio with Repevax.

Primary endpoint:

- Immunogenicity with respect to the components of the study vaccines.
  One month after booster vaccination:
  - Booster responses to the diphtheria and tetanus antigens.
- Anti-poliovirus types 1, 2 and 3 antibody titres, anti-PT, anti-FHA and anti-PRN antibody concentrations.

Secondary endpoints:

- Immunogenicity with respect to the components of the study vaccines.
  Prior to and one month after booster vaccination:
  - Anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-mumps, anti-measles, antirubella, anti-poliovirus types 1, 2 and 3 seroprotection/ seropositivity status.
  - Anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-mumps, anti-measles, antirubella, anti-poliovirus types 1, 2 and 3 antibody concentrations/titres.

  One month after booster vaccination:
  - Booster response to the PT, FHA and PRN antigens.
  - Booster response to the poliovirus antigens.
  - Seroconversion for anti-measles, anti-mumps and anti-rubella.
- Solicited local and general symptoms.
  - Occurrence of solicited local and general symptoms during the 4-day (Days 0-3) follow-up period after booster vaccination.
- Unsolicited adverse events (AEs).
  - Occurrence of unsolicited AEs during the 31-day (Days 0–30) follow-up period after booster vaccination.
- Serious adverse events.
  - Occurrence of SAEs from the booster dose up to study end.

Study population

Study population (Total vaccinated cohort)		
Number of subjects	**Boostrix Polio Group**	**Control Group**
Planned, N	256	128
Randomised, N (Total Vaccinated Cohort)	255	130
Completed, n (%)	254 (99.6)	126 (96.9)
Demographics	**Boostrix Polio Group**	**Control Group**
N (Total Vaccinated Cohort)	255	130
Females: Males	123:132	65:65
Mean Age, years (SD)	3.1 (0.2)	3.1 (0.2)
Median Age, years (minimum, maximum)	3 (3, 4)	3 (3, 4)
White - Caucasian / European Heritage, n (%)	226 (88.6)	111 (85.4)
Other, n (%)	18 (7.1)	9 (6.9)
Asian - Central/South Asian Heritage, n (%)	4 (1.6)	4 (3.1)

Boostrix Polio Group = Subjects who received booster dose of Boostrix Polio and Priorix
Control Group = Subjects who received booster dose of Repevax and Priorix
SD = Standard Deviation
N = Total number of subjects enrolled in the study
n/% = Number / percentage of subjects in a given category

Supportive studies:

Study dTpa -IPV-010

Methods

An open-label, randomised [1:1] multicentre phase IIIb study in children of 5-6 years. Concomitant use of MMRV (Priorix Tetra).

Primary Objective: Non-inferiority to Sanofi Pasteur MSD DTPa-IPV vaccine [Tetravac] in terms of seroprotection rates against diphtheria, tetanus and poliovirus types 1, 2 and 3 one month post-vaccination

Secondary Objectives: Immune response in terms of percentages of subjects with booster response to diphtheria, tetanus, pertussis and polio antigens, one month after vaccination; the immune response in terms of antibody concentrations/titres against all vaccine antigens, one month after vaccination; immune response to the pertussis component of the study vaccines in terms of seropositivity rates, one month after vaccination; immune response to MMRV in terms of seroconversion rates, one month after vaccination; and safety and reactogenicity.

Study dTpa - IPV-001

Methods

A partially blinded, multicentre, randomised [2:2:2:1], phase III study in children 4-8years. Lot-to-lot consistency.

Primary Objective: Consistency of the immune response to three lots of Boostirx Polio in terms of GMCs/GMTs to diphtheria, tetanus, pertussis and polio antigens one month after booster vaccination.

Secondary Objectives: Non-inferiority of the immune response to dTpa + IPV vaccines in terms of GMCs to pertussis antigens and seroprotection rates for diphtheria, tetanus and polio antigens one month after booster vaccination; reactogenicity of the study vaccines.

Study dTpa - IPV-002

Methods

An open-label, randomised [4:2:1], multicentre phase II study in children 10-14 years.

Primary Objective: Non-inferiority of the immune response to dTpa + IPV vaccines in terms of GMCs to pertussis antigens and seroprotection rates for diphtheria, tetanus and polio antigens one month after booster vaccination.

Secondary Objectives: Immune response to vaccine antigens one month after booster vaccination; reactogenicity of the study vaccines.

Study dTpa - IPV-003

Methods

An open-label, randomised [1:1:1], multicentre phase III study in adolescents and adults of ≥15years

Primary Objective: Non-inferiority of the immune response to dTpa + IPV vaccines in terms of GMCs to pertussis antigens and seroprotection rates for diphtheria, tetanus and polio antigens one month after booster vaccination in subjects ≥ 18 years of age.

Secondary Objectives: Non-inferiority of the immune response to Td-IPV vaccine in terms of seroprotection rates for diphtheria, tetanus and polio antigens one month after booster vaccination in subjects ≥ 18 years of age; circulating antibodies before booster vaccination; immune response to tetanus toxoid ten days after vaccination in a subset of 180 subjects; reactogenicity of the study vaccines.

Study dTpa - IPV-006

Methods

An open-label, single group, single centre, phase III study in children 6-8 years.

Primary Objective: Immunogenicity of study vaccine one month after booster vaccination in term of anti-diphtheria and antitetanus toxoid, anti-PT, anti-PRN and anti-FHA antibody concentrations, and anti-poliovirus types 1, 2 and 3 antibody titres.

Secondary Objectives: Reactogenicity and safety of the study vaccine

Study HPV-042

A phase IIIb, randomized, open, multicentre study to evaluate the immunogenicity and safety of GlaxoSmithKline Biologicals. HPV-16/18 L1 AS04 vaccine co-administered with GlaxoSmithKline Biologicals' combined reduced-antigen diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine (Boostrix® Polio) in healthy female subjects aged 10.18 years.

Methods

A phase IIIb, multicentre, controlled, open study to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 AS04 vaccine (580299) co-administered with Boostrix Polio in healthy female subjects aged 10-18 years. Subjects were randomised to one of three study groups: the HPV group received three doses of HPV- 16/18 L1 AS04 vaccine at 0, 1 and 6 months; the HPV + dTpa-IPV group received HPV- 16/18 L1 AS04 and dTpa-IPV vaccines co-administered at Month 0, followed by HPV-16/18 L1 AS04 vaccine alone at Months 1 and 6; and the dTpa-IPV/HPV group received dTpa-IPV at Month 0, then three doses of HPV-16/18 L1 AS04 vaccine at Months 1, 2, and 7.
Objectives: The primary objective was to demonstrate the immune response to dTpa-IPV co-administered with HPV-16/18 L1 AS04 vaccine at Month 1 was non-inferior to administration of dTpa-IPV alone. Secondary objectives included demonstration of noninferiority of the HPV immune response at Month 7 when HPV was co-administered with dTpa-IPV compared to when HPV was administered alone, the evaluation of the immune response against HPV-16 and HPV-18 one month after the first dose of HPV-16/18 L1 AS04 in all HPV vaccine recipients, the evaluation of the immune response against all vaccine components of the dTpa-IPV vaccine one month after administration in all dTpa-IPV vaccine recipients, and assessment of reactogenicity and safety after vaccination.
Population: Healthy females between 10 and 18 years of age were enrolled. The demographic profiles for the three subject groups were similar for mean age and racial distribution.

Results

1. Age indication

The age-wise comparison of GMCs and achievement of the respective seroprotection / seropositivity levels per antigen shows that for:

- Anti-diphtheria, the age group 3-4 years (8.113 EU/ml) is well within the results seen in >4 years (0.789 – 9.207 EU/ml). The post-vaccination concentration of anti-diphtheria decreases with ascending age, possibly due to the longer interval to the last dose.
- Anti-tetanus, the age group 3-4 years (6.787 EU/ml) is also within the results seen in >4 years (6.11 – 14.322 EU/ml).
- Anti-PT, the age group 3-4 years (70.1 EL.U/ml) is well within the results seen in >4 years (52 – 105.6 EL.U/ml)).
- Anti-FHA, the age group 3-4 years (358.3 EL.U/ml) is somewhat below the results seen in >4 years (535.8 – 743.8 EL.U/ml)). The fold increase pre/post vaccination in the younger age group is nevertheless 29.3 and seropositivity is shown for all subjects.
- Anti-PRN, the age group 3-4 years (151.4 EL.U/ml) is somewhat below the results seen in >4 years (290.7 – 477 EL.U/ml)). The fold increase pre/post vaccination in the younger age group is nevertheless 37.8 and seropositivity is shown for 97.2% of the subjects.
- Anti-IPV1, the age group 3-4 years (2183.3 ED_{50}) is well within the results seen in >4 years (1145.6 – 6020 ED_{50}).
- Anti-IPV2, the age group 3-4 years (2693.1 ED_{50}) is well within the results seen in >4 years (1076.4– 3622.5 ED_{50}).
- Anti-IPV3, the age group 3-4 years (3762.4 ED_{50}) is well within the results seen in >4 years (1937.8– 5528.8 ED_{50}).

For more details please see Table 2-Table 4.

The age-wise comparison of the respective booster response rate shows a high similarity of the results irrespective of age for all antigens as well (Table 5+Table 6).

Table 2 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies before and one month after the booster dose (ATP cohort for immunogenicity) (source: Table 19, summary clin efficacy)

				≥ 0.1 IU/ml				≥ 1 IU/ml				GMC[1]		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
dTpa-IPV-001 (4-8 years of age)														
Anti-diphtheria	Boostrix Polio groups	Pre	778	523	67.2	63.8	70.5	65	8.4	6.5	10.5	0.194	0.178	0.211
		Post	779	779	100	99.5	100	708	90.9	88.6	92.8	4.462	4.156	4.791
Anti-tetanus	Boostrix Polio groups	Pre	778	653	83.9	81.2	86.4	132	17.0	14.4	19.8	0.329	0.302	0.358
		Post	779	778	99.9	99.3	100	775	99.5	98.7	99.9	13.894	13.111	14.724
dTpa-IPV-002 (10-14 years of age)														
Anti-diphtheria	Boostrix Polio Group	Pre	429	316	73.7	69.2	77.8	48	11.2	8.4	14.6	0.221	0.198	0.247
		Post	428	428	100	99.1	100	378	88.3	84.9	91.2	2.725	2.514	2.953
Anti-tetanus	Boostrix Polio Group	Pre	428	410	95.8	93.4	97.5	147	34.3	29.9	39.1	0.604	0.547	0.667
		Post	428	428	100	99.1	100	428	100	99.1	100	13.362	12.465	14.324
dTpa-IPV-003 (≥18 years of age)														
Anti-diphtheria	Boostrix Polio Group	Pre	242	125	51.7	45.2	58.1	41	16.9	12.4	22.3	0.182	0.150	0.220
		Post	242	199	82.2	76.8	86.8	130	53.7	47.2	60.1	0.789	0.638	0.977
Anti-tetanus	Boostrix Polio Group	Pre	242	211	87.2	82.3	91.1	142	58.7	52.2	64.9	1.026	0.842	1.250
		Post	242	241	99.6	97.7	100	233	96.3	93.1	98.3	6.111	5.434	6.873
dTpa-IPV-006 (6-8 years of age)														
Anti-diphtheria	Boostrix Polio	Pre	80	63	78.8	68.2	87.1	5	6.3	2.1	14.0	0.223	0.178	0.279
		Post	82	82	100.0	95.6	100.0	77	93.9	86.3	98.0	4.393	3.529	5.469
Anti-tetanus		Pre	82	70	85.4	75.8	92.2	20	24.4	15.6	35.1	0.419	0.308	0.569
		Post	82	82	100.0	95.6	100.0	82	100.0	95.6	100.0	14.322	11.899	17.240
dTpa-IPV-009 (3-4 years of age)														
Anti-diphtheria	Boostrix Polio Group	Pre	177	136	76.8	69.9	82.8	17	9.6	5.7	14.9	0.228	0.194	0.267
		Post	195	195	100	98.1	100	194	99.5	97.2	100	8.113	7.259	9.068
	Control Group	Pre	90	75	83.3	74.0	90.4	8	8.9	3.9	16.8	0.259	0.209	0.320
		Post	96	96	100	96.2	100	96	100	96.2	100	11.948	10.003	14.271
Anti-tetanus	Boostrix Polio Group	Pre	177	116	65.5	58.0	72.5	22	12.4	8.0	18.2	0.209	0.173	0.253
		Post	194	194	100	98.1	100	189	97.4	94.1	99.2	6.787	5.961	7.727
	Control Group	Pre	90	63	70.0	59.4	79.2	15	16.7	9.6	26.0	0.241	0.184	0.315
		Post	96	96	100	96.2	100	96	100	96.2	100	9.194	7.565	11.175
dTpa-IPV-010 (5-6 years of age)														
Anti-diphtheria	Boostrix Polio Group	Pre	136	120	88.2	81.6	93.1	20	14.7	9.2	21.8	0.312	0.261	0.374
		Post	139	139	100	97.4	100	138	99.3	96.1	100	9.207	8.057	10.522
	Control Group	Pre	145	128	88.3	81.9	93.0	22	15.2	9.8	22.1	0.343	0.276	0.427
		Post	144	144	100	97.5	100	144	100	97.5	100	21.393	19.165	23.880
Anti-tetanus	Boostrix Polio Group	Pre	137	118	86.1	79.2	91.4	13	9.5	5.1	15.7	0.289	0.244	0.341
		Post	139	139	100	97.4	100	137	98.6	94.9	99.8	12.527	10.957	14.323
	Control Group	Pre	145	130	89.7	83.5	94.1	9	6.2	2.9	11.5	0.308	0.266	0.357
		Post	144	144	100	97.5	100	143	99.3	96.2	100	11.070	9.872	12.413
HPV-042 (10-18 years of age)														
Anti-diphtheria	Boostrix Polio Group	Pre	232	216	93.1	89.0	96.0	81	34.9	28.8	41.4	0.611	0.517	0.722
		Post	233	233	100	98.4	100	226	97.0	93.9	98.8	5.466	4.896	6.103
Anti-tetanus		Pre	232	227	97.8	95.0	99.3	125	53.9	47.2	60.4	1.014	0.883	1.164
		Post	233	233	100	98.4	100	233	100	98.4	100	9.039	8.321	9.818

Boostrix Polio Group = Subjects who received a booster dose of Boostrix Polio and Priorix (in study dTpa-IPV-009) or Boostrix Polio and Priorix Tetra (in study dTpa-IPV-010) or Boostrix Polio alone (in studies dTpa-IPV-001, dTpa IPV-002, dTpa-IPV-003, dTpa-IPV-006 and HPV-042) For study dTpa-IPV-001, results are the pooled data from the three consistency lots

Control Groups = Subjects who received a booster dose of Repevax and Priorix (in study dTpa-IPV-009) or Tetravac and Priorix Tetra (in study dTpa-IPV-010). For studies dTpa-IPV-001, dTpa-IPV-002, dTpa-IPV-003, and HPV-042

GMC = geometric mean antibody concentration calculated on all subjects

[1] GMT in study HPV-042

N = number of subjects with available results;

n (%) = number (percentage) of subjects with concentration within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Pre =Pre-vaccination blood sampling time-point; Post = Post vaccination blood sampling time-point

Table 3 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies before and one month after the booster dose (ATP cohort for immunogenicity) (source: Table 21, summary clin efficacy)

				≥ 5 EL.U/ml				GMC[1]		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
dTpa-IPV-001 (4-8 years of age)										
Anti-PT	Boostrix Polio groups	Pre	777	289	37.2	33.8	40.7	4.4	4.1	4.6
		Post	775	772	99.6	98.9	99.9	52.0	48.9	55.2
Anti-FHA	Boostrix Polio groups	Pre	776	755	97.3	95.9	98.3	61.5	56.0	67.5
		Post	779	779	100	99.5	100	535.8	509.3	563.7
Anti-PRN	Boostrix Polio groups	Pre	779	694	89.1	86.7	91.2	30.5	27.8	33.5
		Post	779	778	99.9	99.3	100	477.0	446.9	509.2
dTpa-IPV-002 (10-14 years of age)										
Anti-PT	Boostrix Polio Group	Pre	424	227	53.5	48.7	58.4	6.7	6.0	7.5
		Post	424	421	99.3	97.9	99.9	96.9	89.0	105.5
Anti-FHA	Boostrix Polio Group	Pre	429	424	98.8	97.3	99.6	57.3	51.5	63.7
		Post	428	428	100	99.1	100	743.8	699.5	791.0
Anti-PRN	Boostrix Polio Group	Pre	429	338	78.8	74.6	82.6	13.7	12.2	15.4
		Post	428	428	100	99.1	100	356.2	319.8	396.7
dTpa-IPV-003 (≥18 years of age)										
Anti-PT	Boostrix Polio Group	Pre	242	137	56.6	50.1	62.9	7.0	6.1	8.0
		Post	238	232	97.5	94.6	99.1	66.8	59.0	75.7
Anti-FHA	Boostrix Polio Group	Pre	241	239	99.2	97.0	99.9	50.0	44.5	56.3
		Post	241	241	100	98.5	100	606.8	550.1	669.3
Anti-PRN	Boostrix Polio Group	Pre	242	144	59.5	53.0	65.7	8.4	7.2	9.8
		Post	242	236	97.5	94.7	99.1	290.7	231.5	365.0
dTpa-IPV-006 (6-8 years of age)										
Anti-PT	Boostrix Polio Group	Pre	80	41	51.3	39.8	62.6	5.9	4.8	7.3
		Post	77	77	100.0	95.3	100.0	105.6	82.9	134.4
Anti-FHA		Pre	81	74	91.4	83.0	96.5	28.3	22.1	36.3
		Post	82	82	100.0	95.6	100.0	562.4	468.7	674.8
Anti-PRN		Pre	82	56	68.3	57.1	78.1	10.8	8.4	13.8
		Post	82	81	98.8	93.4	100.0	292.3	219.5	389.4
dTpa-IPV-009 (3-4 years of age)										
Anti-PT	Boostrix Polio Group	Pre	171	31	18.1	12.7	24.7	3.4	3.0	3.9
		Post	194	194	100	98.1	100	70.1	62.2	79.0
	Control Group	Pre	90	18	20.0	12.3	29.8	3.2	2.9	3.6
		Post	96	96	100	96.2	100	47.8	39.9	57.3
Anti-FHA	Boostrix Polio Group	Pre	174	112	64.4	56.8	71.5	12.9	10.0	16.6
		Post	195	195	100	98.1	100	358.3	312.5	410.8
	Control Group	Pre	85	60	70.6	59.7	80.0	10.7	7.9	14.5
		Post	95	95	100	96.2	100	164.8	138.5	196.1
Anti-PRN	Boostrix Polio Group	Pre	175	61	34.9	27.8	42.4	4.3	3.8	5.0
		Post	195	194	99.5	97.2	100	151.4	127.5	179.6
	Control Group	Pre	91	37	40.7	30.5	51.5	4.3	3.7	5.0
		Post	94	94	100	96.2	100	209.8	168.5	261.3
dTpa-IPV-010 (5-6 years of age)										
Anti-PT	Boostrix Polio Group	Pre	137	37	27.0	19.8	35.3	3.8	3.3	4.4
		Post	139	139	100	97.4	100	59.8	52.2	68.5
	Control Group	Pre	143	25	17.5	11.6	24.7	3.5	3.0	4.0

				≥ 5 EL.U/ml				GMC[1]		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
		Post	144	144	100	97.5	100	75.9	65.7	87.7
Anti-FHA	Boostrix Polio Group	Pre	136	125	91.9	86.0	95.9	42.9	33.3	55.2
		Post	139	139	100	97.4	100	556.2	491.4	629.5
	Control Group	Pre	142	139	97.9	94.0	99.6	50.0	40.1	62.3
		Post	144	144	100	97.5	100	613.5	547.0	688.2
Anti-PRN	Boostrix Polio Group	Pre	137	85	62.0	53.4	70.2	9.5	7.6	11.8
		Post	139	138	99.3	96.1	100	354.8	280.2	449.4
	Control Group	Pre	145	86	59.3	50.8	67.4	7.9	6.6	9.5
		Post	144	87	60.4	51.9	68.5	7.8	6.5	9.2
HPV-042 (10-18 years of age)										
Anti-PT	Boostrix Polio Group	Pre	232	127	54.7	48.1	61.3	7.8	6.6	9.2
		Post	229	222	96.9	93.8	98.8	75.4	65.6	86.8
Anti-FHA		Pre	226	217	96.0	92.6	98.2	52.2	43.9	62.2
		Post	233	233	100	98.4	100	615.2	552.3	685.2
Anti-PRN		Pre	230	181	78.7	72.8	83.8	17.5	14.3	21.3
		Post	233	231	99.1	96.9	99.9	360.0	299.3	433.1

Boostrix Polio Group = Subjects who received a booster dose of Boostrix Polio and Priorix (in study dTpa-IPV-009) or Boostrix Polio and Priorix Tetra (in study dTpa-IPV-010) or Boostrix Polio alone (in studies dTpa-IPV-001, dTpa-IPV-002, dTpa-IPV-003, dTpa-IPV-006 and HPV-042). For study dTpa-IPV-001, results are the pooled data from the three consistency lots

Control Groups = Subjects who received a booster dose of Repevax and Priorix (in study dTpa-IPV-009) or Tetravac and Priorix Tetra (in study dTpa-IPV-010). For studies dTpa-IPV-001, dTpa-IPV-002, dTpa-IPV-003, and HPV-042

GMC = geometric mean antibody concentration calculated on all subjects

N = number of subjects with available results

n (%) = number (percentage) of subjects with concentration within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Pre =Pre-vaccination blood sampling time-point

Post = Post vaccination blood sampling time-point

Table 4 Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies before and one month after the booster dose (ATP cohort for immunogenicity) (source: Table 23, summary clin efficacy)

				≥ 8 ED_{50}				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
dTpa-IPV-001 (4-8 years of age)										
Anti-poliovirus Type 1	Boostrix Polio groups	Pre	748	733	98.0	96.7	98.9	103.8	94.8	113.7
		Post	749	749	100	99.5	100	3514.2	3292.0	3751.5
Anti-poliovirus Type 2	Boostrix Polio groups	Pre	749	746	99.6	98.8	99.9	141.7	131.0	153.3
		Post	733	733	100	99.5	100	3388.5	3190.6	3598.5
Anti-poliovirus Type 3	Boostrix Polio groups	Pre	734	650	88.6	86.0	90.8	47.3	42.1	53.1
		Post	715	715	100	99.5	100	3771.9	3528.1	4032.6
dTpa-IPV-002 (10-14 years of age)										
Anti-poliovirus Type 1	Boostrix Polio Group	Pre	128	124	96.9	92.2	99.1	59.4	47.6	73.9
		Post	426	426	100	99.1	100	4200.5	3883.5	4543.5
Anti-poliovirus Type 2	Boostrix Polio Group	Pre	127	124	97.6	93.3	99.5	63.3	51.4	78.0
		Post	424	424	100	99.1	100	2863.3	2642.0	3103.0
Anti-poliovirus Type 3	Boostrix Polio Group	Pre	126	100	79.4	71.2	86.1	15.6	13.1	18.6
		Post	404	404	100	99.1	100	4113.7	3795.0	4459.3
dTpa-IPV-003 (≥18 years of age)										
Anti-poliovirus Type 1	Boostrix Polio Group	Pre	59	56	94.9	85.9	98.9	110.6	74.4	164.4
		Post	235	234	99.6	97.7	100	2156.6	1842.2	2524.7
Anti-poliovirus Type 2	Boostrix Polio Group	PrePre	68	62	91.2	81.8	96.7	65.7	47.2	91.5
		Post	229	228	99.6	97.6	100	1407.4	1163.9	1701.8
Anti-poliovirus Type 3	Boostrix Polio Group	Pre	64	58	90.6	80.7	96.5	56.8	39.2	82.2
		Post	219	217	99.1	96.7	99.9	2417.9	2027.7	2883.1
dTpa-IPV-006 (6-8 years of age)										
Anti-poliovirus type 1	Boostrix Polio Group	Pre	81	80	98.8	93.3	100.0	76.2	60.5	96.1
		Post	81	80	98.8	93.3	100.0	6020.0	4888.9	7412.8
Anti-poliovirus type 2		Pre	79	78	98.7	93.1	100.0	54.5	45.7	64.9
		Post	79	79	100.0	95.4	100.0	3622.5	2918.6	4496.0
Anti-poliovirus type 3		Pre	80	76	95.0	87.7	98.6	28.4	22.8	35.5
		Post	74	74	100.0	95.1	100.0	5528.8	4559.0	6704.9
dTpa-IPV-009 (3-4 years of age)										
Anti-poliovirus type 1	Boostrix Polio Group	Pre	160	95	59.4	51.3	67.1	12.8	10.6	15.5
		Post	157	156	99.4	96.5	100	2183.3	1812.4	2630.1
	Control Group	Pre	77	49	63.6	51.9	74.3	13.2	10.2	17.1
		Post	75	75	100	95.2	100	1876.1	1472.8	2389.7
Anti-poliovirus	Boostrix Polio Group	Pre	159	109	68.6	60.7	75.7	15.5	12.8	18.8
		Post	124	123	99.2	95.6	100	2693.1	2176.3	3332.5

				≥ 8 ED_{50}				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
type 2	Control Group	Pre	79	55	69.6	58.2	79.5	14.6	11.3	18.8
		Post	71	71	100	94.9	100	2203.8	1681.0	2889.4
Anti-poliovirus type 3	Boostrix Polio Group	Pre	156	100	64.1	56.0	71.6	15.4	12.7	18.8
		Post	159	158	99.4	96.5	100	3762.4	3080.9	4594.6
	Control Group	Pre	79	47	59.5	47.9	70.4	14.5	10.4	20.1
		Post	81	81	100	95.5	100	4185.1	3318.3	5278.3
dTpa-IPV-010 (5-6 years of age)										
Anti-poliovirus type 1	Boostrix Polio Group	Pre	139	132	95.0	89.9	98.0	89.9	72.9	110.8
		Post	139	139	100	97.4	100	1145.6	978.7	1340.9
	Control Group	Pre	146	144	98.6	95.1	99.8	96.6	78.7	118.4
		Post	144	144	100	97.5	100	948.0	817.5	1099.4
Anti-poliovirus type 2	Boostrix Polio Group	Pre	139	136	97.8	93.8	99.6	87.1	70.3	107.9
		Post	139	139	100	97.4	100	1076.4	908.7	1274.9
	Control Group	Pre	145	141	97.2	93.1	99.2	84.5	68.5	104.1
		Post	144	144	100	97.5	100	1315.3	1123.1	1540.3
Anti-poliovirus type 3	Boostrix Polio Group	Pre	139	123	88.5	82.0	93.3	76.1	58.2	99.5
		Post	138	138	100	97.4	100	1937.8	1631.4	2301.8
	Control Group	Pre	146	130	89.0	82.8	93.6	81.3	62.6	105.8
		Post	144	144	100	97.5	100	1657.3	1385.5	1982.6
HPV-042 (10-18 years of age)										
Anti-poliovirus type 1	Boostrix Polio Group	Pre	232	222	95.7	92.2	97.9	88.7	74.0	106.4
		Post	231	231	100	98.4	100	2390.5	2021.4	2826.9
Anti-poliovirus type 2	Boostrix Polio Group	Pre	232	227	97.8	95.0	99.3	81.0	68.4	95.9
		Post	232	232	100	98.4	100	2158.1	1821.3	2557.1
Anti-poliovirus type 3	Boostrix Polio Group	Pre	231	183	79.2	73.4	84.3	37.7	29.7	47.8
		Post	232	232	100	98.4	100	2732.5	2318.0	3221.2

Boostrix Polio Group = Subjects who received a booster dose of Boostrix Polio and Priorix (in study dTpa-IPV-009) or Boostrix Polio and Priorix Tetra (in study dTpa-IPV-010) or Boostrix Polio alone (in studies dTpa-IPV-001, dTpa-IPV-002, dTpa-IPV-003, dTpa-IPV-006 and HPV-042).
For study dTpa-IPV-001, results are the pooled data from the three consistency lots.
Control Groups = Subjects who received a booster dose of Repevax and Priorix (in study dTpa-IPV-009) or Tetravac and Priorix Tetra (in study dTpa-IPV-010). For studies dTpa-IPV-001, dTpa-IPV-002, dTpa-IPV-003, and HPV-042
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre =Pre-vaccination blood sampling time-point
Post = Post vaccination blood sampling time-point

Table 5 Studies dTpa-IPV-001, -002, 003, 006, 009, 010 and HPV-042: Seroprotection rate to diphtheria, tetanus and poliovirus antigens one month after the booster dose (ATP cohort for immunogenicity) (source: Table 6, Overview)

Study	Anti-Diphtheria				Anti-Tetanus				Anti-polio type 1				Anti-polio type 2				Anti-polio type 3			
			95% CI				95% CI				95% CI				95% CI				95% CI	
	N	%	LL	UL	N	%	LL	UL	N	%	LL	UL	N	%	LL	UL	N	%	LL	UL
Subjects 3-5 years (N*=1195)																				
dTpa-IPV-001 (4-6 years)	779	100	99.5	100	779	99.9	99.3	100	749	100	99.5	100	733	100	99.5	100	715	100	99.5	100
dTpa-IPV-006 (5-8 years)	82	100	95.6	100	82	100	95.6	100	81	98.8	93.3	100	79	100	95.4	100	74	100	95.1	100
dTpa-IPV-009 (3-4 years)	195	100	98.1	100	194	100	98.1	100	157	99.4	96.5	100	124	99.2	95.6	100	159	99.4	96.5	100
dTpa-IPV-010 (5-6 years)	139	100	97.4	100	139	100	97.4	100	139	100	97.4	100	139	100	97.4	100	138	100	97.4	100
Subjects 10-93 years (N*=923)																				
dTpa-IPV-002 (10-14 years)	428	100	99.1	100	428	100	99.1	100	426	100	99.1	100	424	100	99.1	100	404	100	99.1	100
dTpa-IPV-003 (≥ 15 years)	242	82.2	76.8	86.8	242	99.6	97.7	100	235	99.6	97.7	100	229	99.6	97.6	100	219	99.1	96.7	99.9
HPV-042 (10-18 years)	233	100	98.4	100	233	100	98.4	100	231	100	98.4	100	232	100	98.4	100	232	100	98.4	100

N = number of subjects in the ATP cohorts for immunogenicity for whom assay results are available

N* = total number of subjects in the ATP cohorts for immunogenicity

% = percentage of subjects with antibody concentration equal or above the seroprotection threshold; 95% CI: 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Data source: dTpa-IPV-001 Report (21-Feb-2003) Tables 13 and 19; dTpa-IPV-002 Report Amendment (11-Oct-2005) Tables 11 and 18; dTpa-IPV-003 Report Amendment 3 (13-Oct-2005) Tables 13 and 21; dTpa-IPV-006 Report (29-Jul-2005) Tables 7 and 11; dTpa-IPV-009 Report (18-Feb-16) Tables 24 and 26; dTpa-IPV-010 Report Amendment 1 (16-Dec-2013) Tables 16 and 20; Data source: HPV-042 Report Amendment 1 (09-Dec-2013) Tables 32 and 36

Table 6 Studies dTpa-IPV-001, -002, 003, 006, 009, 010 and HPV-042: Booster response rate to pertussis antigens one month after the booster dose (ATP cohort for immunogenicity) (source: Table 7, Overview)

Study	Anti-PT				Anti-FHA				Anti-PRN			
			95% CI				95% CI				95% CI	
	N	%	LL	UL	N	%	LL	UL	N	%	LL	UL
Subjects 3-8 years (N*=1195)												
dTpa-IPV-001 (4-8 years)	773	84.6	81.9	87.1	776	98.1	87.8	92.1	779	96.8	94.4	97.3
dTpa-IPV-006 (6-8 years)	75	89.3	80.1	95.3	81	98.8	93.3	100	82	96.3	89.7	99.2
dTpa-IPV-009 (3-4 years)	170	98.6	85.2	94.5	174	94.8	90.4	97.6	175	96.6	92.7	98.7
dTpa-IPV-010 (5-6 years)	137	89.8	83.4	94.3	136	94.9	89.7	97.9	137	94.2	88.8	97.4
Subjects 10-93 years (N*=923)												
dTpa-IPV-002 (10-14 years)	419	94.0	91.3	96.1	428	97.2	95.2	98.5	428	96.7	94.6	98.2
dTpa-IPV-003 (≥ 15 years)	257	84.0	79.0	88.3	259	98.9	94.0	98.7	261	90.4	86.2	93.7
HPV-042 (10-18 years)	228	79.8	74.0	84.8	226	98.7	86.1	94.2	230	90.9	85.4	93.6

N = number of subjects in the ATP cohorts for immunogenicity for whom assay results are available

N* = total number of subjects in the ATP cohorts for immunogenicity

% = percentage of subjects for whom a booster response was observed; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Booster response in defined in Section 4.1.3

Data source: dTpa-IPV-009 Report (18-Feb-16) Table 22; dTpa-IPV-010 Report Amendment 1 (16-Dec-2013) Table 19; HPV-042 Report Amendment 1 (09-Dec-2013) Table 35; For studies dTpa-IPV-001, dTpa-IPV-002, DTPA-IPV-003 and dTpa-IPV-006 see Module 2.7.3 Section 3.2.3.2.

Assessor's comment:
The rate of subjects successfully achieving seroprotection and booster responses as defined is similar between the age groups. The GMCs/GMTs of the respective antibodies are also similar for all antigens except FHA and PRN. For those the fold-increase after vaccination is nevertheless 30-38%. Thus, a clinical impact of the observed slightly lower GMCs is not expected.

2. Co-administration of MMR or MMRV

Co-administration of Boostrix-Polio with MMR/MMRV was evaluated in 2 studies also allows for a comparison of the age-groups 3-4 years (dTpa-IPV-009) with 5-6 years (dTpa-IPV-010). No control group without the concomitant use was included in either study.

The age-wise comparison of GMCs and achievement of the respective seropositivity levels per antigen shows that for Anti-measles, Anti-mumps, and Anti-rubella, the GMCs are either similar or higher in the younger age-group compared to the older children. The percentage of subjects achieving the threshold of protection is identical in both age-groups.

Anti-varicella was only measured in the older age-group due to the vaccines used.

For details please see Table 7.

Table 7 Studies dTpa-IPV-009 and dTpa-IPV-010: Percentage of subjects with antibody concentration above predefined threshold and antibody geometric mean concentrations (GMCs) for MMR(V) antigens one month post-vaccination when co-administered with Boostrix Polio (ATP cohort for immunogenicity) (source: Table 5, Overview)

Study	Group		Percentage of subjects above predefined threshold					GMC (IU/ml)		
			N	n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
Anti-Measles (≥ 150 mIU/ml) - seropositivity										
009	*Boostrix Polio + MMR*	Pre	159	155	**97.5**	93.7	99.3	**2644,0**	2261.3	3091.6
		Post	136	136	**100**	97.3	100	**3817.7**	3422.3	4258. 9
010	*Boostrix Polio + MMRV*	Pre	139	137	**98.6**	94.9	99.8	**2184.9**	1848.1	2583.1
		Post	139	139	**100**	97.4	100	**2743.9**	2411.4	3122.2
Anti-mumps (≥ 231U/ml) - seropositivity										
009	*Boostrix Polio + MMR*	Pre	156	140	**89.7**	83.9	94.0	**1035.3**	869.8	1232.3
		Post	133	133	**100**	97.3	100	**6801.9**	6155.0	7516.8
010	*Boostrix Polio + MMRV*	Pre	138	125	**90.6**	84.4	94.9	**1331.7**	1077.9	1645.3
		Post	139	139	**100**	97.4	100	**4141.3**	3590.5	4776.5
Anti-rubella(≥ 4 IU/ml) - seropositivity										
009	*Boostrix Polio + MMR*	Pre	158	158	**100**	97.7	100	**66.5**	59.1	74.8
		Post	134	134	**100**	97.3	100	**134.3**	120.7	149.4
010	*Boostrix Polio + MMRV*	Pre	139	139	**100**	97.4	100	**77.2**	67.4	88.5
		Post	139	139	**100**	97.4	100	**154.5**	141.3	168.9
Anti-varicella (≥ 25 mIU/ml) - seropositivity										
009	*Boostrix Polio + MMR*	Pre	n.a	n.a.	**n.a.**	n.a.	n.a.	**n.a.**	n.a.	n.a.
		Post	n.a	n.a.	**n.a.**	n.a.	n.a.	**n.a.**	n.a.	n.a.
010	*Boostrix Polio + MMRV*	Pre	139	103	**74.1**	66.0	81.2	**132.7**	99.6	176.7
		Post	139	138	**99.3**	96.1	100	**856.7**	671.8	1092.4
Anti-varicella (≥ 50 mIU/ml)										
009	*Boostrix Polio + MMR*	Pre	n.a	n.a.	**n.a.**	n.a.	n.a.	**n.a.**	n.a.	n.a.
		Post	n.a	n.a.	**n.a.**	n.a.	n.a.	**n.a.**	n.a.	n.a.
010	*Boostrix Polio + MMRV*	Pre	139	100	**71.9**	63.7	79.2	**132.7**	99.6	176.7
		Post	139	135	**97.1**	92.8	99.2	**856.7**	671.8	1092.4

Boostrix Polio + MMR = Subjects who received one dose of *Boostrix Polio* and *Priorix* vaccine on Day 0;
Boostrix Polio + MMRV = Subjects received one dose of *Boostrix Polio* and *Priorix-Tetra* vaccine on Day 0
N: number of subjects with available results;
n/%: number/percentage of subjects with concentration within the specified range; 95% CI: 95% confidence interval;
GMC = Geometric Mean Concentration; LL = Lower Limit, UL = Upper Limit
n.a. non applicable Data source: DTPA-IPV-009 Report (18-Feb-16) Tables 27, 28 and 29; DTPA-IPV-010 Report Amendment 1 (16-Dec-2013) Tables 22 and 23.

Assessor's comment:
There is no relevant difference between the two age groups and all children 3-4 years old achieve at least the antibody concentrations that are seen in the 5-6 year olds for MMR. It is not expected that the results would be strikingly different for varicella.

Safety

Studies dTpa-IPV-009 and -010 are included here; results are generated from the total vaccinated cohort. There was a difference in the intensity scale of redness and swelling as solicited events in the two studies. Redness diameter grade 3 in dTpa-IPV-009 (>20mm) was only grade 2 in study dTpa-IPV-010. Grade 3 in study dTpa-IPV-010 was defined as >50mm.
The rate of any solicited local reactions after 1 dose of Boostrix Polio is lower in the younger age group for pain and redness and similar for swelling. In the MMR/ MMRV groups it is lower in the younger age group for pain, higher for redness and similar for swelling. Grade 3 pain is seen less often in the younger age group and comparing the >50mm size of swelling this also occurs less often in the younger children. For details please see Table 8 - Table 10.

Table 8 Study dTpa-IPV-009: Incidence and nature of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort) (source: Table7, summary safety)

			Boostrix Polio Group					Control Group				
						95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	dTpa-IPV	All	255	127	49.8	43.5	56.1	125	70	56.0	46.8	64.9
		Grade 3	255	3	1.2	0.2	3.4	125	6	4.8	1.8	10.2
		Medical advice	255	0	0.0	0.0	1.4	125	1	0.8	0.0	4.4
	MMR	All	255	86	33.7	27.9	39.9	125	36	28.8	21.1	37.6
		Grade 3	255	2	0.8	0.1	2.8	125	0	0.0	0.0	2.9
		Medical advice	255	0	0.0	0.0	1.4	125	0	0.0	0.0	2.9
Redness (mm)	dTpa-IPV	All	255	146	57.3	50.9	63.4	125	73	58.4	49.2	67.1
		>20 mm	255	28	11.0	7.4	15.5	125	23	18.4	12.0	26.3
		Medical advice	255	0	0.0	0.0	1.4	125	2	1.6	0.2	5.7
	MMR	All	255	102	40.0	33.9	46.3	125	48	38.4	29.8	47.5
		>20 mm	255	2	0.8	0.1	2.8	125	2	1.6	0.2	5.7
		Medical advice	255	0	0.0	0.0	1.4	125	0	0.0	0.0	2.9
Swelling (mm)	dTpa-IPV	All	255	92	36.1	30.2	42.3	125	53	42.4	33.6	51.6
		>20 mm	255	18	7.1	4.2	10.9	125	17	13.6	8.1	20.9
		Medical advice	255	0	0.0	0.0	1.4	125	1	0.8	0.0	4.4
	MMR	All	255	41	16.1	11.8	21.2	125	19	15.2	9.4	22.7
		>20 mm	255	4	1.6	0.4	4.0	125	2	1.6	0.2	5.7
		Medical advice	255	0	0.0	0.0	1.4	125	0	0.0	0.0	2.9

Table 9 Study dTpa-IPV-009: Incidence of any large injection site reaction (defined as swelling with a diameter>50mm, noticeable diffuse swelling or noticeable increase in limb circumference) within 4 days (Day 0-3) after booster vaccination (source: Table 8, summary safety)

		Boostrix Polio Group N = 255				Control Group N = 125			
				95% CI				95% CI	
Product	Type of swelling	n	%	LL	UL	n	%	LL	UL
dTpa-IPV	Missing	2	0.8	0.1	2.8	2	1.6	0.2	5.7
	Local swelling	2	0.8	0.1	2.8	4	3.2	0.9	8.0
MMR	Local swelling	1	0.4	0.0	2.2	0	-	0.0	2.9

Table 10 Study dTpa-IPV-010: Incidence and nature of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period in study dTpa-IPV-010 (Total Vaccinated cohort) (source: Table 9, summary safety)

			Boostrix Polio Group					Control Group				
						95 % CI					95 % CI	
Symptom	Product*	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	dTpa-IPV	Any	151	89	58.9	50.7	66.9	152	93	61.2	53.0	69.0
		Grade 3	151	10	6.6	3.2	11.8	152	14	9.2	5.1	15.0
		Medical advice	151	0	0.0	0.0	2.4	152	2	1.3	0.2	4.7
	MMRV	Any	151	70	46.4	38.2	54.6	152	66	43.4	35.4	51.7
		Grade 3	151	3	2.0	0.4	5.7	152	4	2.6	0.7	6.6
		Medical advice	151	0	0.0	0.0	2.4	152	2	1.3	0.2	4.7
Redness (mm)	dTpa-IPV	Any	151	45	29.8	22.6	37.8	152	58	38.2	30.4	46.4
		>50 mm	151	6	4.0	1.5	8.4	152	14	9.2	5.1	15.0
		Medical advice	151	0	0.0	0.0	2.4	152	3	2.0	0.4	5.7
	MMRV	Any	151	32	21.2	15.0	28.6	152	34	22.4	16.0	29.8
		>50 mm	151	1	0.7	0.0	3.6	152	2	1.3	0.2	4.7
		Medical advice	151	0	0.0	0.0	2.4	152	0	0.0	0.0	2.4
Swelling (mm)	dTpa-IPV	Any	151	44	29.1	22.0	37.1	152	59	38.8	31.0	47.0
		>50 mm	151	8	5.3	2.3	10.2	152	5	3.3	1.1	7.5
		Medical advice	151	0	0.0	0.0	2.4	152	0	0.0	0.0	2.4
	MMRV	Any	151	27	17.9	12.1	24.9	152	25	16.4	10.9	23.3
		>50 mm	151	0	0.0	0.0	2.4	152	2	1.3	0.2	4.7
		Medical advice	151	0	0.0	0.0	2.4	152	0	0.0	0.0	2.4

For the general solicited symptoms only fever is comparable as all other symptoms are defined differently ("fatigue", "GI-symptoms", "headache" in the older, "drowsiness", "irritability" and "loss of appetite" in the younger children). Again, the younger age group shows a lower frequency for the different grades of this symptom. For details please see Table 11 + Table 12.

Table 11 Study dTpa-IPV-009: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort) (source: Table 10, summary safety)

		Boostrix Polio Group					Control Group				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	255	77	30.2	24.6	36.2	125	39	31.2	23.2	40.1
	Grade 3	255	4	1.6	0.4	4.0	125	1	0.8	0.0	4.4
	Related	255	66	25.9	20.6	31.7	125	35	28.0	20.3	36.7
	Grade 3*Related	255	3	1.2	0.2	3.4	125	1	0.8	0.0	4.4
	Medical advice	255	0	0.0	0.0	1.4	125	0	0.0	0.0	2.9
Irritability	All	255	107	42.0	35.8	48.3	125	49	39.2	30.6	48.3
	Grade 3	255	4	1.6	0.4	4.0	125	1	0.8	0.0	4.4
	Related	255	94	36.9	30.9	43.1	125	44	35.2	26.9	44.2
	Grade 3*Related	255	4	1.6	0.4	4.0	125	0	0.0	0.0	2.9
	Medical advice	255	0	0.0	0.0	1.4	125	0	0.0	0.0	2.9
Loss of appetite	All	255	67	26.3	21.0	32.1	125	30	24.0	16.8	32.5
	Grade 3	255	6	2.4	0.9	5.1	125	3	2.4	0.5	6.9
	Related	255	60	23.5	18.5	29.2	125	25	20.0	13.4	28.1
	Grade 3*Related	255	6	2.4	0.9	5.1	125	2	1.6	0.2	5.7
	Medical advice	255	1	0.4	0.0	2.2	125	0	0.0	0.0	2.9
Temperature/(Axillary) (°C)	All	255	18	7.1	4.2	10.9	125	9	7.2	3.3	13.2
	≥37.5	255	18	7.1	4.2	10.9	125	9	7.2	3.3	13.2
	>38.0	255	8	3.1	1.4	6.1	125	6	4.8	1.8	10.2
	>39.0	255	4	1.6	0.4	4.0	125	1	0.8	0.0	4.4
	Related	255	16	6.3	3.6	10.0	125	9	7.2	3.3	13.2
	>39.0*Related	255	4	1.6	0.4	4.0	125	1	0.8	0.0	4.4
	Medical advice	255	1	0.4	0.0	2.2	125	0	0.0	0.0	2.9

Table 12Study dTpa-IPV-010: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period following booster dose (Total Vaccinated cohort) (source: Table 11, summary safety)

		Boostrix Polio Group					Control Group				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Fatigue	Any	151	40	26.5	19.6	34.3	152	36	23.7	17.2	31.3
	Grade 3	151	2	1.3	0.2	4.7	152	0	0.0	0.0	2.4
	Medical advice	151	1	0.7	0.0	3.6	152	2	1.3	0.2	4.7
	Related	151	34	22.5	16.1	30.0	152	30	19.7	13.7	27.0
	Grade 3*Related	151	0	0.0	0.0	2.4	152	0	0.0	0.0	2.4
Gastrointestinal symptoms	Any	151	23	15.2	9.9	22.0	152	15	9.9	5.6	15.8
	Grade 3	151	1	0.7	0.0	3.6	152	1	0.7	0.0	3.6
	Medical advice	151	0	0.0	0.0	2.4	152	0	0.0	0.0	2.4
	Related	151	19	12.6	7.7	19.0	152	12	7.9	4.1	13.4
	Grade 3*Related	151	1	0.7	0.0	3.6	152	1	0.7	0.0	3.6
Headache	Any	151	18	11.9	7.2	18.2	152	20	13.2	8.2	19.6
	Grade 3	151	1	0.7	0.0	3.6	152	0	0.0	0.0	2.4
	Medical advice	151	1	0.7	0.0	3.6	152	1	0.7	0.0	3.6
	Related	151	15	9.9	5.7	15.9	152	17	11.2	6.7	17.3
	Grade 3*Related	151	1	0.7	0.0	3.6	152	0	0.0	0.0	2.4
Fever (Axillary) (°C)	Any	151	32	21.2	15.0	28.6	152	30	19.7	13.7	27.0
	≥37.5°C	151	31	20.5	14.4	27.9	152	30	19.7	13.7	27.0
	>38°C	151	16	10.6	6.2	16.6	152	15	9.9	5.6	15.8
	>38.5°C	151	4	2.6	0.7	6.6	152	5	3.3	1.1	7.5
	>39°C	151	1	0.7	0.0	3.6	152	1	0.7	0.0	3.6
	Medical advice	151	1	0.7	0.0	3.6	152	3	2.0	0.4	5.7
	Related	151	31	20.5	14.4	27.9	152	27	17.8	12.0	24.8
	>39°C * Related	151	1	0.7	0.0	3.6	152	1	0.7	0.0	3.6

In neither study was there deaths or anaphylactic reactions nor the only SAE (pneumonia) recorded in the younger age group was not related to the vaccination.

Assessor's comment:
The younger age group of 3-4 years does not show an increase of rate or severity of adverse events in comparison to the older age group of 5-6 years. No safety issues are recorded.

II.2 <Product information>

<Harmonisation of PL and labelling is included as part of this procedure.>

<III.4.1 Summary of Product Characteristics>

Please refer for more details to the texts supplied with this variation.

III. OVERALL CONCLUSION <AND BENEFIT-RISK ASSESSMENT>

Regarding immunogenicity and safety the extension to a younger age of 3 years can be accepted as the immune responses are similar to older age groups and adverse reactions are even fewer than seen in the age group already in the licensure. Concomitant use of MMR/MMRV in this younger age is also supported by the immunogenicity data submitted and discussed.

Procedural notes:

Comments for the procedure mentioned above have been received from [redacted]

F

The concerns of [redacted] are acknowledged by the RMS but we would like to address them as follows (for the detailed comments please see the respective emails): F

1. [redacted] would have liked a statement that the information in 4.8 is applicable for the age 3 years onwards F
RMS reply: The data in 3 years of age are listed under the concomitant use paragraph in 4.8. A general statement is not endorsed as there were no data without concomitant use in the study, thus, Table 1 is not generally applicable.

2. [redacted] would like to combine the information of the three tables in 4.8 F
RMS reply: We endorse the attached reply from the MAH and would like to stress that the tables mentioned were just approved in the second to last WS for Boostrix and Boostrix Polio (DE/H/xxxx/WS/161) in this Summer. We do not think it advisable to change everything back now for just one product. This could be discussed in a future WS with both products if the need still arises.

In conclusion the RMS ends the procedure as planned (26th November).

The final texts were provided on 25.11.16 in clean and tracked changes versions and incorporate all changes from these procedures:

DE/H/0466/003-004/II/125/G (3-year age indication)
DE/H/xxxx/WS/161 (use during pregnancy)
DE/H/xxxx/WS/166 (use in unvaccinated adolescents)

IV. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

V.1 < Potential serious risks to public health>

<N/A>

V.2 < Points for clarification>

<Text below relevant subheadings as detailed below> <N/A>

<V.2.3 Clinical efficacy>

-

<V.2.5 Product information>