

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

Boostrix

DE/W/0030/pdWS/002

Marketing Authorisation Holder:
GlaxoSmithKline GmbH & Co. KG

Rapporteur:	Germany (PEI)
Finalisation procedure (day 120):	4 February 2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Boostrix
INN (or common name) of the active substance(s):	Diphtheria toxoid (D) Tetanus toxoid (T) Pertussis toxoid (PT) Filamentous Haemagglutinin (FHA) Pertactin (PRN)
MAH:	GlaxoSmithKline GmbH & Co. KG
Currently approved Indication(s)	Boostrix is indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards.
Pharmaco-therapeutic group (ATC Code):	J07AJ52
Pharmaceutical form(s) and strength(s):	Suspension for injection

I. EXECUTIVE SUMMARY

Overall, safety data of Study dTpa-044 are in concordance to those in Section 4.8 of the SmPC. No SmPC and PL changes are proposed.

II. RECOMMENDATION

No regulatory action required.

(Please refer to Section VII for further details.)

III. INTRODUCTION

On 6 March 2015, the MAH submitted a completed paediatric study report for Boostrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

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

IV. SCIENTIFIC DISCUSSION

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

The commercially available formulation of Boostrix (Lot number: C37B117A) was used in the study.

IV.2 Clinical aspects

1. Introduction

The MAH submitted the final report for:

- 115739 (dTpa-044)
A phase III, single-group, open-label study to assess the safety and reactogenicity of GSK Biologicals' combined reduced-antigen-content diphtheria-tetanus-acellular pertussis (dTpa) vaccine Boostrix administered as a booster vaccine dose in healthy Vietnamese children.

2. Clinical study

Study: 115739 (dTpa-044)

Study title: A phase III, single-group, open-label study to assess the safety and reactogenicity of GSK Biologicals' combined reduced-antigen-content diphtheria-tetanus-acellular pertussis (dTpa) vaccine Boostrix administered as a booster vaccine dose in healthy Vietnamese children.

➤ Description

- Phase III, open-label, single group, single centre safety study in healthy Vietnamese children 6-10 years of age
- The study lasted from 22-Feb2014 (FSFV) to 10-May-2014 (LSLV).

➤ Methods

• Objective

Assessment of the safety and reactogenicity of the study vaccine in terms of solicited symptoms, unsolicited symptoms and serious adverse events (SAEs).

• Study design

Phase III, open-label, single group, single-centre, safety study in Hanoi, Vietnam. A single dose of Boostrix was administered to all the subjects at 6-10 years of age. No biological samples were collected in this study.

Type of study: Self-contained.

Inclusion criteria (all to be fulfilled):

- Subjects who the investigator believed that their parent(s)/ subject's legally acceptable representative (LAR)(s) could and would comply with the requirements of the protocol, e.g. completion of the diary cards, return for follow-up visits.
- A male or female between, and including, 6 and 10 years of age at the time of the vaccination (from and including the 6th birthday up to but excluding the 11th birthday).
- Written informed consent obtained from the subject's parent(s)/LAR(s).
- Written informed assent obtained from the subject, as required by local regulations.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Subjects who had previously completed their routine vaccinations against diphtheria, tetanus and pertussis diseases according to the local recommended vaccination schedule at that time and had not received the vaccine in the last two years prior to study dose administration.

Exclusion criteria (any of the following):

- Child in care (i.e., placed under control or protection of an agency, organization, or government body).
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the study vaccination, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to vaccination. Inhaled and topical steroids were allowed.
- Administration of a vaccine not foreseen by the study protocol within 30 days prior to the booster vaccine dose, or planned administration during the study period.
- Administration of immunoglobulins and/or any blood products within the three months preceding Visit 1 or planned administration during the study period.
- Occurrence of transient thrombocytopenia or neurological complications following an earlier immunisation against diphtheria and/or tetanus.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or would have been exposed to an investigational or a non-investigational product (pharmaceutical product or device)
- A history of previous or intercurrent diphtheria, tetanus or pertussis disease.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Major congenital defects or serious chronic illness.
- Acute disease and/or fever (temperature $\geq 37.5^{\circ}\text{C}$ on oral, axillary or tympanic setting or 38.0°C on rectal setting) at the time of enrolment.
- Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever were allowed to be enrolled at the discretion of the investigator.
- Pregnant or lactating female.

Table 1 List of study procedures

Epoch	Epoch 001	
Age	6-10 years	
Type of contact	Visit 1	Visit 2
Time points	Day 0	Day 30
Written informed consent from subject's parent(s)/LAR(s)	●	
Written informed assent from subject *	○	
Checked inclusion/exclusion criteria	●	
Collected demography data	●	
Medical and vaccination history	●	
Physical examination including height and weight measurement	●	
Checked warnings and precautions	○	
Measurement of pre-vaccination body temperature	●	
Urine pregnancy test †	●	
Treatment allocation in SBIR	○	
Recording of treatment number	●	
Vaccination	●	
Distribution of diary cards	○	
Daily post-vaccination recording of solicited adverse events (Day 0–Day 3) by subjects' parent(s)/LAR(s)	●	
Recording of non-serious adverse events within 31 days (Day 0–Day 30) post-vaccination, by the subject's parent(s)/LAR(s)	●	●
Recording of any large injection site reactions in the eCRF by the investigator **	●	●
Return of Diary card and transcription by the investigator		●
Recorded any concomitant medication and vaccination	●	●
Reporting of serious adverse events and pregnancies	●	●
Study conclusion		●

● is used to indicate a study procedure that require documentation in the individual eCRF

○ is used to indicate a study procedure that did not require documentation in the individual eCRF

* The study purpose and procedures were explained to the subject and the written informed assent was obtained.

† Urine pregnancy test was done for female subjects of childbearing potential, as per the investigator's clinical judgement.

** Refer to the table notes under Table 5 for a detailed explanation on the reporting of large injection site reactions by the parent(s)/LAR(s).

Source: Table 1, CSR dTPa (Boostrix)-044

• Study population /Sample size

Healthy male or female subjects between 6 and 10 years of age at the time of vaccination were invited to participate. Written informed assent was obtained from the subjects in addition to the informed consent signed by the parent(s)/ the subject's legally acceptable representative(s), as required by local regulations.

Subjects who had previously completed their routine vaccinations against diphtheria, tetanus and pertussis diseases according to the local recommended vaccination schedule at that time and had not received the vaccine in the last two years prior to the study dose administration were enrolled.

For the purpose of product registration in Vietnam, the sample size of 300 subjects was considered for the analysis of safety according to regulatory requirements.

- **Treatments**

All subjects received a single dose of Boostrix (commercially available formulation; Lot number: C37B117A) as a deep intramuscular (IM) injection into the deltoid muscle of the non-dominant arm.

- **Endpoints:**

Safety and reactogenicity within 1 month after booster vaccination :

- Solicited local and general AEs
 - Occurrence of solicited local (any and Grade 3) and general (any, Grade 3 and related) AEs during the 4-day (Day 0–Day 3) follow-up period after booster vaccination.
 - Solicited local AEs were pain, redness, and/or swelling
 - Grade3 redness/swelling: >50 mm
 - Solicited general AEs were fatigue, fever, headache, and/or gastrointestinal symptoms (nausea, vomiting, diarrhoea, and/or abdominal pain)
 - Grade 3 fever was defined as > 39.0 °C
- Unsolicited adverse events
 - Occurrence of unsolicited AEs during the 31-day (Day 0–Day 30) follow-up period after booster vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
 - Grade 3 (severe) AEs: an AE which prevented normal, everyday activities
e.g., prevented attendance at school/day-care centre and caused the parent(s)/LAR(s) to seek medical advice.
- SAEs
 - Occurrence of SAEs from the receipt of booster dose up to study end.

- **Statistical Methods**

Descriptive statistics were performed on the **Total Vaccinated Cohort (TVC)**.

For the 4-day (Days 0–3) follow-up period the incidence of

- local and general AEs (solicited and unsolicited) (any and those of Grade 3),
- AEs considered related to vaccination (any and those of Grade 3),
- AEs that resulted in a medically-attended visit
- concomitant medication

was calculated.

For the 31-day (Days 0–30) follow-up period the incidence of

- unsolicited AEs (any, Grade 3, those related to vaccination, and Grade 3 related to vaccination)
- concomitant medication

was calculated.

Safety data were tabulated as percentage of subjects with exact 95% CI. **Table 2** presents the exact two-sided 95% confidence interval (CI) for a sample size of 300 subjects reporting at least one AE (solicited or unsolicited).

Table 2 Exact two-sided 95 percent CI for the percentage of subjects reporting at least one AE (solicited or unsolicited) for a sample size of 300 subjects

Observed rate expressed as a percentage (number of subjects reporting at least one symptom)	Exact two-sided 95% CI for this observed rate for a sample size of 300 subjects	
	Lower Limit	Upper Limit
40 (120)*	34.4	45.8
50 (150)	44.2	55.8
60 (180)	54.2	65.6
65 (195)	59.3	70.4
70 (210)	64.5	75.1
75 (225)	69.7	79.8
78.3 (235)#	73.2	82.9
80 (240)	75.0	84.4
85 (255)	80.4	88.8
90 (270)	86.0	93.2
95 (285)	91.9	97.2

* Reference data: study 263855/038(108638), subjects from China having received booster dose of dTpa vaccine at the age of 6 to 8 years with solicited period of 4 days post vaccination.

Reference data: study 263855/008, subjects from Taiwan having received booster dose of dTpa vaccine at the age of 6 to 8 years with solicited period of 15 days post vaccination.

Source: Table 8, CSR dTPa (Boostrix)-044

Rapporteur's comment:

The general study outline as well as inclusion/ exclusion criteria and safety investigation are acceptable.

➤ **Results**

• **Recruitment/ Number analysed**

302 subjects were screened for the study. Two subjects were discontinued during screening due to allergic reaction to the study vaccine and acute upper respiratory infection, respectively. All the 300 enrolled subjects completed the study. All 300 subjects enrolled received a booster dose of Boostrix. The symptom sheets used for the collection of local and general solicited AEs were returned for every subject. Thus, all 300 subjects completed the study.

There were 151 (50.3%) females and 149 males. Their mean age was 7.9 years. All subjects were of South-East Asian ancestry.

Table 3 Summary of demographic characteristics (TVC)

		dTpa Group N = 300	
Characteristics	Parameters or Categories	Value or n	%
Age (years) at vaccination dose	Mean	7.9	-
	SD	1.38	-
	Median	8.0	-
	Minimum	6	-
	Maximum	10	-
Gender	Female	151	50.3
	Male	149	49.7
Geographic Ancestry	Asian - South East Asian Heritage	300	100

Source: Table 14, CSR dTPa (Boostrix)-044

The individual subject's interval between vaccination and study Visit 2 (study discharge) ranged from 34 to 36 days.

• Safety results

During the 4-day (Days 0-3) follow-up period after vaccination, for 134 subjects (44.7%) at least one AE (solicited or unsolicited) was reported. Almost all AEs (132 subjects / 44.0%) were causally related to vaccination. For 5 subjects (1.7%) at least one Grade 3 AE (solicited or unsolicited) was reported, all of which were vaccine-related. For 3 subjects (1.0%) the observed AEs (solicited or unsolicited) required medical attention (**Table 4**).

Solicited local AEs (Days 0-3):

Pain was the most frequently reported solicited local AE, reported for 105 subjects (35.0%). Swelling was the most frequently reported solicited local AE of Grade 3 (i.e., > 50 mm) intensity, reported for 3 subjects (1.0%) (**Table 5**).

No large injection site reactions (defined as a swelling with diameter > 100 mm, noticeable diffuse swelling or noticeable increase in limb circumference) were reported.

Solicited systemic AEs (Days 0-3):

Fatigue was the most frequently reported systemic AE reported in 42 subjects (14.0%) with causal relation to vaccination in most subjects (40 / 13.3%). For 1 subject (0.3%) fatigue of Grade 3 intensity (vaccine-related) was reported. All other solicited systemic AEs were mild to moderate (i.e., Grade 1 to 2) (**Table 6**).

Unsolicited AEs (Days 0-30):

At least one unsolicited AE was reported for 19 subjects (6.3%). Pharyngitis was the most frequently reported unsolicited AE, reported for 7 subjects (2.3%) (**Table 7**).

Within the 31-day post-vaccination period, no Grade 3 unsolicited AEs classified by MedDRA Primary System Organ Class and Preferred Term and no unsolicited AEs causally related to vaccination were reported.

All unsolicited AEs recovered without sequelae.

Concomitant medications:

During the 4-day follow-up period, 6 subjects (2.0%) received at least one **concomitant medication**, 3 of which (1.0%) received an anti-pyretic medication. No subjects received a prophylactic anti-pyretic medication (**Table 8**).

During the 31-day (Days 0-30) follow-up period, concomitant medication was given to 20 subjects (6.7%), 7 of which (2.3%) received an anti-pyretic medication. No subjects received a prophylactic anti-pyretic (**Table 8**).

There were no **SAEs**, no large injection site reactions, and no pregnancies reported in the study. No AEs were observed that led to premature discontinuation of the study and no subjects were withdrawn from the study due to an AE.

In summary, the study vaccine Boostrix was well tolerated.

Table 4 Solicited and unsolicited AEs reported during the 4-day (Days 0-3) post-vaccination period (TVC)

	Any symptom					General symptoms					Local symptoms				
	95% CI					95% CI					95% CI				
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
any AE	300	134	44.7	39.0	50.5	300	61	20.3	15.9	25.3	300	120	40.0	34.4	45.8
Grade 3 AEs	300	5	1.7	0.5	3.8	300	1	0.3	0.0	1.8	300	4	1.3	0.4	3.4
related	300	132	44.0	38.3	49.8	300	56	18.7	14.4	23.5	300	120	40.0	34.4	45.8
Grade 3 related	300	5	1.7	0.5	3.8	300	1	0.3	0.0	1.8	300	4	1.3	0.4	3.4
requiring medical attention	300	3	1.0	0.2	2.9	300	3	1.0	0.2	2.9	300	0	0.0	0.0	1.2

N = number of subjects with the administered dose

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

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

Sources: Tables 18 to 22, CSR dTPa (Boostrix)-044

Table 5 Solicited local AEs reported during the 4-day post-vaccination period (TVC)

		dTPa Group				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Pain	All	300	105	35.0	29.6	40.7
	Grade 2 or 3	300	18	6.0	3.6	9.3
	Grade 3 (severe) *	300	1	0.3	0.0	1.8
	Medical advice	300	0	0.0	0.0	1.2
Redness (mm)	All	300	55	18.3	14.1	23.2
	>20	300	3	1.0	0.2	2.9
	>50 (=Grade3)	300	1	0.3	0.0	1.8
	Medical advice	300	0	0.0	0.0	1.2
Swelling (mm)	All	300	40	13.3	9.7	17.7
	>20	300	3	1.0	0.2	2.9
	>50 (=Grade 3)	300	3	1.0	0.2	2.9
	Medical advice	300	0	0.0	0.0	1.2

N = number of subjects with the administered dose

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

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

* Grade 3 pain: significant pain at rest; prevents normal everyday activities

Source: Table 23, dTPa (Boostrix)-044

Table 6 Solicited systemic AEs reported during the 4-day post-vaccination period (TVC)

		dTpa Group				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Fatigue	All	300	42	14.0	10.3	18.4
	Grade 2 or 3	300	5	1.7	0.5	3.8
	Grade 3 *	300	1	0.3	0.0	1.8
	Related	300	40	13.3	9.7	17.7
	Grade 3 related	300	1	0.3	0.0	1.8
	Medical advice	300	1	0.3	0.0	1.8
Gastrointestinal symptoms	All	300	15	5.0	2.8	8.1
	Grade 2 or 3	300	0	0.0	0.0	1.2
	Grade 3 *	300	0	0.0	0.0	1.2
	Related	300	14	4.7	2.6	7.7
	Grade 3 related	300	0	0.0	0.0	1.2
	Medical advice	300	0	0.0	0.0	1.2
Headache	All	300	33	11.0	7.7	15.1
	Grade 2 or 3	300	1	0.3	0.0	1.8
	Grade 3 *	300	0	0.0	0.0	1.2
	Related	300	33	11.0	7.7	15.1
	Grade 3 Related	300	0	0.0	0.0	1.2
	Medical advice	300	1	0.3	0.0	1.8
Temperature/(Axillary) (°C)	All	300	14	4.7	2.6	7.7
	≥37.5	300	14	4.7	2.6	7.7
	>38.0	300	3	1.0	0.2	2.9
	>38.5	300	1	0.3	0.0	1.8
	>39.0 (=Grade 3)	300	0	0.0	0.0	1.2
	Related	300	13	4.3	2.3	7.3
	>39.0 (Grade 3) Related	300	0	0.0	0.0	1.2
	Medical advice	300	1	0.3	0.0	1.8

N = number of subjects with the administered dose

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

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

* Grade 3: preventing normal activities

Source: Table 24, CSR dTPa (Boostrix)-044

Table 7 Unsolicited AEs classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day post-vaccination period (TVC)

		dTpa Group N = 300			
		95% CI			
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL
At least one symptom		19	6.3	3.9	9.7
General disorders and administration site conditions (10018065)	Pyrexia (10037660)	2	0.7	0.1	2.4
Infections and infestations (10021881)	Bronchitis (10006451)	2	0.7	0.1	2.4
	Nasopharyngitis (10028810)	2	0.7	0.1	2.4
	Pharyngitis (10034835)	7	2.3	0.9	4.7
	Respiratory tract infection (10062352)	3	1.0	0.2	2.9
	Tonsillitis (10044008)	1	0.3	0.0	1.8
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	3	1.0	0.2	2.9
	Rhinorrhoea (10039101)	1	0.3	0.0	1.8
Skin and subcutaneous tissue disorders (10040785)	Pruritus allergic (10063438)	1	0.3	0.0	1.8

N = number of subjects with the administered dose

n/% = number/percentage of subjects who started to take the specified concomitant medication at least once during the mentioned period

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

Source: Table 25, CSR dTPa (Boostrix)-044

Table 8 Number and percentage of subjects starting a concomitant medication (TVC)

	dTpa Group				
	95% CI				
4-day post-vaccination period	N	n	%	LL	UL
Any	300	6	2.0	0.7	4.3
Any antipyretic	300	3	1.0	0.2	2.9
Prophylactic antipyretic	300	0	0.0	0.0	1.2
31-day post-vaccination period					
Any	300	20	6.7	4.1	10.1
Any antipyretic	300	7	2.3	0.9	4.7
Prophylactic antipyretic	300	0	0.0	0.0	1.2

N = number of subjects with the administered dose

n/% = number/percentage of subjects who started to take the specified concomitant medication at least once during the mentioned period

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

Sources: Tables 26 and 27, CSR dTPa (Boostrix)-044

Overall, rate of occurrence of solicited and unsolicited AEs in study dTPa-044 was in concordance to the frequency documented in the SmPC.

However, the MAH mentioned a somewhat higher incidence of headache (11%; 95% CI: 7.7 to 15.1%) as compared to that in the SmPC (1 to <10%). SmPC data are based on pooled clinical data in children 4-8 years with headache observed with an incidence of 6.7% (95% CI: 2.5 to 13.9%). Since the incidence observed in study dTPa-044 was within the 95% CI, the MAH considered changes to the SmPC not necessary.

Rapporteur's comment:

Overall, headache incidences observed in 6-10 years old Vietnamese children were somewhat higher than those calculated for pooled clinical data on children 4-8 years of age which represent the basis for SmPC safety data. However, study dTPa-044 includes 10 years old children for which higher incidences are already mentioned in the SmPC (adolescents and adults ≥ 10 years: headache with a frequency 'very common' [$\geq 10\%$]).

It should be checked whether an adaptation of headache frequencies in SmPC might be appropriate.

Additionally, pharyngitis was observed with an incidence of 2.3% (95% CI: 0.9-4.7%). This is also higher than the frequency mentioned in the SmPC (term 'respiratory infections': uncommon, $\geq 0.1\%$ to <1%).

In order to appropriately review the safety profile of Boostrix per age categories as shown in the SmPC, the MAH is asked to provide safety data for age-stratified subsets and to provide the (pooled) safety data (including descriptive statistics) that currently represent the basis of SmPC data.

3. Discussion on clinical aspects

Overall, the safety results of study dTPa-044 implemented in Vietnamese children following a booster dose of Boostrix are in concordance to the known safety profile of this vaccine. Boostrix was well tolerated.

However, the incidences of headache and respiratory infections need some further look in order to decide on whether an update of AE incidences in the SmPC is indicated.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Boostrix was well tolerated, no new safety signals arose.
The safety data of study dTPa-044 fit to the well-known safety profile of Boostrix.

However, the incidences of headache and respiratory infections need some further look in order to decide on whether an update of AE incidences in the SmPC is indicated.

➤ Recommendation

An overview of safety results in age-stratified subsets in comparison to those mentioned in the SmPC is indicated before a final recommendation can be given regarding section 4.8 update.

Based on the data submitted, the MAH should provide

- safety data for age-stratified subsets of study dTPa-044 compatible to those seen in the SmPC and
- (pooled) safety data (including descriptive statistics) that currently represent the basis of SmPC data

as part of this worksharing procedure (see section IV “Request for Supplementary Information”).

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

List of questions:

In order to appropriately review the safety profile of Boostrix per age categories as shown in the SmPC, the MAH is asked to provide safety data for age-stratified subsets and to provide the (pooled) safety data (including descriptive statistics) that currently represent the basis of SmPC data.

Alternatively the MAH could provide a different categorization for the Adverse Event structure of this part of section 4.8: Children (4-10y), adolescents (11-17y) and adults (≥18y) with frequencies rated accordingly. With this structure, the safety data of 9 years old children would be covered in the product information, whereas with the current structure they are lost. Concordant PL changes need to be submitted.

VII. ASSESSMENT OF THE RESPONSES TO THE REQUEST FOR SUPPLEMENTARY INFORMATION

MAH response:

1. Safety data representing the basis of the current Boostrix SmPC

The safety data for the subjects aged 4 - 8 years (N=839) and the subjects aged 10 - 76 years (N = 1931) were provided in the variation entitled: "V 201000189-Safety revision of section 4.8 - GDS 006" (procedure number: DE/H/0210/001-002/II/40). In that submission, the Company updated the safety section of the SmPC with data coming from a pooling of 17 clinical studies:

- Studies conducted in children 4 – 8 years of age:
APV-118, dTpa-008, dTpa-014, dTpa-033, dTpa-036 and dTpa-037
- Studies conducted in adolescents from the age of 10 years onwards and adults:
dTpa-001, dTpa-002, dTpa-003, dTpa-004, dTpa-007, dTpa-009, dTpa-010, dTpa-019, dTpa-020, dTpa-028 and dTpa-029

The methodology used in the trials was essentially similar, and therefore, the Company had pooled the results from different studies to simplify the data provided in the revised sections of the PI taking into account the age strata children (4 to 8 years of age) and adolescents/adults (from 10 years of age onwards). The study groups that were pooled are highlighted in bold in **Table 1**.

Only solicited and unsolicited symptoms reported as having at least a reasonable possibility of being causally linked to vaccination (i.e. events reported as 'related' or 'possibly related' by the investigator using the above mentioned classification regarding causality) had been considered for the pooling.

Table 1 Overview of clinical studies included in the review of *Boostrix* safety

Study Number Country	Type of study	Population	Groups	Number of subjects) (TVC)
Children 4-8 years of age				
APV-118 (208355/118) Germany	Immunogenicity and reactogenicity	Children 4-6 years of age, previously vaccinated with 4 doses DTPa	Group dTpa Group DTPa Group Td	211 107 103
dTpa-008 (263855/003) Taiwan	Immunogenicity and reactogenicity	Children 6-8 years of age	Group dTpa	60
dTpa-014 (263855/014) Thailand	Immunogenicity and reactogenicity	Children 4-6 years of age	Group DTPw Group dTpa	165 165
dTpa-033 (263855/033) Australia	Immunogenicity and reactogenicity	Children 4-6 years of age, previously vaccinated with 4 doses DTPa	Group DTPa Group dTpa	27 26
dTpa-036 (263855/036) India	Safety and reactogenicity	Booster given to children 4-6 years of age, previously vaccinated with 4 doses of DTPw or DTPa	Group dTpa	347
dTpa-037 (107924) China	Safety and reactogenicity	Booster given to children 6-8 years of age, previously primed with 4 doses of DTP	Group dTpa	30

Adults and adolescents from the age of 10 years onwards				
dTpa-001 (263855/001) Germany	Immunogenicity and reactogenicity	Adolescents 10-18 years of age, previously vaccinated with DTpw in the first 3 years of life	Group dTpa Group pa + Td (Lederlee) Group Td (Chiron-Behring) + pa	46 46 46
dTpa-002 (263855/002) Australia	Immunogenicity and reactogenicity	Adults ≥ 18 years of age	Group dTpa Group Td + pa (1 month later) Group pa + Td (1 month later)	438 55 55
dTpa-003 (263855/003) Belgium	Immunogenicity and reactogenicity	Adults ≥ 18 years of age	Group pa Group dTpa Group Td	100 99 100
dTpa-004 (263855/004) Finland	Immunogenicity and reactogenicity	Adolescents 10-14 years of age	Group dTpa lot 1 Group dTpa lot 2 Group dTpa lot 3 Group Td + pa	150 150 150 60
dTpa-007 (263855/007) Taiwan	Immunogenicity and reactogenicity	Adults 15-20 years of age	Group dTpa	120
dTpa-009 (263855/009) Chile	Immunogenicity and reactogenicity	Adolescents 10-11 years of age	Group dTpa	60
dTpa-010 (263855/010) Chile	Immunogenicity and reactogenicity	Adults ≥ 18 years of age	Group dTpa	60
dTpa-019 (263855/019) Germany	Immunogenicity and reactogenicity	Adolescents 11-18 years of age	Group dTpa	127
dTpa-020 (263855/020) Singapore	Immunogenicity and reactogenicity	Adults ≥ 18 years of age	Group dTpa	150
dTpa-028 (263855/028) Norway	Immunogenicity and reactogenicity	Adults ≥ 18 years of age	Group Tetavax Group dTpa	163 157
dTpa-029 (263855/029) Belgium	Immunogenicity and reactogenicity	Adolescents 10-18 years of age	Group dTpa 0.5mg Al (Boostrix) Group dTpa 0.3 mg Group dTpa 0.133 mg	224 209 214

Trials were conducted in the European area (Belgium, Germany, Finland, Norway), in Australia, in Asia (China, India, Singapore, Taiwan, Thailand) and in Latin America (Chile). The safety data used for the current SmPC are considered a good representation of different ethnicities, including Asian population. In total, 839 children and 1931 adolescents and adults were vaccinated.

The frequencies of solicited local symptoms and solicited general local symptoms across studies and pooled incidences are presented in Annex 1 and Annex 2. In addition, the incidence of unsolicited adverse events reported following vaccination with Boostrix and considered to have at least a possible causal relationship to vaccination by the investigator were pooled across the studies conducted in children and the studies conducted in adolescents and adults and are also presented in Annex 3.

Rapporteur's comment:

Annexes are not included in this AR. For details please refer to Applicant's response documentation.

2. Study dTPa-044

Study dTPa-044 was conducted with the purpose of product (i.e. Boostrix) registration in Vietnam. The sample size of approximately 300 subjects was considered for the analysis of safety according to local Vietnamese regulatory requirements, based on the reference data, statistical calculations and sample size of similar registration studies conducted in Vietnam previously.

All the safety analyses performed in the framework of dTPa-044 study were descriptive (i.e. no inferential criteria). The safety analysis included all the subjects (6-10 years of age) in order to provide reasonably robust estimates of incidences with 95% confidence interval.

With respect to the assessors comment on the headache frequencies

[Extracted from draft assessment report for Boostrix DE/W/0030/pdWS/002:

Overall, headache incidences observed in 6-10 years old Vietnamese children were somewhat higher than those calculated for pooled clinical data on children 4-8 years of age which represent the basis for SmPC safety data. However, study dTPa-044 includes 10 years old children for which higher incidences are already mentioned in the SmPC (adolescents and adults >10 years: headache with a frequency 'very common' [>10%]). It should be checked whether an adaptation of headache frequencies in SmPC might be appropriate.],

the position of the Company is detailed below.

In the dTPa-044 study, the **headache** cases were reported as part of the general solicited symptoms within 4-days following vaccination, meaning that the headache symptoms were proactively collected. Among the 6 studies included in the 4-8 years of age SmPC stratum for Boostrix, headache was solicited in 2 studies (see **Table 2** below). No spontaneous reports of headache as unsolicited symptom were received in the other studies.

Table 2 Percentage of headache considered as having at least a possible relationship to booster vaccination with Boostrix in Children 4-8 years of age (TVC)

Study	N	Headache (%) solicited general symptoms
APV-118	211	Not solicited
dTpa-008	60	10 (3.8-20.5)
dTpa-014	165	Not solicited
dTpa-033	26	Not solicited
dTpa-036	345	Not solicited
dTpa-037	30	0.0 (0.0-11.6)
Overall (95% CI)	837	6.7 (2.5-13.9)

In the dTPa-044 study, 11% (n=33) of the study participants reported headache within 4 days post-vaccination as part of general solicited symptoms. None of the cases were reported as having Grade 3 (i.e. headache that prevent normal activity). No headache cases were reported as unsolicited adverse events within 30-days following vaccination. From the 33 cases of headache reported in the dTPa-044 study, 20 cases were reported in 6-8 years old (N=192 subjects), leading to a calculated headache incidence 10.4% subjects) of age, 10.0% in the 9 years of age (i.e. 6 cases reported in 60 subjects) and 14.6% in the 10 years of age (i.e. 7 cases reported in 48 subjects). Therefore, the incidence of headache in the dTPa-044 study is borderline exceeding the SmPC common incidence (i.e. 1-10%) in age stratum 4-8 years of age and within range of the SmPC very common incidence (i.e. $\geq 10\%$) of headache in ≥ 10 years of age. Given the limited number of subjects in each age stratum as compared with the overall population which contributed to the SmPC (for solicited and unsolicited symptoms), the data presented above should be interpreted with caution and hence the Company believes that based on the dTPa-044 study data, no change to the currently shown incidence of headache in 4-8 year old stratum is warranted. The clinical significance of this finding is limited.

With respect to the assessors comment on the **pharyngitis** frequencies
[Extracted from draft assessment report for Boostrix DE/W/0030/pdWS/002:
Additionally, pharyngitis was observed with an incidence of 2.3% (95% CI: 0.9-4.7%). This is also higher than the frequency mentioned in the SmPC (term 'respiratory infections': uncommon, > 0.1% to <1%).]
the position of the Company is detailed below.

All seven pharyngitis cases were reported between March 15, 2014 and April 15, 2014 (study period: February 22, 2014 to May10, 2014). All of the reports started within 3-15 days post-vaccination, were assessed by the investigator as not related with the vaccination, of intensity 1-2 (i.e. CTCAE grading v4.0: localized, local intervention indicated [e.g. topical antibiotic, antifungal or antiviral]), and recovered without sequelae within 3 to 11 days. Overall in the dTpa-044 study, 22 out of 23 reported unsolicited adverse events were respiratory system related (e.g. pharyngitis, nasopharyngitis, respiratory infection, runny nose). Considering the clinical context (i.e. study enrolment period and the seasonality of influenza-like illness in Vietnam) it is reasonable to assume that the pharyngitis cases reported in the dTpa-044 study were probably due to a seasonal effect (Thai et al. 2015). Based exclusively on the dTpa-044 study, it cannot be concluded that the vaccination with Boostrix would induce more pharyngitis as compared with the frequencies in the approved SmPC in the age strata 4-8 years of age or ≥ 10 years of age (both listed as uncommon).

3. Conclusion

In conclusion, based on the above, the Company proposes to keep the categorization of the Adverse Events structure in section 4.8 as is (i.e. subjects aged 4 - 8 years and subjects aged 10 - 76 years), as the studies done in adults and adolescents (listed in Table 1) are starting from the age of 10 years. Changing to a different categorization for the Adverse Event structure (Children (4-10y), adolescents (11-17y) and adults ($\geq 18y$)), as proposed as alternative by the Agency, would imply the need to stratify the safety data in different age groups for those studies, which is not in line with the initial objectives of these studies. The Company wishes to maintain the age groups described in the Boostrix SmPC (children 4 – 8 years of age and adolescents from the age of 10 years onwards and adults), to keep the age strata harmonized for Boostrix and Boostrix Polio. The Company will envisage the widening of the age group 4-8 to 4-9 when sufficient data become available in the 9-year-old segment (currently 60 subjects of 9 years evaluated in study dTpa-044 compared to a total of 839 subjects representing the basis of the current SmPC age stratum 4-8 year old children).

In addition, based on the above argumentation with respect to the headache and pharyngitis frequencies, the Company proposes not to include the data from study dTpa- 044 in a new safety pooling and not to change the SmPC, as the safety data from study dTpa-044 are generally in line with the current basis of the SmPC.

4. References

Thai PQ, Choisy M, Duong TN, Thiem VD, Yen NT, Hien NT, Weiss DJ, Boni MF, Horby P (2015) Seasonality of absolute humidity explains seasonality of influenza-like illness in Vietnam. *Epidemics* 13:65–73.

Assessment of the MAH's responses:

The Applicant has provided detailed information regarding data basis of adverse event incidences as mentioned in Section 4.8 of SmPC. There were 6 studies implemented worldwide that supplied the (pooled) safety data for children aged 4-8 years, and 11 studies that provided the data for adolescents from 10 years onwards and adults. Headache was solicited in only 2 studies on children with an overall incidence of 6.7% (95% CI: 2.5-13.9%). In the other studies, no spontaneous reports of headache as unsolicited symptom were received.

In the dTpa-044 study, 11% (n=33) of the study participants reported headache within 4 days post-vaccination as a solicited systemic symptom, none of the cases were of Grade 3. Headache cases were reported for 10.4% of subjects 6-8 years old, for 10.0% of subjects aged 9 years and 14.6% of subjects aged 10 years. The incidence of headache in the dTpa-044 study is thus overall in the range of SmPC common incidence in children and the very common incidence in subjects ≥ 10 years of age.

The Assessor agrees with the MAH that, following dTpa-044 study data, no change to the currently shown incidence of headache in children aged 4-8 years is warranted.

Regarding the increased pharyngitis frequencies in study dTpa-044 the MAH has provided further information. All pharyngitis cases were reported within 3 and 15 days post-vaccination between March 15 and April 15, 2014, thus within the influenza-like illness season in Vietnam.

The explanation of the MAH is acknowledged. Further, the MAH's proposal as to keep the age categorization of AE structure in Section 4.8 is accepted.

VIII. FINAL MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

Overall, safety data of Study dTpa-044 are in concordance to those in Section 4.8 of the SmPC. No SmPC and PL changes are proposed.

Recommendation

No further action required.