Vaccines and Related Biological Products Advisory Committee

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FDA Clinical Briefing Document for

GlaxoSmithKline (GSK) Biologicals
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
Boostrix™

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1.0 General Information

Product name

Proper name: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed

Proposed trade name: BOOSTRIX™

Product composition

Table 1. Vaccine Formulation per 0.5 ml/dose and comparison to Infanrix® (DTaP manufactured by GSK for use in infants and children less than 7 years of age)

Component	**Boostrix™ US formulation**	**Infanrix®**
Diphtheria toxoid (D/d)	2.5 Lf	25 Lf
Tetanus toxoid (T)	5.0 Lf	10 Lf
Pertussis toxoid (PT)	8.0 µg	25 µg
Filamentous hemagglutinin (FHA)	8.0 µg	25 µg
Pertactin (PRN)	2.5 µg	8.0 µg
Aluminum	0.3 mg (as $AlOH_3$)	≤0.625 mg (as $AlOH_3$)
Preservative	None	2.5 mg 2-PE

2-PE: 2-phenoxyethanol
Lf: limit of flocculation unit

Manufacturer GlaxoSmithKline (GSK) Biologicals

Proposed indication Single-dose booster immunization against tetanus, diphtheria and pertussis in adolescents (10-18 years of age)

Dosing regimen and Route of administration Single dose, intramuscularly

Executive Summary:

This briefing document contains a summary of the safety and immunogenicity data provided by GSK to support approval of their Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine, Adsorbed (Tdap; Trade name: Boostrix™), for single dose booster immunization of adolescents 10-18 years of age who have previously received the recommended series of diphtheria, tetanus and pertussis vaccine (DTP) in childhood. The data demonstrate that, in adolescents administered Boostrix™, the immune response to the diphtheria and tetanus toxoids was non-inferior to the immune response of adolescents administered a U.S.-licensed Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Massachusetts Public Health Biologic Laboratories [MPHBL], Td_{MPHBL}). Submitted data demonstrate that Boostrix™ induced a booster response to each of the pertussis antigens contained in the vaccine. Additionally, the immune response (Geometric Mean antibody Concentrations, GMCs) of adolescents to each of the pertussis antigens contained in Boostrix™ was non-inferior to the immune response induced by a three dose primary series of Infanrix® given to infants who participated in a previously conducted household contact efficacy study.

Safety data from the pivotal clinical study demonstrates that, with the exception of any pain and ≥ grade 2 pain, the incidence of solicited adverse events was similar between adolescents who received Boostrix™ or Td_{MPHBL}. The incidence of any pain and ≥ grade 2 pain within 72 hours post-vaccination and during the 15-day reporting period for solicited adverse events was significantly higher in Boostrix™ recipients.

Additional safety data from eleven supportive, non-IND studies are summarized in this document.

2.0 Introduction and Background

2.1 Epidemiology of Pertussis infections

Routine vaccination of infants and children from 6 weeks through the age of six years with diphtheria-tetanus and pertussis vaccine (DTP) has been effective in decreasing pertussis disease in the United States. However, in the last two decades increasing rates of pertussis infection and disease have been reported in infants younger than 6 months of age who have not completed a primary series, and in adolescents and adults.[1]

Comparison of national surveillance data from the years 1994-1996, to data from the years 1997-2000, shows an increase in the incidence of reported pertussis disease of 11% among infants, an 8% decrease among children aged 1-4 years and no change among children aged 5-9 years.[1,2] This national surveillance comparison also showed that the incidence of reported pertussis among adolescents and adults increased by 62% and 60%, respectively.[1,2] During 1997-2000, 29,134 pertussis cases were reported, to give a crude average annual incidence rate of 2.9 cases/100,000 population. Of the reported cases with known age, 29% were among adolescents 10-19 years old (8529 cases over the four year period;/age specific average annual incidence rate 5.5 per 100,000 population). [1]

2.2 Regulatory Background

The GlaxoSmithKline (GSK) Tdap vaccine (Boostrix™) containing 0.3 mg of aluminum has been formulated using the same antigens contained in the company's Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP, Infanrix®) indicated for use in infants and children less than seven years of age. Another Tdap vaccine containing 0.5 mg aluminum and 2-phenoxyethanol (2-PE) is also manufactured by GSK and marketed under the trade name Boostrix™. This formulation has been licensed for use in adolescents and adults in 22 countries outside the United States since 2000 (countries include: Germany, Colombia, Costa Rica, Mexico, Australia, Switzerland, New Zealand, Denmark, Portugal, Norway, Finland, and the UK).

The proposed trade name, Boostrix™, will be used throughout this document to indicate the formulation of the Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine, Adsorbed, studied in the pivotal study 776423/001 (Tdap/001) and intended for licensure. Other formulations of this product will be referred to as Tdap.

2.3 Basis for Licensure

There is no generally accepted serological correlate of protection against pertussis. Therefore, on June 5, 1997 the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) agreed that the antibody levels attained after a primary series of an acellular pertussis vaccine in infants could serve as the basis for demonstrating the efficacy of a booster vaccine containing the same pertussis antigens in an older population. Thus, efficacy in adolescents would be inferred by demonstration of an immune response to the pertussis antigens comparable to those of infants.

The development strategy followed by GSK to support licensure of Boostrix™ was based upon the following:

- Demonstration of safety of Boostrix™ in adolescents compared to U.S.- licensed Td_{MPHBL} vaccine
- Demonstration of non-inferior immune responses in adolescents to the tetanus and diphtheria toxoids contained in Boostrix™ compared with U.S.-licensed Td_{MPHBL}
- Demonstration of a booster response to the pertussis antigens contained in Boostrix™
- Demonstration of non-inferior immune responses (GMC) in adolescents to the pertussis antigens contained in Boostrix™ compared to responses observed in infants primed with Infanrix®
- Demonstration of clinical lot-to-lot consistency in the immune responses to the tetanus and diphtheria toxoids and pertussis antigens contained in Boostrix™

3.0 Clinical Overview

The Biologics License Application (BLA) contains safety data from one pivotal study (776423/001-Tdap/001), and two major supportive studies (2638855/029 and 263855/004). For each of these studies full study reports were submitted. Study Tdap/001 evaluated safety and immunogenicity of the formulation of Boostrix™ intended for US-licensure (0.3mg Al/0.5mL dose; no preservative). Non-IND Study 2638855/029 evaluated three preservative free formulations of Tdap containing different concentrations of aluminum (0.5, 0.3 and 0.133 mg Al/0.5mL dose). All other studies included in the BLA evaluated a formulation of Tdap containing 2-phenoxyethanol as preservative and 0.5mg Al/0.5mL dose. Antibody persistence was evaluated 3 years (Study 263855/017) and 5 years (Study 263855/017) following receipt of vaccine in Study 263855/004. See Table 2 for an overview of studies submitted as full study reports.

Synopses of safety data from nine additional studies were also included in the application. In most of these studies the safety evaluation was limited by lack of a control group or lack of a U.S.-licensed comparator vaccine. Five of these studies enrolled subjects older than 18 years of age. One study enrolled subjects 4 to 6 years of age who had received four previous doses of DTaP (Infanrix®). These studies were submitted to provide additional data on the safety of Boostrix™. As noted above, these studies evaluated formulations of Tdap that contained 0.5mg Al/dose and thus differ from that intended for U.S. licensure. See Table 3 for an overview of studies submitted as synopses reports.

The overall safety database comprised 5452 subjects who received Boostrix ™ or another Tdap formulation.

Immunogenicity data from pivotal study 776423/001 (Tdap/001) was the basis for establishing efficacy of Boostrix™.

Table 2. Overview of Clinical Studies Contained in License Application (Full Study Reports)

Study (Country)	Age (years)	Objectives	Groups	ATP* for Immuno-genicity N	TVC* for Safety N
776423 / 001 Tdap/001 **(US)**	10-18	*Primary:* -- Lot-to-lot consistency -- Non-inferiority (immunogenicity) compared to Td_{MPHBL} -- Immunogenicity of pertussis (pa) components -- Non-inferiority (grade 3 pain) compared to Td_{MPHBL} *Secondary:* -- Reactogenicity / safety	- Boostrix™ lot 1 - Boostrix™ lot 2 - Boostrix™ lot 3 - Td_{MPHBL}	926 928 946 923	1024 1024 1032 1034
263855 / 029 Belgium	10-18	*Primary:* -- Immunogenicity and reactogenicity/safety of three Tdap formulations (with differing amounts of aluminum adjuvant)	- Tdap (0.5 mg Al) - Boostrix™ (0.3 mg Al) - Tdap (0.133 mg Al)	218 202 211	224 209 214
263855 / 004 Finland	10-14	*Primary:* -- Lot-to-lot consistency (immunogenicity) *Secondary*: -- Immunogenicity and reactogenicity/safety compared to Td and pa	- Tdap lot 1 - Tdap lot 2 - Tdap lot 3 - $Td_{Lederle}$+ pa_{GSK}	150 149 148 57	150 150 150 60
/017	13-15	*Primary:* Antibody persistence three years after vaccination in 263855/004	- Tdap (pooled) - $Td_{Lederle}$+ pa_{GSK}	264 30	N/A N/A
/030	15-17	*Primary:* Antibody persistence 5 years after vaccination in 263855/004	- Tdap (pooled) - $Td_{Lederle}$+ pa_{GSK}	257 34	N/A N/A
Total Boostrix™ + Tdap	10-18				**4177**

* ATP: According to Protocol, TVC: Total Vaccinated Cohort

Td_{MPHBL}: Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (manufactured by Massachusetts Public Health Biologic Laboratory), $Td_{Lederle}$: Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (manufactured by Lederle)

pa_{GSK}: Pertussis antigen vaccine (manufactured by GlaxoSmithKline), N/A: not applicable

Table 3: Safety Data in subjects 4 to ≥18 years of age: Synopses Reports

Study (Country)	Age (range)	Tdap* N
263855 / 001 (Germany)	11-17y	46
263855 / 002 (Australia)	≥ 18y (19-70)	438
263855 / 003 (Belgium)	≥ 18y (18-73)	98
263855 / 007 (Taiwan)	15-20y	102
263855 / 009 (Chile)	10-11y	60
263855 / 010 (Chile)	≥ 18y (20-56)	60
263855 / 020 (Singapore)	≥ 18y (19-66)	135
263855 / 028 (Norway)	≥ 18y (19-78)	156
208355 / 118 (Germany)	4-6 y	180
Total Tdap (Synopses Reports)		**1275**

*formulated to contain 0.5mg Al/dose and 2.5mg 2-PE as preservative

3.1 Pivotal Safety and Immunogenicity Study 776423/001 (Tdap/001)

A phase 3, observer-blinded, randomized, multi-center, clinical study of the safety, immunogenicity and consistency of three manufacturing lots of a booster dose of GlaxoSmithKline Biologicals' (GSK) Tdap candidate vaccine as compared to a U.S.-licensed Td vaccine (Massachusetts Public Health Biologic Laboratories) when given as a booster dose to healthy adolescents (10-18 years of age).

3.1.1 Objectives

Primary Objectives

- To demonstrate the lot-to-lot consistency of three production lots of GSK Boostrix™ in terms of immunogenicity of each antigen.
- To demonstrate the non-inferiority of Boostrix™ compared to the control Td_{MPHBL} vaccine in terms of immunogenicity, with respect to anti-diphtheria toxoid (anti-D) and anti-tetanus toxoid (anti-T) seroprotection rates.
- To demonstrate the non-inferiority of Boostrix™ compared to the control Td_{MPHBL} vaccine in terms of immunogenicity, with respect to anti-D and anti-T booster responses.
- To demonstrate that anti-pertussis toxoid (anti-PT), anti-filamentous hemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) booster responses occur in at least 80% of vaccinees administered Boostrix™.
- To demonstrate the non-inferiority of GSK Biologicals' candidate Tdap vaccine compared to the control Td vaccine in terms of safety, with respect to Grade 3 pain at the injection site.

Secondary Objective

- To assess the safety of each study vaccine in terms of non-serious solicited and unsolicited adverse events (AEs) and serious adverse events (SAEs).

3.1.2 Design

A prospective, randomized, observer-blinded, comparative, multicenter study with four groups of adolescents 10-18 years of age. Enrollment was stratified by age into two groups, 10-14 years of age (N=3000) and 15-18 years of age (N=1000).

- Boostrix™ (Lot 1, N = 1,000)
- Boostrix™ (Lot 2, N = 1,000)
- Boostrix™ (Lot 3, N = 1,000)
- Td_{MPHBL} (control) (N = 1,000)

Participants were enrolled at forty-five centers in the United States.

3.1.3 Population

Inclusion/Exclusion Criteria
Prior to enrollment participants would have previously completed routine childhood vaccinations against diphtheria, tetanus and pertussis diseases according to the recommended vaccination schedule at the time. At least five years were to have elapsed since receipt of the pre-school dose of DTP. Subjects who had received a booster Td within the previous 10 years were excluded. Routine vaccination schedules during the time period enrolled subjects received their infant and booster DTP doses are shown in Table 4.

Table 4. Study Tdap/001: Recommended U.S. vaccination schedule 1984-1998

Time period	Vaccine	Schedule
1984-1990	DTwP (doses 1-5)	2, 4, 6, 15 months and 4-6 years*
1991-1996	DTwP (doses 1-3), DTwP or DTaP (doses 4-5)	2, 4, 6, 15 months and 4-6 years*
1997-1998	DTwP or DTaP (doses 1-5)	2, 4, 6, 15 months and 4-6 years*

*If the fourth dose was received after the fourth birthday, no fifth dose was necessary.
Source: 2.7.3 Summary of Clinical Efficacy page 31, Table 3
DTwP: Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, "whole cell DTP" vaccine
DTaP: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed

3.1.4 Vaccine administration

Boostrix™ was administered as a single dose intramuscularly.
Td_{MPHBL} was administered as a single dose intramuscularly.

Table 5: Study Tdap/001: Study Vaccine Composition per 0.5mL dose

Component	Boostrix™ (Tdap) U.S. formulation	Td_{MPHBL}
Diphtheria toxoid (D/d)	2.5 Lf	2.0 Lf
Tetanus toxoid (T)	5.0 Lf	2.0 Lf
Pertussis toxoid (PT)	8.0 µg	--
Filamentous hemagglutinin (FHA)	8.0 µg	--
Pertactin (PRN)	2.5 µg	--
Aluminum	0.3 mg (as $AlOH_3$)	0.45 mg (as $AlPO_4$)
Preservative	None	Thimerosal 1:30,000 (8.3 µg Hg/dose)

3.1.5 Endpoints

Immunogenicity

Primary immunogenicity endpoints:
The primary immunogenicity endpoints are shown in Table 6.

Table 6. Study Tdap/001: Primary immunogenicity endpoints one month following vaccination

Boostrix™ vs. Td_{MPHBL}	**Endpoint**	**Non-inferiority Criteria**
anti-D	% ≥ 0.1 IU/mL	UL of 2-sided 95% CI on difference (Td-Tdap) ≤ 10%
anti-D	% booster*****	UL of 2-sided 95% CI on difference (Td-Tdap) ≤ 10%
anti-T	% ≥ 0.1 IU/mL	UL of 2-sided 95% CI on difference (Td-Tdap) ≤ 10%
anti-T	% booster*****	UL of 2-sided 95% CI on difference (Td-Tdap) ≤ 10%
Boostrix™ anti-pertussis antigens	**Endpoint**	**Evaluation criteria**
anti-PT	% booster******	LL of 2-sided 95% CI on observed rate ≥80%
anti-FHA	% booster******	LL of 2-sided 95% CI on observed rate ≥80%
anti-PRN	% booster******	LL of 2-sided 95% CI on observed rate ≥80%

UL: Upper Limit
LL: Lower Limit
*****booster response for anti-D and anti-T defined as: pre-titer < 0.1 IU/mL should have post-titer ≥ 0.4; pre-titer ≥ 0.1 IU/mL should have ≥ 4 fold rise one month post vaccination
******booster response to pertussis antigens defined as: pre-titer < 5 EU/mL should have post-titer ≥ 20 EU/mL; pre-titer ≥ 5 EU/mL and < 20 EU/mL should have 4-fold rise, pre-titer ≥ 20 EU/mL should have ≥ 2-fold rise one month post vaccination

Secondary immunogenicity analyses
- Percentage of subjects with anti-D concentrations ≥ 0.1 IU/mL and anti-T concentrations ≥ 0.1 IU/mL by ELISA before vaccination.
- Percentage of subjects with anti-D concentrations ≥ 1.0 IU/mL and anti-T concentrations ≥ 1.0 IU/mL by ELISA before and one month after vaccination.
- Percentage of subjects with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥ 5.0 EL.U./mL, before and one month after vaccination.

Safety

Primary safety endpoint
- The incidence of Grade 3 injection site pain during the 15 day follow-up period post-vaccination, where Grade 3 pain is defined as spontaneously painful and/or prevented normal everyday activities.

Non-inferiority of Boostrix™ compared to Td_{MPHBL} would be demonstrated if the upper limit of the two-sided 95% CI of the difference (Boostrix™ minus Td_{MPHBL}) in the rate of grade 3 pain within 15 days post-vaccination was ≤ 4%.

Secondary safety endpoints
- The occurrence of solicited local adverse events (AEs) and solicited systemic AEs within 72 hours and 15 days post-vaccination.
- The occurrence of large injection site swelling within 15 days post-vaccination, pre-defined as follows:
  - any local swelling with a diameter > 100 mm and/or

  - any increased circumference of the injected limb > 50 mm above baseline measurements and/or
  - any diffuse swelling that interfered with or prevented normal everyday activities during the 15 day reporting period.
- The occurrence of unsolicited AEs within days 0-30 post-vaccination.
- The occurrence of Serious Adverse Events (SAEs) and new onset chronic illness during the 6-month study period.

3.1.6 Laboratory methods, surveillance and monitored parameters

Blood samples
A pre-vaccination blood sample was taken at the first study visit prior to vaccination. Subjects returned to the clinic 30-48 days following vaccination and a second blood sample was taken for serologic assays.

Laboratory Methods
All assays were performed at GSK Laboratory, Rixensart, Belgium. Assay methodology and validation reports have been submitted to the license application and have been found to be acceptable. The data submitted demonstrate stability of the anti-PT, anti-FHA and anti-PRN assays over time.

Table 7. Study Tdap/001: Serological Assay Methods and Assay Limit-of-Detection (LOD)

Antigen	Assay Method	LOD	Assay Unit
D	ELISA	0.1	IU/mL
T	ELISA	0.1	IU/mL
PT	ELISA	5	EL.U/mL
FHA	ELISA	5	EL.U/mL
PRN	ELISA	5	EL.U/mL

Source: Study Tdap/001, Table 3, page 54
IU/mL: International units per milliliter
EL.U/mL: Enzyme-linked immunoabsorbent assay (ELISA) units per milliliter

All serological testing was performed in a blinded manner. If there was insufficient blood sample volume to perform all assays for all antibodies, sera were analyzed according to a pre-specified priority ranking (in descending order D, T, PRN, PT, FHA).

Safety surveillance and monitoring
- **Immediate reactions:** 30 minutes post-vaccination
- **Solicited local and systemic adverse events:** These events were recorded on a subject diary card for days 0-14 following vaccination. Solicited local reactions included erythema, swelling, increased mid-upper arm circumference of the vaccinated arm, and pain. Solicited systemic symptoms included: fever measured by oral or axillary temperature, headache, fatigue, gastrointestinal symptoms. In addition to recording local swelling, subjects were instructed to contact the investigator and visit the study site for an evaluation if large injection site swelling occurred.
- **Unsolicited adverse events:** Information was collected for six months post-vaccination.
- **Serious adverse events** were reported and recorded during the 6-month study period following vaccination. A serious adverse event was defined as any untoward medical occurrence resulting in death, life-threatening experience, inpatient hospitalization, prolonged existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. According to the definition of SAEs, elective surgeries for pre-existing conditions were not to be reported as AEs or SAEs.
- **Extended safety follow-up:** Follow-up for SAEs, onset of chronic illness, AEs resulting in an emergency room visit and AEs resulting in a non-routine visit to a physician's office was accomplished by a telephone interview conducted by study personnel at 6 months post-vaccination.

3.1.7 Statistical considerations

Statistical power
Allowing for up to 10% of subjects who may not be evaluable for analysis the power to meet the evaluation criteria for each of the endpoints was >99% for each of the primary endpoints. Overall power to meet all the primary endpoints was estimated to be at least 95%.

Populations for analysis

Total Vaccinated Cohort (TVC)
The primary analysis of safety was based on the TVC. The TVC for safety consisted of all participants who received one dose of vaccine and for whom safety information was available. Analyses were performed according to the vaccine received.

Total Vaccinated Cohort (TVC) for immunogenicity:
The TVC for immunogenicity consisted of all participants who received one dose of vaccine and for whom immunogenicity data were available. Analyses were performed according to the vaccine administered. This population was to be analyzed only if the population excluded from the ATP cohort for immunogenicity exceeded 5%.

According to protocol (ATP) cohort for immunogenicity:
The primary analysis for immunogenicity was performed on the ATP cohort for immunogenicity. This included all participants who had received one dose of vaccine according to treatment assignment, who had blood samples drawn, and for whom a sufficient quantity of sera was available for analysis of at least one study vaccine antigen. Post-vaccination samples were obtained 21-138 days after vaccination. The post-vaccination blood sample window used to define the ATP cohort for immunogenicity was wider than that prescribed in the protocol (30-48 days).

3.2 Results

3.2.1 Population enrolled

Demographic characteristics
A total of 4116 subjects were enrolled, of whom 4114 subjects were vaccinated. The distribution of subjects, based on age, gender, race and ethnicity, was similar among all vaccine groups. The study population enrolled was predominately Caucasian (85.7%), but also included African-Americans (5.6%), Hispanics (5.7%) and Asians (0.8%). Over 2% of participants listed their race as "Other". The mean age for the Total Vaccinated Cohort was 12.9 years; 52.1% males and 47.9% females. Subjects 9-14 years of age comprised 75.2% of enrollees (one subject, who received Td_{MPHBL} was 9 years of age at vaccination). Subjects 15-18 years comprised 24.8% of enrollees.

Vaccination history
Of enrolled subjects, 98% had previously received four or five of diphtheria-tetanus containing vaccines (DTwP, DTaP and/or Td). Because of the routine U.S. vaccination schedule in place during the time these adolescents received the first three doses of DTP it is likely that DTwP was administered for these doses. The type of vaccine administered for the fourth and fifth dose was dependent upon the age of the subject and availability of the vaccine (DTwP or DTaP).

3.2.2 Immunogenicity Analyses

Boostrix™ lot consistency

Lot consistency of the three Boostrix™ lots was demonstrated (data not shown). Therefore, subsequent analyses of the immune response to Boostrix™ were based upon the pooled data.

Immune response to diphtheria and tetanus toxoids

Interim Analysis
Due to lack of available data on the immunogenicity of Td_{MPHBL}, an interim analysis was performed to evaluate the feasibility of demonstrating non-inferiority of the booster responses to the tetanus and diphtheria antigens of Boostrix™ compared to Td_{MPHBL}. This analysis was performed on sera from the first 408 participants who had post-vaccination results available. These subjects were excluded from the final analyses for non-inferiority of diphtheria and tetanus antigens of Boostrix™ as compared to Td_{MPHBL}.

Pre-vaccination anti-diphtheria and anti-tetanus seroprotection rates
Table 8 shows the percentage of subjects with anti-tetanus and anti-diphtheria seroprotection levels ≥ 0.1 IU/mL level and ≥ 1.0 IU/mL prevaccination.

Table 8. Study Tdap/001: Healthy adolescents 10-18 years of age: Pre-vaccination anti-diphtheria and anti-tetanus levels ≥ 0.1 IU/mL and ≥ 1.0 IU/mL (ATP cohort for immunogenicity)

Antigen	Boostrix™ N=2466-2471	Td_{MPHBL} N=814-817
	% (95% CI)	% (95% CI)
anti-D ≥ 0.1 IU/mL	85.8 (84.3, 87.1)	84.8 (82.1, 87.2)
anti-D ≥ 1.0 IU/mL	17.1 (15.6, 18.6)	19.5 (16.9, 22.4)
anti-T ≥ 0.1 IU/mL	97.7 (97.1, 98.3)	96.8 (95.4, 97.9)
anti-T ≥ 1.0 IU/mL	36.8 (34.9, 38.7)	39.9 (36.5, 43.4)

Source: Study Tdap/001, Table 26, page 106
N: number of subjects with available results

Post-vaccination seroprotection and booster response to diphtheria and tetanus toxoids
Table 9 presents the differences in anti-tetanus and anti-diphtheria seroprotection and booster response rates between the Boostrix™ vaccine group and the Td_{MPHBL} group. Non-inferiority of Boostrix™ compared to Td_{MPHBL} in terms of seroprotection rates (% ≥ 0.1 IU/mL) and booster response rates was demonstrated.

Although not prospectively defined as a criterion for evaluation of non-inferiority, the upper limit of the 95% CI for the difference in the percentage of subjects with anti-diphtheria and anti-tetanus titers ≥1.0 IU/mL was also ≤10%.

Table 9. Study Tdap/001. Healthy adolescents 10-18 years of age: Differences in response rates between the Boostrix™ Vaccine Groups and Td_{MPHBL} Vaccine Group with 95% CIs one month post Boostrix™ or Td vaccination (ATP cohort for immunogenicity)

Endpoint	Boostrix™ N=2463-2516	Td_{MPHBL} N=814-834	Td_{MPHBL} minus Boostrix™	
	Rate (%)	Rate (%)	Difference (%)	95% CI
anti-diphtheria				
≥ 0.1 IU/mL *(primary endpoint)*	99.9	99.9	0.0	(-0.6, 0.3)**
booster response *(primary endpoint)*	90.6	95.9	5.3	(3.4, 7.0)**
≥ 1.0 IU/mL	97.3	99.3	2.0	(1.0, 2.8)§
anti-tetanus				
≥ 0.1 IU/mL *(primary endpoint)*	100	100	0.0	(-0.4, 0.2)**
booster response *(primary endpoint)*	89.7	92.5	2.9	(0.6, 4.9)**
≥ 1.0 IU/mL	99.5	99.8	0.3	(-0.4, 0.7)§

Source: Study Tdap/Study 001, Table 28, page 109
N: number of subjects with available results
Booster response to D and T is defined as:
- For initially seronegative subjects (pre-vaccination antibody concentrations <0.1 IU/mL): post-vaccination antibody concentrations at least four times the cut-off (≥0.4 IU/mL)
- For initially seropositive subjects (pre-vaccination antibody concentrations ≥0.1 IU/mL): post-vaccination increase of at least four times the pre-vaccination antibody concentrations
** Non-inferiority criterion met: upper limit 95% CI below the pre-defined limit for non-inferiority
§ Non-inferoirity criteria were not pre-specified

Geometric mean antibody concentration to diphtheria and tetanus toxoids
Table 10 presents the GMCs (adjusted for baseline titer) to diphtheria and tetanus toxoids one month following administration of Boostrix™ or Td_{MPHBL}.

No pre-defined criteria for non-inferiority of the GMC response was prespecified although an analysis of the ratio of GMCs was presented.

Table 10. Study Tdap/001. Healthy adolescents 10-18 years of age: Ratios of post-vaccination GMCs (adjusted for baseline titer) between Boostrix™ and Td_{MPHBL} vaccine groups with their 95% CIs one month following vaccination (ATP cohort for immunogenicity)

Endpoint	Boostrix™ N= 2463-2469	Td_{MPHBL} N=814-817	Td_{MPHBL}/Boostrix™**	
	Adjusted GMC	Adjusted GMC	Ratio	95% CI
anti-diphtheria	7.4	14.2	1.91	(1.79, 2.04)
anti-tetanus	15.8	20.8	1.32	(1.24, 1.40)

Source: Study Tdap/001, Supplement 27, page 192
N: number of subjects with pre- and post-vaccination results available
**No pre-defined criteria for non- inferiority were specified

Immune response to pertussis antigens contained in Boostrix™

Table 11 presents the anti-PT, anti-FHA and anti-PRN booster response rates (primary endpoint) following administration of Boostrix™. An acceptable booster response to each pertussis antigen was observed since the lower limit of the exact two-sided 95% CI for the booster response rate exceeded the pre-defined criterion of ≥ 80% for each antigen.

Table 11. Study Tdap/001. Healthy adolescents 10-18 years of age: Booster response to the pertussis antigens one month following administration of Boostrix™ (ATP cohort for immunogenicity)

	Boostrix™ N=2677-2752	
Booster response to:	**Rate (%)**	**95% CI**
PT *(primary endpoint)*	84.5	(83.0, 85.8)**
FHA *(primary endpoint)*	95.1	(94.2, 95.9)**
PRN *(primary endpoint)*	95.4	(94.5, 96.1)**

Source: Study Tdap/001, Table 30 page 113
N: number of subjects with pre- and post-vaccination results available
Booster response to PT, FHA and PRN defined as:
- For initially seronegative subjects (pre-vaccination antibody concentrations <5 EL.U./mL): post-vaccination antibody concentrations at least four times the cut-off (≥20 EL.U./mL)
- For initially seropositive subjects with pre-vaccination antibody concentrations ≥5 EL.U./mL and <20 EL.U./mL: post-vaccination increase of at least four times the pre-vaccination antibody concentrations
- For initially seropositive subjects with pre-vaccination antibody concentrations ≥20 EL.U./mL: post-vaccination increase of at least two times the pre-vaccination antibody concentrations
** Primary endpoint met

Table 12 presents the anti-pertussis antigen seropositivity rates and GMCs pre- and one-month post immunization with Boostrix™. There were no pre-defined criteria for evaluation of seropositivity or anti-pertussis GMCs.

Table 12. Study Tdap/001. Healthy adolescents 10-18 years of age: Anti-pertussis antigen seropositivity rates and GMCs pre- and one month post-administration of Boostrix™ (ATP cohort for immunogenicity)

	Boostrix™	
Endpoint	**Pre-vaccination (95% CI) N= 2710-2745**	**Post-vaccination (95% CI) N= 2677-2752**
% ≥ 5 EL.U/mL		
anti-PT	65.1 (63.3, 66.9)	98.9 (98.4, 99.3)
anti-FHA	96.3 (95.5, 97.0)	100 (99.9, 100)
anti-PRN	72.9 (71.2, 74.5)	99.7 (99.5, 99.9)
GMC		
anti-PT	9.5 (9.1, 10.0)	85.9 (82.9, 89.0)
anti-FHA	41.9 (40.0, 43.9)	623.8 (604.8, 643.4)
anti-PRN	13.0 (12.3, 13.7)	472.8 (448.4, 498.4)

Source: Study Tdap/001, p. 106 and 112,
N: number of subjects with pre-vaccination results available as well as data for the specified time point
Seropositivity defined as values ≥ 5.0 EL.U/mL.

Immunogenicity analyses of the Total Vaccinated Cohort
The primary immunogenicity analyses were based on the ATP cohort for immunogenicity (Boostrix™ N=2800, Td_{MPHBL} N=923). The percent of subjects excluded from the ATP cohort for immunogenicity was more than 5% (391 of 4114 subjects in the TVC were excluded [9.5%]). Therefore, immunogenicity analyses using the Total Vaccinated Cohort (Boostrix N=3080, Td_{MPHBL} N=1034) were performed.

In these analyses, the pre-defined criteria for all primary endpoints were met (data not shown).

3.2.3 Serologic Bridge of Boostrix™ to Infanrix®

The pertussis antibody responses of adolescents 10-18 years of age immunized with Boostrix™ in Study Tdap/001 were compared to those of infants immunized with Infanrix® in a household contact clinical efficacy study (APV-039 and APV-050)

Study APV-039, a safety and immunogenicity study of Infanrix®, provided the population for a household contact study to evaluate the clinical efficacy of Infanrix® (Study APV-050). In this study the protective efficacy of a three-dose series of Infanrix®, administered at 3, 4 and 5 months of age, was calculated to be 89% (95% CI: 77% to 95%) against WHO-defined pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of Infanrix® against ≥7 days of any cough was 67% (95% CI: 52% to 78%) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68% to 89%). The corresponding efficacy rates of Infanrix® against ≥14 days of any cough or paroxysmal cough were 73% (95% CI: 59% to 82%) and 84% (95% CI: 71% to 91%), respectively.

Table 13 presents results of the primary analysis of GMCs one month following a three dose series of Infanrix® in infants and following a single dose of Boostrix™ in adolescents. Pre-defined non-inferiority criteria (upper limit of the 95% CI of the ratio of GMCs, Infanrix®/Boostrix™, < 1.5 for each pertussis antigen) for non-inferiority of the anti-pertussis responses following Boostrix™, as compared to those following three doses of Infanrix® in infants, were met for the Total Vaccinated Cohort. When these analyses were repeated using the ATP cohort from each study the pre-defined non-inferiority criteria were also met (Table 14).

Table 13: Ratios of GMCs between Boostrix™ (single dose in adolescents) and Infanrix® (three dose series in infants) with their 95% CIs one month post-vaccination (TVC)*

Antigen	Infanrix® (Study APV-039)		Boostrix™ (Study Tdap/001)		Infanrix®/Boostrix™
	N	GMC	N	GMC	Ratio (95% CI)
anti-PT	2884	45.7	2941	86.9	0.53 (0.50, 0.55)**
anti-FHA	685	83.6	2979	614.8	0.14 (0.13, 0.15)**
anti-PRN	631	112.3	2978	470.7	0.24 (0.21, 0.27)**

Source: Study Tdap/001 Table 31, page 115
* TVC for Study 039: Subjects who had serological data for at least one pertussis antigen. The majority of subjects had anti-pertussis toxoid serological data only. Serologic assays of infant sera were performed in 1994.
N: number of subjects with available post-vaccination results available
**pre-specified non-inferiority criteria met.

Table 14. Ratios of GMCs between Boostrix™ (single dose in adolescents) and Infanrix® (three dose series in infants) with their 95% CIs one month post-vaccination (ATP cohort for immunogenicity)*

Antigen	Infanrix® (Study APV-039)		Boostrix™ (Study Tdap/001)		Infanrix®/Boostrix™
	N	GMC	N	GMC	Ratio (95% CI)
anti-PT	580	48.6	2762	85.9	0.57 (0.52, 0.61)**
anti-FHA	580	89.1	2799	617.3	0.14 (0.13, 0.16)**
anti-PRN	580	124.2	2798	469.3	0.26 (0.23, 0.30)**

Source: Study Tdap/001, Supplement 43, page 210
* ATP cohort for Study 039: all subjects with reactogenicity data for all three doses, met all eligibility criteria, had pre- and post-vaccination results available for all pertussis antigens and had complied with the protocol defined windows for vaccinations and blood draws. Serologic assays of infant sera were performed in 1994.
N: number of subjects with available post- vaccination results available
**pre-specified non-inferiority criteria met.

3.2.4 Safety Analyses

Lot consistency was demonstrated (based on immunologic criteria not discussed in this briefing document) therefore analyses of safety following administration of Boostrix™ were based upon the pooled data.

Immediate reactions
No immediate reactions were reported in the 30-minutes following vaccination.

Solicited local adverse events
Pain was the most frequently reported solicited local adverse event in both groups.

Table 15 presents the incidence of pain at the injection site during the 72 hours and 15-day follow-up period. The rate of Grade 3 pain was similar for the group that received Boostrix™ and Td_{MPHBL} vaccine. The upper limit of the 95% CI for the difference in rate of Grade 3 pain between the two groups within 15 days following vaccine administration was ≤ 4%. Thus, the pre-specified non-inferiority criterion for this endpoint was met.

The incidence of any and ≥ Grade 2 pain at 72 hours and at 15 days post-vaccination was significantly higher ($p<0.05$) in Boostrix™ recipients as compared to Td_{MPHBL} recipients.

Table 15. Study Tdap/001: Incidence of Pain within 72-hours and 15 days post-vaccination in adolescents 10-18 years of age (Total Vaccinated Cohort)

Follow-up period	Intensity^	Boostrix™ N= 3032	Td_{MPHBL} N= 1013	Boostrix™ minus Td_{MPHBL}
		%	%	Difference (95% CI*)
72 hours	Any	75.0	71.4	3.59 (0.47,6.83)**
	Grade ≥2	50.7	42.2	8.57 (5.03,12.07)**
	Grade 3	4.5	3.7	0.80 (-0.70, 2.08)
15 days	Any	75.3	71.7	3.66 (0.55, 6.89)**
	Grade ≥2	51.2	42.5	8.67 (5.13, 12.17)**
	Grade 3	4.6	4.0	0.54 (-1.01, 1.87) §

Source: Study Tdap/001 Table 35, page 124
N: number of subjects with available safety data
^Pain Intensity grade:
any = painful on touch,
grade 2 = painful when limb moved,
grade 3 = spontaneously painful and/or prevented normal activity
*standardized asymptotic CI
**difference between groups were statistically significant (p-value <0.05, 2-sided Fisher's exact test)
§ non-inferiority criterion met (upper limit 95% CI on the difference ≤4%)

No significant differences ($p<0.05$) in the rates of other solicited local adverse events were observed between the two vaccine groups during the 72 hours or 15 days following vaccine administration (Table 16).

Table 16. Study Tdap/001: Incidence of solicited local symptoms (other than pain) in adolescents 10-18 years of age within 72 hours and 15 days following administration Boostrix™ or Td_{MPHBL}(Total Vaccinated Cohort)

Event	Follow-up period	Intensity	Boostrix™ N = 3032		Td_{MPHBL} N = 1013	
			%	95% CI	%	95% CI
Redness	72 hours	Any	21.9	(20.4,23.4)	19.5	(17.1, 22.1)
		Grade ≥2	4.0	(3.4, 4.8)	3.8	(2.7, 5.1)
		Grade 3	1.6	(1.2, 2.1)	1.5	(0.8, 2.4)
	15 days	Any	22.5	(21.0, 24.0)	19.8	(17.4, 22.4)
		Grade ≥2	4.1	(3.4, 4.9)	3.9	(2.8, 5.3)
		Grade 3	1.7	(1.3, 2.2)	1.6	(0.9, 2.6)
Swelling	72 hours	Any	20.2	(18.8,21.7)	19.8	(17.4, 22.4)
		Grade ≥2	5.0	(4.3, 5.9)	4.8	(3.6, 6.3)
		Grade 3	2.4	(1.9, 3.0)	3.2	(2.2, 4.4)
	15 days	Any	21.1	(19.7, 22.6)	20.1	(17.7, 22.7)
		Grade ≥2	5.3	(4.5, 6.1)	4.9	(3.7, 6.5)
		Grade 3	2.5	(2.0, 3.1)	3.2	(2.2, 4.4)
Increased mid-upper arm circumference (injected arm)	72 hours	Any	21.4	(19.9, 22.9)	23.2	(20.6, 25.9)
		Grade ≥2	1.6	(1.1, 2.1)	1.5	(0.8, 2.4)
		Grade 3	0.3	(0.2, 0.6)	0.3	(0.1, 0.9)
	15 days	Any	28.3	(26.7, 29.9)	29.5	(26.7, 32.4)
		Grade ≥2	2.0	(1.5, 2.5)	2.2	(1.4, 3.3)
		Grade 3	0.5	(0.3, 0.8)	0.3	(0.1, 0.9)
Increased mid-upper arm circumference (opposite arm)	72 hours	Any	15.3	(14.0, 16.6)	16.2	(14.0, 18.6)
		Grade ≥2	0.9	(0.6, 1.3)	0.9	(0.4, 1.7)
		Grade 3	0.1	(0.0, 0.3)	0.6	(0.2, 1.3)
	15 days	Any	22.5	(21.0, 24.0)	23.8	(21.2, 26.5)
		Grade ≥2	1.3	(0.9, 1.8)	1.2	(0.6, 2.1)
		Grade 3	0.2	(0.1, 0.4)	0.6	(0.2, 1.3)

Source: Study Tdap/001 Table 35, page 124.
N: number of subjects with local Symptom Sheets completed
Redness and Swelling:
Any: any solicited local event reported, regardless of intensity
Grade 2: redness and swelling >20 mm but <50 mm
Grade 3: redness and swelling ≥50 mm
Increase mid-upper arm circumference:
Any: increase in mid-upper arm circumference >5mm
Grade 2: mid-upper arm circumference increase >20 mm but ≤40 mm
Grade 3: mid-upper arm circumference increase >40 mm

As shown in Table 16 an increase over baseline in the mid-upper arm circumference of the unvaccinated (opposite arm) arm was observed in approximately 15-20% of subjects in both vaccine groups. These data should be taken into account in interpreting any increase in mid-arm circumference of the vaccinated arm.

Large injection site swelling
As predefined in the protocol, subjects who experienced large injection site swelling within 15 days post-vaccination (pre-defined as follows: any local swelling with a diameter > 100 mm, and/or any increased

circumference of the injected limb > 50 mm above baseline measurements, and/or any diffuse swelling that interfered with or prevented normal everyday activities) were to be evaluated by the investigator.

Two subjects, one who had received Boostrix™ and another who had received Td_{MPHBL} reported large injection site swelling in the vaccinated arm.

The subject who had received Boostrix™ presented for clinical evaluation of diffuse swelling three days post-vaccination. The diffuse swelling was associated with local redness (90mm) and local swelling (90mm). There was an increase in mid-upper arm circumference of 8mm above baseline. The subject reported grade 3 pain and functional impairment. The investigator prescribed antibiotic therapy, the event resolved 3 days later without sequelae.

The subject who had received Td_{MPHBL} reported large swelling of the injected arm three days following vaccination but did not present for a clinical evaluation. Review of the diary card documented local redness (80mm) and swelling (102mm) with an increase in mid-arm circumference of 13mm. The subject reported grade 1 pain. Duration of reported large swelling was unknown but resolved without treatment or sequelae.

A retrospective review of subject diary cards showed that six subjects, three who had received Boostrix™ and three who had received Td_{MPHBL}, had recorded an increase of > 50 mm in the mid-upper arm circumference of the vaccinated arm. None of these subjects presented for clinical evaluation of swelling. Upon questioning, all subjects denied there had been swelling of the vaccinated arm. These subjects reported that they had incorrectly measured the mid-upper arm circumference of their arms.

Subgroup analysis of solicited local AEs by age
A sub-group analysis was performed to assess the occurrence of solicited local events within 72 hours and 15 days by age (10-14 years and 15-18 years).

Sub-group analyses of the incidence of ≥ grade 2 pain within 72 hours in subjects 10-14 and 15-18 years of age demonstrated that the incidence of ≥ grade 2 pain was higher in the group which had received Boostrix™ (non-overlapping 95% CI). In subjects 10-14 years of age 49.1% (95% CI: 47.0-51.2) of Boostrix™ recipients reported ≥ grade 2 pain versus 41.9 % (95% CI:38.4-45.6) of Td_{MPHBL} recipients. In subjects 15-18 years 55.9% (95% CI: 52.2-59.5) of Boostrix™ recipients reported ≥ grade 2 pain versus 42.7% (95% CI: 36.8-48.8) of Td_{MPHBL} recipients. At 15 days following vaccine administration the incidence of ≥ grade 2 pain remained higher in Boostrix™ recipients (non-overlapping 95% CI).

The incidence of other local adverse events was similar between groups and did not differ from the 10-18 year old cohort (data not shown).

Analysis of solicited local AEs by DTP vaccine received in childhood
A sub-group analysis was performed of the data collected at 72 hours and 15 days to assess the occurrence of solicited local events by DTP vaccine administered in childhood.

In children administered DTaP vaccine the incidence and severity of local adverse events has been shown to increase with successive doses of DTaP, particularly following the fourth and fifth doses. Study Tdap/001 was not designed to evaluate differences in the incidence of adverse events as a function of the number of the previous doses of DTaP administered. Information on the number of doses of DTwP and DTaP received was available for a subset of subjects. For the majority of subjects information pertaining to the type of DTP vaccine administered in childhood was unknown. The frequency of local AEs within 3 days in subjects with a known vaccination history is shown in Table 17. For subjects with a known type of vaccine administered in childhood there was no consistent trend toward increasing reactogencity with increasing doses of DTaP administered. However, this analysis is limited by the small subset of subjects for whom the type of vaccine administered was known. The frequency of local AEs within 15 days is not shown but was similar to the incidence within 3 days.

Table 17. Study Tdap/001: Incidence of solicited local symptoms in subjects 10-18 years of age within 72 hours following administration of Boostrix™ by type of DTP administered in childhood (Total Vaccinated Cohort)

Event	Intensity	Boostrix™					
		5 previous doses of DTwP N=383		4 previous doses of DTwP +1 dose of DTaP N= 273		3 doses of DTwP+ 2 Doses of DTaP N=98	
		%	95% CI	%	95% CI	%	95% CI
Pain	Any	75.5	(70.8, 79.7)	73.6	(68.0, 78.8)	73.5	(63.6, 81.9)
	Grade ≥2	52.2	(47.1, 57.3)	46.9	(40.8, 53.0)	52.0	(41.7, 62.2)
	Grade 3	2.9	(1.4, 5.1)	5.5	(3.1, 8.9)	0.0	(0.0, 3.7)
Redness	Any	16.4	(12.9, 20.5)	19.4	(14.9, 24.6)	16.3	(9.6, 25.2)
	Grade ≥ 2	2.3	(1.1, 4.4)	4.0	(2.0, 7.1)	6.1	(2.3, 12.9)
	Grade 3	0.8	(0.2, 2.3)	1.5	(0.4, 3.7)	0.0	(0.0, 3.7)
Swelling	Any	17.8	(14.1, 22.0)	12.5	(8.8, 17.0)	22.4	(14.6, 32.0)
	Grade ≥2	3.1	(1.6, 5.4)	3.3	(1.5, 6.2)	6.1	(2.3, 12.9)
	Grade 3	1.8	(0.7, 3.7)	1.5	(0.4, 3.7)	2.0	(0.2, 7.2)

Source: Study Tdap/001 Supplement 62, page 234-235
N: number of subjects with local Symptom Sheets completed
Pain: Any = painful on touch,
Grade 2 = painful when limb moved,
Grade 3 = spontaneously painful and/or prevented normal activity
Redness and Swelling:
Any: any solicited local event reported, regardless of intensity
Grade 2: redness and swelling >20 mm but <50 mm
Grade 3: redness and swelling ≥50 mm

Solicited systemic adverse events
The rates of solicited systemic adverse events which occurred within 72-hours and 15-days following vaccination were analyzed. Solicited AEs included fever, headache, fatigue, and gastrointestinal symptoms.

Headache and fatigue were the most commonly reported solicited systemic AEs in both vaccine groups. There was a significantly higher ($p<0.05$) incidence of ≥ Grade 2 headache in Boostrix™ group 15 days post vaccination (15.7% versus 12.7% in the Td_{MPHBL} group).

The incidence of all other solicited systemic AEs were similar between the two vaccine groups within both the 72-hour and the 15-day follow-up periods.

Table 18. Study Tdap/001: Incidence of solicited systemic symptoms in adolescents 10-18 years of age within 72 hours and 15 days following administration Boostrix™ or Td_{MPHBL} (Total Vaccinated Cohort)

Event	Follow-up period	Intensity	Boostrix™ N =3030		Td_{MPHBL} N =1013	
			%	95% CI	%	95% CI
Fever*	72 hours	≥37.5ºC	6.5	(5.6, 7.4)	5.4	(4.1,7.0)
		≥38ºCºC	1.8	(1.3, 2.3)	1.5	(0.8, 2.4)
		>39.0ºC	0.4	(0.2, 0.6)	0.3	(0.1, 0.9)
	15 days	≥37.5ºC	13.4	(12.2, 14.7)	13.1	(11.1, 5.4)
		≥38.0ºC	5.0	(4.3, 5.9)	4.7	(3.5, 6.2)
		>39.0ºC	1.4	(1.0, 1.8)	1.0	(0.5, 1.8)
Headache	72 hours	Any	31.1	(29.5, 32.8)	30.9	(28.1, 33.9)
		Grade ≥2	7.8	(6.8, 8.8)	6.8	(5.3, 8.5)
		Grade 3	1.4	(1.0, 1.9)	1.2	(0.6, 2.1)
	15 days	Any	43.1	(41.3, 44.9)	41.5	(38.4, 44.6)
		Grade ≥2	15.7	(14.5, 17.1)	12.7	(10.8, 15.0)
		Grade 3	3.7	(3.1, 4.4)	2.7	(1.8, 3.9)
Fatigue	72 hours	Any	29.9	(28.3, 31.6)	30.6	(27.8, 33.6)
		Grade ≥2	8.8	(7.8, 9.9)	8.6	(6.9, 10.5)
		Grade 3	1.6	(1.2, 2.1)	1.9	(1.1, 2.9)
	15 days	Any	37.0	(35.3, 38.7)	36.7	(33.7, 39.7)
		Grade ≥2	14.4	(13.2, 15.7)	12.9	(10.9, 15.2)
		Grade 3	3.7	(3.0, 4.4)	3.2	(2.2, 4.4)
Gastro-intestinal Symptoms	72 hours	Any	17.0	(15.7, 18.4)	17.4	(15.1, 19.9)
		Grade ≥2	4.9	(4.1, 5.7)	4.9	(3.7, 6.5)
		Grade 3	1.3	(0.9, 1.8)	1.6	(0.9, 2.6)
	15 days	Any	26.0	(24.5, 27.6)	25.8	(23.1, 28.6)
		Grade ≥2	9.8	(8.8, 11.0)	9.7	(7.9, 11.7)
		Grade 3	3.0	(2.4, 3.6)	3.2	(2.2, 4.4)

Source: Study Tdap/001 Table 35, page 130-131
N = number of subjects with general Symptom Sheets completed
*oral or axillary temperature
Headache, Fatigue and Gastrointestinal symptoms:
Any = any report of the event regardless of intensity,
Grade 2 = interfered with normal activity,
Grade 3 = prevented normal activity

Unsolicited adverse events

In the Boostrix™ vaccine group, 771 of 3034 subjects (25.4%) reported at least one unsolicited AE within the 0-30 days post-vaccination. In the Td_{MPHBL} vaccine group, 248 of 1013 subjects (24.5%) reported at least one unsolicited AE within the same time period following vaccination (Active phase). The most frequently reported unsolicited AEs in each group were pharyngitis (4.6% of the subjects in the Boostrix™ vaccine group and 4.3% of the subjects in the Td_{MPHBL} vaccine group) and upper respiratory infections (4.3% and 4.8% respectively).

Serious adverse events – Active phase Day 0-30

No serious adverse events occurred during the Active Phase of the study (Day 0-30). Three subjects underwent elective surgeries, these were reported AEs.

Adverse Events during the 5-month follow-up period

Onset of new chronic illnesses was reported by 22 subjects in the Boostrix™ group (0.7%) versus 9 subjects (0.9%) in the Td_{MPHBL} group. The most commonly reported diseases in the Boostrix™ group were gastrointestinal illness (0.2%) allergy (0.1%), impaired concentration (0.1%)and asthma (0.1%).

Table 19. Study Tdap/001: Percentage of subject (10 to 18 years of age) reporting AEs during the 5-month follow-up period, by type (Total Vaccinated Cohort)

AE type*	Boostrix™ N = 3005			Td_{MPHBL} N = 1003		
	n	%	95% CI	n	%	95% CI
Chronic illness	22	0.7	(0.5, 1.1)	9	0.9	(0.4, 1.7)
Emergency room visit	101	3.4	(2.7, 4.1)	25	2.5	(1.6, 3.7)
Non-routine physician's office visit	52	1.7	(1.3, 2.3)	16	1.6	(0.9, 2.6)
SAE	14	0.5	(0.3, 0.8)	2	0.2	(0.0,0.7)

Source: Study Tdap/001 Table 43, page 145.
*An AE may be reported in more than one category, e.g., a chronic illness diagnosed during a hospitalization would be counted as a chronic illness and as an SAE.
N: number of subjects with data available beyond the 31-day (Days 0-30) post-vaccination period, including subjects withdrawn from the study but for whom data were available
n/% = number/percentage of subjects reporting at least one AE in specified category

The percentages of subjects reporting an SAE, a new onset chronic illness, or AE that required an emergency room or non-routine physician's office visit were similar between the two vaccine groups.

Fourteen (14) of the 3,005 (0.5%) subjects in the Boostrix™ group and two of the 1,003 (0.2%) subjects in the Td_{MPHBL} group reported the occurrence of SAEs during the five month follow-up period (Table 20). The percentage of subjects reporting SAEs in both groups was ≤0.5%.

Table 20. Study Tdap/001: Summary of Serious Adverse Events (SAEs) during the five month follow-up period by vaccine, age, gender and onset

Vaccine	Age/ Gender	Event	Onset (days after vaccination)
Boostrix™ N=3005	12 / M	Knee laceration/wounds	102
	15 / F	Overdose	92
	15 / F	Depression	32
	16 / M	ADHD	64
	19 / M	Drug Abuse	61
	11 / M	Cholecystitis (chronic)	68
	13 / F	Ankle fracture	52
	17 / F	Overdose	64
	13 / M	Tibia fracture	161
	14 / F	Headache	36
	17 / F	Spontaneous abortion	159
	13 / F	Menorrhagia with anemia	45
	14 / F	Sinusitis and migraine	93
	15 / M	Forearm fracture	114
	15 / M	Pleural effusion with pneumothorax status-post surgery for repair of pectus excavatum	76
Td_{MPHBL} N=1003	12 / F	Perforated appendicitis	60
	14 / M	Tooth Abscess	150

Source: Study Tdap/001 Table 47, page 151.
N=number of subjects with safety data available after days 0-30 post vaccination. Includes subjects withdrawn from the study but for whom follow-up safety data were available.

Pregnancy
Four pregnancies occurred during the study: Two in subjects who had received Boostrix and two in Td recipients. Both pregnancies in Boostrix recipients occurred ≥4 months post-vaccination. One of these subjects experienced a spontaneous abortion within the first trimester. All other subjects delivered healthy infants.

3.3 Additional Studies -Overview of serious adverse events

Nine additional non-IND clinical studies were submitted to support the evaluation of safety. The Tdap formulation used in these studies differed from that intended for U.S.-licensure. Safety monitoring parameters differed from study to study.

A total of 2372 additional subjects received Tdap or Boostrix™. Eight serious adverse events were reported among participants that had received Tdap or Boostrix™. Diagnoses included diabetes mellitus, diabetic coma, concussion, alcohol intoxication, syncope, uveitis, appendicitis and polypectomy (Table 21).

Table 21. Occurrence of SAEs in supportive safety studies

Vaccine received / Study	Age/ Gender	Event	Onset (days after vaccination)/resolution
263855/029 Belgium			
Tdap 0.5 mg Al	13 / M	Syncope resulting in fall and concussion	21/resolved
Tdap 0.3 mg Al	14 / F	Alcohol intoxication	28/resolved
Tdap 0.5 mg Al	11 / F	Diabetic coma with seizures and vomiting	37/incident resolved
263855/004 Finland			
Tdap 0.5 mg Al	11 / F	Diabetes mellitus diagnosed	20
Tdap 0.5 mg Al	10 / F	Appendicitis	23/resolved
263855/001 Germany			
Tdap 0.5 mg Al	(10-18 years)/ unknown gender	Loss of consciousness 2-3 seconds after vaccination	Immediate reaction/resolved
263855/002 Australia			
Tdap 0.5 mg Al /	(≥ 18 years)/ unknown gender	Uveitis	7/resolved
208355/118 Germany			
Tdap 0.5 mg Al /	(4-6 years) /F	polypectomy	29/resolved

References

1. CDC. Pertussis – United States, 1997-2000. MMWR 51 (04); 73-6.

2. Guris D, Strebel PM, Bardenheier B, et al. Changing epidemiology of Pertussis in the United States increasing reported incidence among adolescents and adults 1990-1996. Clin Infect Dis 1999; 28:1230.