February 15, 2005

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Vaccines & Related Biological Products Advisory Committee
Center for Biologics Evaluation and Research
Rockwall II Building, Room 1113
Food and Drug Administration
FDA/CBER/DSAC/HFM-71
5515 Security Lane
Rockville, MD 20852

Re: STN: BL 125106; Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap)
US License No. 0000
General Correspondence: Advisory Committee Meeting: Briefing Document

Dear Ms. Walsh:

Reference is made to GlaxoSmithKline's (GSK's) Biologics License Application for the vaccine candidate Boostrix™ [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap)] submitted on June 30, 2004.

On March 15, 2005, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet to review the new Biologics License Application for *Boostrix*. As requested, enclosed please find 35 color copies and a CD Rom copy of GSK's briefing document for the March 15, 2005 committee meeting.

GSK grants FDA permission to make this document public without redaction. In addition, the document may be posted on the FDA website without redaction.

Should you have any questions regarding the briefing document, please contact me by telephone at 610-787-3767 or by fax at 610-787-7063.

Sincerely,

for Donna Boyce
Director, CMC, Pediatric Vaccines
US Regulatory Affairs

BOOSTRIX™

(Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed, Tdap)

Vaccines And Related Biological Products Advisory

Committee Meeting

March 15, 2005

Briefing Document

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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ABBREVIATIONS

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
Ads	Adsorbed
Al	Aluminum
Anti-D	Anti-Diphtheria
Anti-T	Anti-Tetanus
Anti-PT	Anti -Pertussis
Anti-FHA	Anti- Filamentous Haemagglutinin
Anti-PRN	Anti-Pertactin
aP	Acellular Pertussis
ATP	According to Protocol
BLA	Biologics License Application
BR	Booster Response
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
D	Diphtheria
DT	Diphtheria and Tetanus
DTP	Diphtheria, Tetanus and Pertussis containing vaccine (whole cell or acellular)
DTaP	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine
DTPw	Diphtheria and Tetanus Toxoids and Whole-Cell Pertussis Vaccine
ELISA	Enzyme-Linked Immunosorbent Assay

EL.U/mL	ELISA units per Milliliter
FDA	Food and Drug Administration
FHA	Filamentous Haemagglutinin
GMU	Geometric Mean Unit
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HBV	Hepatitis B Vaccine
IND	Investigational New Drug Application
Infanrix®	GSK's Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed
IPV	Inactivated Poliovirus Vaccine
IU	International Units
Lf	Limit of flocculation unit
LISS	Large Injection Site Swelling
LL	Lower Limit
MMR	Measles, Mumps, Rubella Vaccine
MPHBL	Massachusetts Public Health Biologic Laboratories
NIH	National Institutes of Health
2-PE	2-phenoxyethanol
pa	GSK Biological's investigational reduced antigen content acellular pertussis vaccine
Pediarix®	GSK's Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Hepatitis B (recombinant) and Inactivated Poliovirus Vaccine Combined
PRN	Pertactin (69 kilodalton outer membrane protein of *B. Pertussis)*
PT	Pertussis toxin (or pertussis toxoid when referring to vaccine component)
RCC	Reverse Cumulative Curve

Ref.	Reference
SAE	Serious Adverse Event
SP	Seroprotection
T	Tetanus
Td	Tetanus and Diphtheria vaccine
TT	Tetanus Toxoid
U/mL	Units per Milliliter
UL	Upper limit
US	United States
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1. INTRODUCTION

On March 15, 2005, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet to review the new Biologics License Application (BLA) for Boostrix™, submitted by GlaxoSmithKline Biologicals, a GlaxoSmithKline (GSK) Company. Boostrix™ (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed, Tdap) is a liquid, sterile vaccine combining tetanus toxoid, diphtheria toxoid and acellular pertussis antigens. The vaccine contains no preservative and no thimerosal, and the 0.5 mL dose is administered intramuscularly. The proposed indication for *Boostrix* is single-dose booster immunization against diphtheria, tetanus, and pertussis in individuals 10-18 years of age. A minimum of five years should have elapsed since the individual's last dose of any vaccine containing diphtheria and/or tetanus toxoids.

Boostrix is a combination of well-known antigens. All components of the vaccine have been previously studied and are licensed for use in the United States (US) as part of GSK Biologicals' pediatric vaccines Infanrix® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), licensed in the US in 1997, and Pediarix® [Diphtheria, and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] licensed in the US in 2002.

Boostrix contains the same diphtheria, tetanus and pertussis antigens as GSK's *Infanrix* and *Pediarix*, but in reduced amounts. The composition of *Boostrix* compared to US-licensed DTaP-containing *Infanrix* and *Pediarix* is shown in Table 1.

Table 1 Composition of *Boostrix* and GSK's US-licensed DTaP–containing vaccines (per 0.5 mL dose)

Vaccine Composition	Tdap (*Boostrix*)	DTaP *(Infanrix)*	DTaP-HepB-IPV Combined (*Pediarix*)[a]
Pertussis Toxoid (PT)	8 µg	25 µg	25 µg
Filamentous haemagglutinin (FHA)	8 µg	25 µg	25 µg
Pertactin (69 kDa outer membrane protein –PRN)	2.5 µg	8 µg	8 µg
Aluminum as salts	0.3 mg	0.5 mg	0.7 mg
2-phenoxyethanol	---	2.5 mg	2.5 mg
Diphtheria Toxoid	≥2 IU (2.5 Lf)	≥40 IU (25 Lf)	≥40 IU (25 Lf)
Tetanus Toxoid	≥20 IU (5 Lf)	≥30 IU (10 Lf)	≥30 IU (10 Lf)

a. Each 0.5 mL dose of *Pediarix* also contains 10 mcg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus, 8 DU of Type 2 poliovirus, and 32 DU of Type 3 poliovirus.

Phamceutical form: liquid suspension for injection

Presentation: monodose in a glass vial or prefilled syringe

The Investigational New Drug Application for *Boostrix* was opened in June 1999. The BLA for *Boostrix* was submitted to the Food and Drug Administration (FDA) on June 30, 2004.

Outside of the US, GSK Biologicals has a licensed formulation of *Boostrix* that is identical to the formulation intended for the US except that it is formulated to contain 0.5 mg of Al as salts and 2.5 mg 2-phenoxyethanol as a preservative. This non-US formulation of *Boostrix* was first approved in Germany in 1999, is currently licensed in 42 countries worldwide, and over 1.9 million doses of this vaccine formulation have been distributed worldwide.

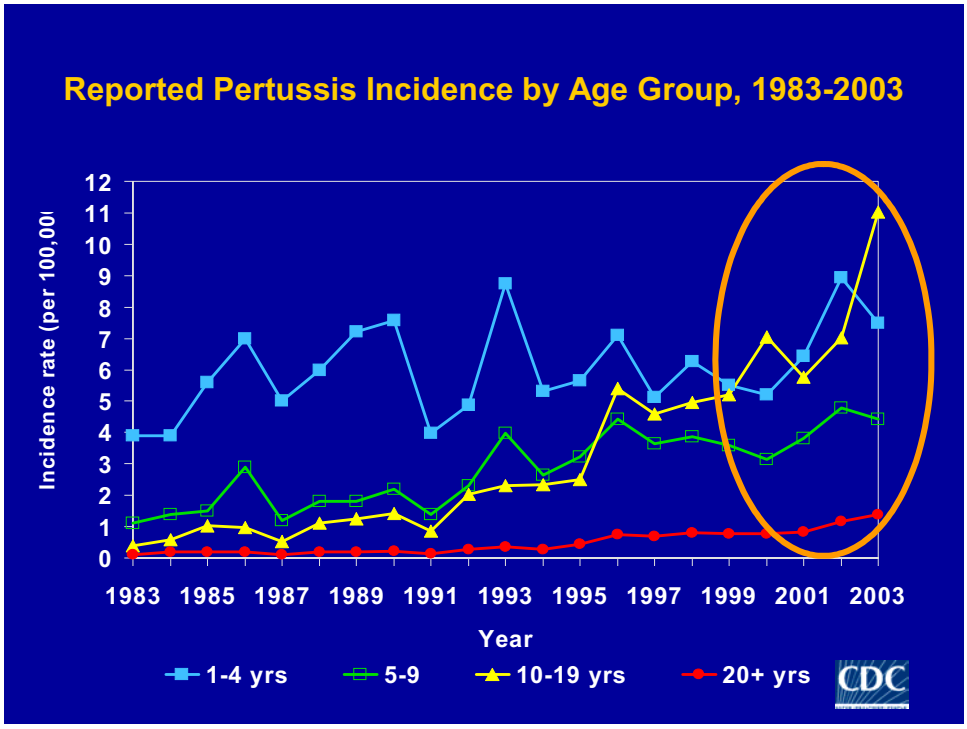
This briefing document provides information regarding the epidemiology of pertussis in the adolescent population and the rationale for GSK's clinical development program in adolescents. Included are the clinical data supporting the immunogenicity and safety of *Boostrix* for the prevention of diphtheria, tetanus, and pertussis in healthy individuals 10-18 years of age.

2. EPIDEMIOLOGY

Bordetella pertussis, the etiologic bacterial agent of the disease pertussis, is transmitted by close contact via aerosolized droplets from infected patients. Pertussis is a highly communicable disease. Widespread immunization of infants and toddlers with pertussis vaccines has been highly successful in reducing pertussis disease, complications and deaths in young children. The introduction of whole-cell pertussis vaccine in the 1940s was followed by a major decline in the incidence of pertussis in the US, with the lowest levels reached in the mid-1970s [CDC,1991, Mortimer , 1979]. In the mid 1990s, acellular pertussis vaccines, shown in large clinical trials to be highly effective in young infants and children, replaced whole-cell vaccines in the routine childhood immunization schedule in order to minimize vaccine adverse effects. The incidence of pertussis among children six months to four years of age has remained stable throughout the 1990s and early 2000s, confirming that acellular pertussis vaccines work well in the age group to which they are given. [CDC, 2002a, Guris , 1999].

Despite good control of pertussis in young children, the overall number of reported pertussis cases in the US has been slowly rising over the past few decades. Among the diseases for which universal childhood vaccination is recommended in the US, only pertussis has increased in incidence during the last 25 years, from 1,010 cases reported to the Centers for Disease Control and Prevention (CDC) in 1976, to 18,957 provisional cases reported in 2004 [CDC, 2004b, CDC , 2005]. This increase has been largely due to the substantial increase of reported cases in persons 10years or older, of which the greatest number of cases is reported in adolescents; adolescents 10-19 years of age accounted for 39% of cases reported to the CDC in 2003 [Guris ,1999; CDC, 2004]. Compared with surveillance data from 1994-1996, the incidence rate among adolescents during 1997-2000 increased 62% [CDC, 2002a]. Figure 1 shows the reported pertussis incidence in the US over the past two decades by age group for populations ≥1 year of age. The incidence rate per 100,000 has gradually increased in all age groups over time, but with the greatest increase in infants less than two months of age (not shown in the figure) and adolescents 10-19 years of age.

Figure 1 Reported Pertussis Incidence by Age Group, 1983-2003



There is substantial underreporting of pertussis and it is likely that the incidence reported by the CDC underestimates the true disease burden in the US [Sutter , 1992]. This is, at least in part, because pertussis can present atypically in those who have been previously vaccinated. Disease in older children, adolescents and adults may present with either a mild or severe and persistent cough, and with or without a "whoop" [Senzilet , 2001; Yih 2000]. Patients with pertussis may not seek medical care and clinicians may consider respiratory tract infections, asthma and allergy in their differential diagnosis rather than pertussis. In addition, laboratory confirmation of pertussis prevents challenges given that negative cultures are common, DNA amplification methods are not yet validated and no single serologic test is diagnostic.

Although not as severe as disease in infants, pertussis causes significant morbidity in adolescents and adults, including choking, vomiting, prolonged cough illnesses (mean duration 44 days), and severe sleep disturbance [Senzilet , 2001; Lee 2004]. Two recent prospective, population-based studies of pertussis in adolescents and adults with active cough illness surveillance found the incidence of pertussis to be 450-507 cases per 100,000 person-years, or more than one million cases in the US each year [Strebel , 2001, Ward , 2001].

Transmission of pertussis among adolescents in schools has been documented [Mink , 1994]. Furthermore, adolescents and adults are frequently the source of infection for susceptible infants and other family members and may serve as a reservoir for infection for infants too young to be protected by immunization, as has been documented from hospital investigations, household case contact studies, outbreak investigations and national surveillance systems. [Aoyama, 1995; Baron, 1998; Crowcroft , 2003; Vitek ,

2003; Wirsing von Konig , 1998]. While some controversy may remain, recent evidence from epidemiological studies suggest that pertussis vaccination reduces pertussis transmission [Preziosi , 2003; Rophani , 2000; Miller , 1997].

While increased disease recognition, improved diagnostic techniques and active surveillance have no doubt contributed in part to the rise in incidence of pertussis among adolescents and adults, the increasing incidence is real, secondary to less opportunity for natural boosting brought about by widespread child immunization, and a subsequent decline in vaccine-induced immunity [Aoyama, 1995; Baron, 1998; Cattaneo , 1996; CDC, 2002a; Yih , 2000].

In addition to the impact on the individual vaccinee, pertussis in adolescents and adults has broader societal effects. Significant economic costs related to management of the illness and loss of productivity are incurred. Pertussis disrupts the local community and containment of epidemics is costly for local health departments. Pertussis impacts on quality of life, causing school, family and community disruption and incurs significant costs in terms of time and money [Lee , 2000; Lieu , 2003; Pichichero, 1997, Lee, 2004].

2.1. Rationale for Development

The US Advisory Committee on Immunization Practices (ACIP)/American Academy of Pediatrics (AAP)/American Academy of Family Physicians (AAFP) currently recommend tetanus and diphtheria toxoid (Td) booster immunization at age 11-12 years (with ages 13-18 years to serve as a catch-up interval) if at least five years have elapsed since the last dose of tetanus and diphtheria toxoid-containing vaccine, with subsequent routine Td boosters every 10 years [CDC, 2002b, CDC, 2004b]. In 1996, the ACIP/AAP/AAFP published recommendations to improve vaccination coverage among adolescents and advised healthcare providers to establish a routine visit for adolescents aged 11- 12 years [CDC, 1996]. The purposes of this visit are to vaccinate adolescents who have not been previously vaccinated with hepatitis B vaccine, varicella virus vaccine or the second dose of the measles, mumps, and rubella vaccine; to provide a booster dose of Td vaccine; to administer other vaccines that may be recommended for certain adolescents; and to provide other recommended preventive services.

The former Director of the CDC's National Immunization Program has written, "The recognition of school-based outbreaks, and the increased incidence of reported pertussis in persons 10-19 years of age suggest that all adolescents should be targeted for vaccination. This could be accomplished at the adolescent visit, now currently recommended at 11-12 years of age. Immunization of adolescents not only would be epidemiologically appropriate, given their higher risk of pertussis than that of older age groups, but should be easier to implement than adult immunization programs [Orenstein , 1999]." In addition, health economic specialists have reported that pertussis immunization of adolescents could be beneficial and cost-effective [Caro, 2003; Lieu , 2003; Purdy, 2004].

Whole-cell pertussis vaccine administration in adults is associated with high rates of local and systemic reactions; therefore, whole-cell pertussis vaccines are not recommended in persons over seven years of age [CDC, 1991; Linnemann , 1975]. Currently, no acellular

pertussis vaccines are licensed in the US for use in persons over seven years of age. The advent of reduced-antigen-content acellular pertussis vaccines offers the opportunity to extend pertussis prevention to older age groups.

Boostrix was developed for single-dose booster diphtheria, tetanus and pertussis immunization in adolescents 10-18 years of age. By combining acellular pertussis antigens with the recommended adolescent Td booster vaccine, *Boostrix* will provide adolescents the needed protection against pertussis, as well as diphtheria and tetanus with no additional injection. In addition to the direct benefit to the vaccinee, the use of *Boostrix* may reduce circulation of *B. pertussis* in the population and, therefore, also reduce the chance that susceptible persons in the community are in contact with *B. pertussis* and become infected. Furthermore, an additional office visit for the immunization is not necessary if coupled with the recommended routine 11-12 year preadolescent assessment.

3. BOOSTRIX CLINICAL DEVELOPMENT PROGRAM

3.1. Summary of the Clinical Program

The clinical studies conducted in support of US licensure were designed to demonstrate that *Boostrix* is safe and immunogenic when administered in the target adolescent population. A total of 14 studies were conducted worldwide and included in the Biologics License Application (BLA): one pivotal safety and immunogenicity study conducted in the US, 4 studies supportive of safety and immunogenicity (two of which evaluated antibody persistence) and nine additional studies supportive of the safety of the vaccine.

The clinical safety experience with *Boostrix* in the US file includes data on a total of 5,520 subjects of which 3,289 were adolescents who received the US formulation with 0.3 mg Al, and 2,231 subjects of all ages who received *Boostrix* formulated with either 0.5mg Al or 0.133 mg Al. US-licensed Td vaccine was administered in 1663 subjects in the pivotal study and one supportive study. Various Td-containing comparator vaccines were administered to 569 subjects in the nine supportive safety studies.

Table 2 summarizes the clinical studies included in the BLA.

Table 2 GSK Biologicals' Summary of Clinical Studies in BLA

Study Number (Country)	Age (years)	Objectives	Groups	ATP cohort for immunogenicity (number of subjects)	Total cohort for safety (number of subjects)
Pivotal Study					
001 US	10 - 18	1°: lot-to-lot consistency (immunogenicity), non-inferiority (immunogenicity) compared MPHBL's Td, immunogenicity of pa components, non-inferiority (safety: Grade 3 pain) compared to Td 2°: reactogenicity/ safety	Boostrix Lot 1: 0.3 mg Al Boostrix Lot 2: 0.3 mg Al Boostrix Lot 3: 0.3 mg Al MPHBL Td	926 928 946 923	1024 1024 1032 1034
Supportive Studies					
029 Belgium	10 - 18	1°: immunogenicity and reactogenicity/safety of 3 *Boostrix* formulations with varying Al content	Boostrix: 0.5 mg Al Boostrix: 0.3 mg Al Boostrix: 0.133 mg Al	218 202 211	224 209 214
004 Finland	10 - 14	1°: lot-to-lot consistency (immunogenicity) 2°: immunogenicity and reactogenicity/ safety compared to Td and pa	Boostrix Lot A: 0.5 mg Al Boostrix Lot B: 0.5 mg Al Boostrix Lot C: 0.5 mg Al Lederle Td + pa	150 149 148 57	150 150 150 60
017 Finland	13 - 15	1°: antibody persistence 3 years after vaccination in 004	Boostrix: 0.5 mg Al Lederle Td + pa	264 30	N/A N/A
030 Finland	15 - 17	1°: antibody persistence 5 years after vaccination in 004	Boostrix: 0.5 mg Al Lederle Td + pa	257 34	N/A N/A
Additional Safety Supportive Studies					
1,2,3,7,9,10, 20,28,118 worldwide (non-US)	4 - 78	Safety	Boostrix: 0.5 mg Al Various Td-containing comparators [a] Other comparators [b]	Immunogenicity results not included in BLA	1343 569 409

Boostrix 0.3 mg Al = GSK Biologicals' 0.3 mg Al formulation
Boostrix 0.5 mg Al = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Boostrix 0.133 mg Al = GSK Biologicals' investigational 0.133 mg Al formulation
ATP = According-to-protocol cohort
1° = primary
2° = secondary
Al = Aluminum

MPHBL Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
Lederle Td = Lederle's tetanus-diphtheria vaccine (Lederject®)
pa = GSK Biological's investigational reduced antigen content acellular pertussis vaccine
N/A = not applicable as safety data were not collected in Study 017 or Study 030
[a] Various non-US-licensed Td-containing comparator vaccines were administered in the nine supportive safety studies
[b] Other compartors in the nine supportive safety studies included investigational acellular pertussis vaccines and *Infanrix*

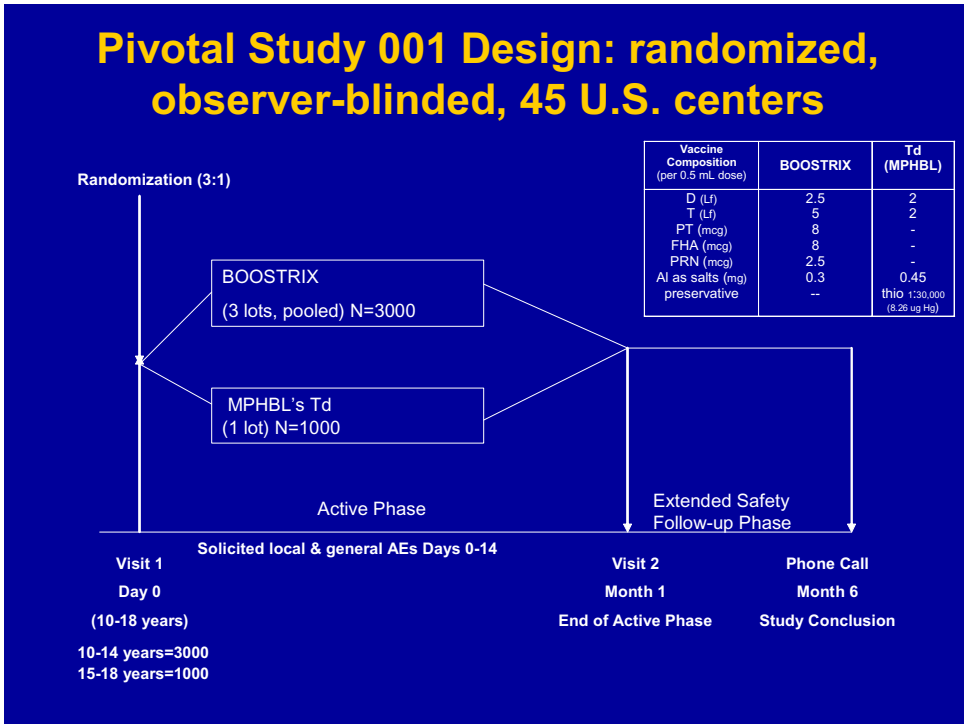
Simultaneous administration of *Boostrix* with other vaccines has not been evaluated as concomitant vaccine studies were not a requirement for licensure and *Boostrix* is not expected to be routinely administered with other vaccines other than Menactra™ (which was only recently licensed in the US in January 2005 after submission of the *Boostrix* BLA). The current ACIP Recommended Childhood and Adolescent Immunization Schedule in the US recommends that adolescents be vaccinated with hepatitis B vaccine (HBV), varicella virus vaccine or the second dose of the measles, mumps, and rubella vaccine (MMR) only if catch-up vaccination is indicated, and that hepatitis A vaccine, polysaccharide pneumococcal vaccine and influenza vaccine be administered for selected populations [CDC, 2004b]. On February 11, 2005 the ACIP voted to include Menactra™ in the routine immunization schedule for adolescents. It is generally well accepted that inactivated vaccines do not interfere with the immune response to other inactivated vaccines or with live vaccines [CDC, 2002b].

No single source exists to estimate comprehensively the immunization coverage rates for all antigens among the US population ages 10 to 18 years (approximately 36 million persons). However, estimates of eligibility for various immunizations can be derived from public and private sources. A review of these data indicate that fewer than 5% of persons age 10-18 years remain eligible for a second dose of MMR vaccine as virtually all US states (n=49) have second dose school entry requirements. Since varicella vaccine was licensed in 1995, immunization rates have risen to approximately 85% in young children, 41 states have school entry requirements and natural disease history estimates range from 65 to 90% for those age 10-18 years, leading to an estimate that approximately 15% of those 10-18 years may remain eligible for vaccination.

Hepatitis B is potentially the only significant catch-up immunization for adolescents based on 2002 CDC estimates that approximately one third of teens had not been fully immunized with three doses of HBV. Immunization rates among infants and young children have reached all-time highs at 92% and 35 states have middle school entry requirements. As improvements in immunization coverage for HBV have occurred and school entry requirements have been in place in many states for some time, the new cohorts of children reaching age 10 will have successively higher HBV coverage from infancy and young childhood. Compared to older teens, HBV immunization rates are also higher among younger persons (11-12 years) for whom primary immunization with a Td booster is currently recommended and for whom *Boostrix* is primarily targeted. It is unlikely that *Boostrix* and HBV co-administration will result in impaired antibody responses or increased rates of adverse events as *Boostrix* contains the same diphtheria, tetanus and pertussis antigens as GSK's *Infanrix* and *Pediarix* (in reduced amounts) and data regarding the immune response and safety of co-administered HBV and *Infanrix* do not point to any negative impact of coadministration. Furthermore, *Pediarix* is a combination vaccine containing DTaP, inactivated poliovirus vaccine (IPV) and HBV.

Pivotal Study 001 and supportive Studies 004 and 029 were prospective, randomized, controlled studies. Study 001 was the pivotal adolescent study conducted in the US which involved more that 4000 adolescents 10-18 years of age and compared the safety and immunogenicity of three lots of *Boostrix* (0.3 mg Al) to a US-licensed Td vaccine manufactured by Massachusetts Public Health Biologic Laboratories (MPHBL). Enrollment was stratified such that 75% were 10-14 years of age and 25% were 15-18 years of age. Immunogenicity was evaluated one month post-vaccination with a safety follow-up phase through six months post-vaccination. The study design for pivotal Study 001 is summarized in Figure 2.

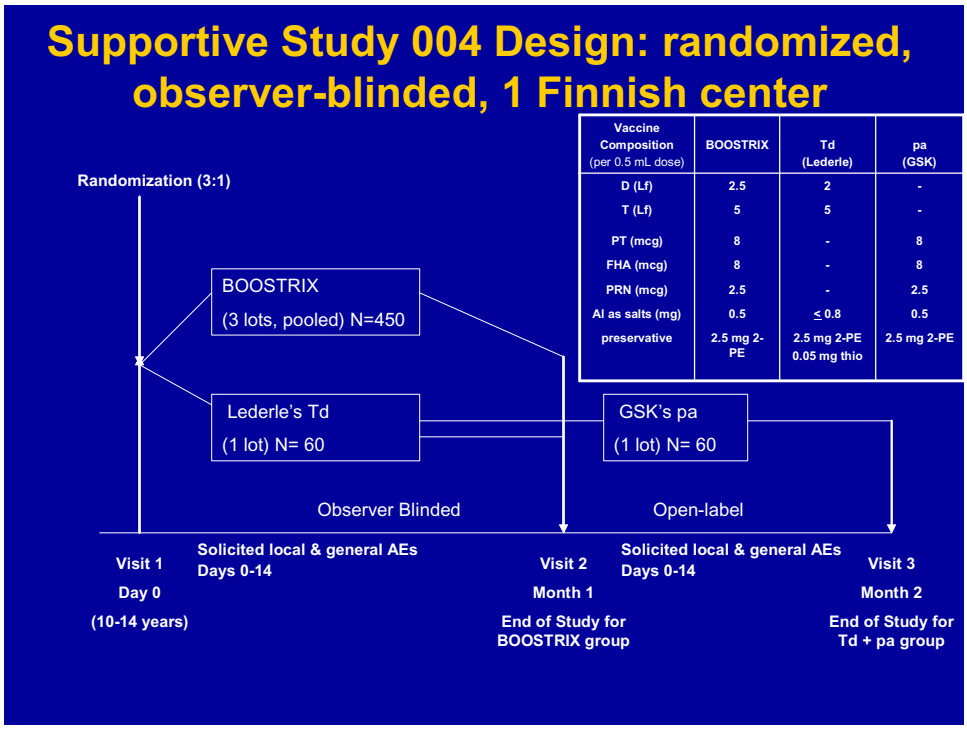
Figure 2 Pivotal Study 001 Design



MPHBL = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria (Td) vaccine
Boostrix = GSK Biologicals' 0.3 mg Al formulation
Al = Aluminum

Study 004 was a supportive study conducted in Finland which involved more than 500 adolescents 10-14 years of age and compared the safety and immunogenicity of three lots of *Boostrix* (0.5 mg Al) to a US-licensed Td vaccine manufactured by Lederle and GSK Biologicals' reduced antigen-content pa investigational vaccine. In this study, the Td vaccine group received pa one month after Td vaccination in an open manner. Antibody persistence following Study 004 was subsequently evaluated out to three and five years post-vaccination, respectively, in Studies 017 and 030. The study design for study 004 is summarized in Figure 3.

Figure 3 Supportive Study 004 Design

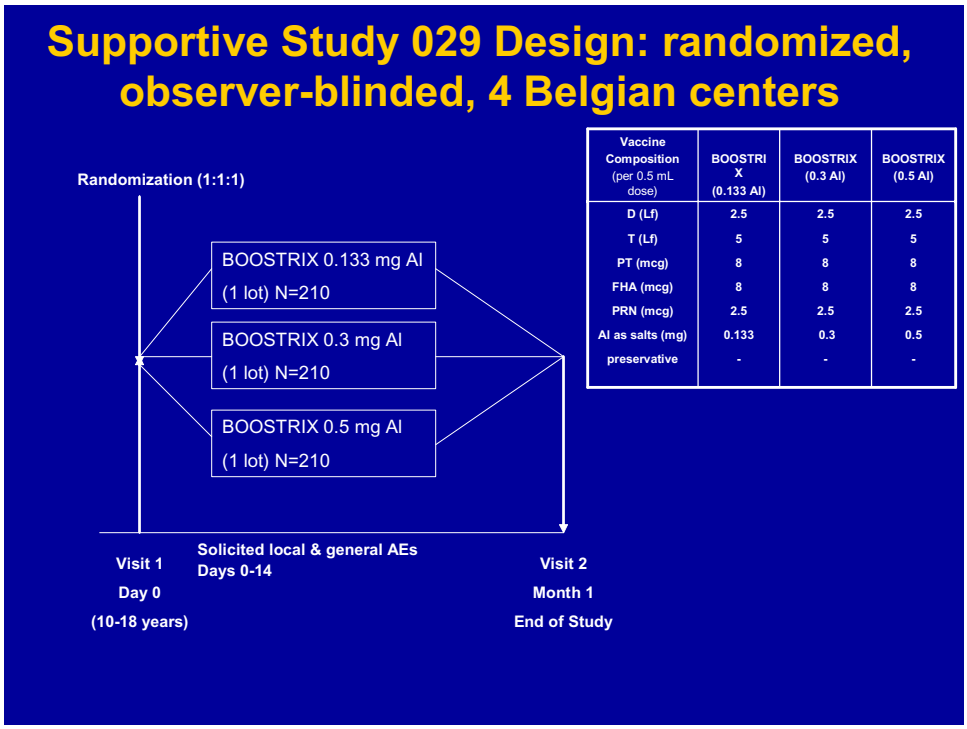


Boostrix = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Al = Aluminum
Lederle Td = Lederle's tetanus-diphtheria vaccine (Lederject®)
pa = GSK Biologicals' investigational reduced antigen content acellular pertussis vaccine
2-PE = 2-phenoxyethanol
Thio = Thimerosal

Study 029, was a supportive study conducted in Belgium in adolescents 10-18 years of age which evaluated the safety and immunogenicity of *Boostrix* adjuvanted with three different doses of Al (0.133 mg, 0.3 mg and 0.5 mg). The immunogenicity of the 0.5 mg Al and 0.3 mg Al vaccines were comparable, therefore, the 0.3 mg dose of Al was

ultimately chosen from this study for US development. The study design for 029 is summarized in Figure 4.

Figure 4 Supportive Study 029 Design



Boostrix = GSK Biologicals' 0.133 mg, 0.3 mg and 0.5 mg Al formulations
Al = Aluminum

Additionally, summary safety data from nine studies involving 1343 subjects four-78 years of age administered the 0.5 mg Al *Boostrix* formulation provided supportive safety data for the file. In total, more than 5500 subjects were vaccinated with *Boostrix* (regardless of Al dose) of which more than 4000 were adolescents. More than 3200 of these adolescents received the 0.3 mg Al *Boostrix* formulation intended for the US.

The focus of this briefing document is on the immunogenicity data from studies 001, 004, and 030, and on the safety data from Studies 001, 004 and 029.

3.1.1. Populations Evaluated

Subjects in all countries were healthy with no previous history of diphtheria or tetanus disease or physician-diagnosed pertussis disease within the previous five years, were not to have previously experienced any of the recognized contraindications or precautions to DTP vaccination (such as temporally associated encephalopathy with or without fever, fever ≥40.5^{o} C, hypotonic-hyporesponsive state, seizure, persistent inconsolable screaming or crying) and were not to have had systemic allergic or neurological reactions or thrombocytopenia following a previous dose of diphtheria or tetanus toxoid vaccine.

In all studies, subjects were to have completed their primary DTP vaccination series in accordance with the recommended schedule for the country in which the studies were conducted. In pivotal Study 001, subjects were not to have received their last DTP vaccination within the previous five years or Td vaccination within the previous 10 years. In supportive Studies 004 and 029, subjects were not to have received their last DTP or Td vaccination within the previous five years.

3.1.2. Demographics

Figure 5 Study 001: Demography

Study 001: Demography

Total Cohort

Characteristics	Parameters or Categories	BOOSTRIX N= 3080	Td N= 1034
Age	Mean	12.9 yrs	12.9 yrs
	9-14 yrs	75.9%	72.9%
	15-18 yrs	24.1%	27.1%
Gender	Male	51.6%	53.6%
	Female	48.4%	46.4%
Race	White	85.8%	85.4%
	Black	5.7%	5.4%
	Hispanic	5.6%	6.0%
	Oriental	0.8%	0.9%
	Other	2.1%	2.3%

Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine

As shown in Figure 5, in pivotal Study 001, there were 4,114 subjects in the Total Vaccinated Cohort for safety (included all enrolled and vaccinated subjects for whom safety data were available). Subjects in the pooled *Boostrix* and the Td groups were similar with respect to age, gender and race. The subjects ranged in age from nine-18 years (mean age was 12.9 years). The population was predominantly White (85.7%); 5.6% were Black, 5.7% were Hispanic, 0.8% were Oriental and 2.1% were categorized as "Other." For pivotal Study 001, the primary immunogenicity and safety objectives were also evaluated by gender and race. These descriptive analyses did not appear to show a gender or race effect on the difference between *Boostrix* and Td vaccines. Ninety-two percent of subjects previously received five doses of DTP, six percent previously received four doses of DTP, and two percent of subjects received either less than four, more than five or an unspecified number of prior DTP doses. Among the subjects who received five prior DTP doses, subjects in both the pooled *Boostrix* and Td groups had a

similar vaccination history with respect to type of DTP vaccine previously administered. In ~70% of subjects, the investigator could not specify if the subjects had previously whole-cell or acellular pertussis vaccine. For these subjects the primary series (first three doses) was most likely whole-cell DTP since all subjects were born before 1993, and DTaP vaccines were first licensed in the US for primary series use in 1996. Eight-five percent of subjects received their last diphtheria-tetanus-containing vaccine within the last five-10 years.

There were 510 subjects in the Total Cohort for safety (included all enrolled and vaccinated subjects for whom safety data were available) in supportive Study 004. There were no differences in the mean age between groups (10.8 years for the pooled *Boostrix* group and 10.9 years for the Td + pa group) and the proportions of male and female subjects in each group were similar. All of the subjects were White.

In supportive Study 029, there were 647 subjects in the Total Cohort for safety (includes all enrolled and vaccinated subjects for whom safety data were available). The mean age of subjects was similar across the three *Boostrix* groups (total population mean was 13.9 years) and the proportions of male and female subjects were similar for the three vaccine groups. Over 95% of the subjects in each group were White.

3.2. Immunogenicity – Assessment

3.2.1. Characterization of Immune Response – Clinical Serology

Serological methods utilized to characterize the immune responses in sera drawn from immunized subjects in the clinical studies were fully validated and shown to be sensitive, specific and reproducible. Sera from all studies were tested in GSK Biologicals' laboratory in Rixensart, Belgium using standard enzyme-linked immunosorbent assays (ELISAs) to vaccine antigens. All of the antigens in the combination are also included in GSK's US-licensed products (e.g., *Infanrix, Pediarix*) and assays employed in these studies were equivalent to those assays previously approved by FDA under the existing license applications for *Infanrix* and *Pediarix*.

Immunological assessment consisted of serological assays of blood samples drawn from each subject prior to and one month after each vaccination. For the serological follow-up studies to Study 004, blood samples drawn at three and five years after vaccination were assayed to determine antibody concentrations to vaccine antigens.

The cut-off in the ELISAs for diphtheria and tetanus was 0.1 international units per milliliter (IU/mL). The cut-off in the ELISAs for PT, FHA and PRN was 5 ELISA units per mL (EL.U./mL). It has been previously demonstrated that a good correlation exists between *in vitro* neutralization testing and ELISA testing for antibodies to diphtheria toxoid, but this correlation may be reduced at antibody concentrations <0.1 IU/mL [Melville-Smith , 1988]. Therefore, 0.1 IU/mL was chosen as the conservative cut-off for the diphtheria ELISA. In Study 004 and the two serologic follow-up studies, samples that were seronegative by ELISA (<0.1 IU/mL) for diphtheria were further tested by a neutralization assay on VERO cells, using a cut-off of 0.016 IU/mL.

3.3. Efficacy Variables for Diphtheria and Tetanus

Well-established serological correlates of protection exist for diphtheria and tetanus [Wassilak, 2003, Wharton, 2003]. For these antigens, efficacy of the vaccine is related to the antibody response to the respective vaccine components. In the ELISAs for both diphtheria and tetanus, an antibody concentration of 0.1 IU/mL is the lowest quantifiable level regarded as protective.

3.4. Efficacy Variables for Pertussis

No serological correlate of protection has been identified for pertussis. However, a vaccine efficacy trial performed in infants with GSK Biologicals' DTaP vaccine, *Infanrix* [Schmitt 1996b], provided a benchmark on which to base the efficacy of *Boostrix* [Schmitt 1996a]. In 1997, at an Advisory Committee to the FDA Center for Biologicals Evaluation and Research, consensus was reached that if efficacy against pertussis disease has been demonstrated following primary immunization with DTaP in infants, and if a booster vaccine containing the same acellular pertussis antigens from the same manufacturer is comparably immunogenic in an older population, then it is reasonable to assume that efficacy of the booster vaccine can be extrapolated to this older population [Vaccines and Related Biological Products Advisory Committee,1997]. Therefore, the efficacy of *Boostrix* was evaluated by comparing the pertussis antibody responses achieved in adolescents in pivotal Study 001 to those observed in the immunogenicity portion (Study 039) of an *Infanrix* efficacy trial in infants (Study 050) [Schmitt 1996a, Schmitt 1996b].

3.5. Immunogenicity Objectives and Statistical Hypotheses

3.5.1. Immunogenicity Endpoints

The following endpoints were included in the analyses of all studies:

- Anti-diphtheria (anti-D) and anti-tetanus (anti-T) seroprotection (SP) rates, i.e., percentage of subjects with anti-D and anti-T antibody concentrations ≥0.1 IU/mL by ELISA before and one month after vaccination. (In Studies 017 and 030, anti-D SP rates were defined as percentage of subjects with anti-D antibody concentrations ≥0.1 IU/mL by ELISA or ≥0.016 IU/mL by VERO-cell assay).
- Percentage of subjects with anti-D antibody concentrations ≥1.0 IU/mL and anti-T antibody concentrations ≥1.0 IU/mL before and one month after vaccination.
- Anti-D and anti-T booster responses one month after vaccination. Booster response to D and T antigens was defined as:
  - for initially seronegative subjects (pre-vaccination antibody concentration below cut-off: <0.1 IU/mL), an antibody concentration of at least four times the cut-off (post-vaccination concentration ≥0.4 IU/mL),
  - for initially seropositive subjects (pre-vaccination antibody concentration ≥0.1 IU/mL), an increase of at least four times the pre-vaccination concentration.

- Anti-PT, anti-FHA and anti-PRN booster responses one month after vaccination. Booster response to pertussis antigens was defined as:
  - for initially seronegative subjects (pre-vaccination antibody concentration below cut-off: <5 EL.U./mL), an antibody concentration of at least four times the cut-off (post-vaccination concentration ≥20 EL.U./mL),
  - for initially seropositive subjects with pre-vaccination concentration ≥5 EL.U./mL and <20 EL.U./mL, an increase of at least four times the pre-vaccination concentration,
  - for initially seropositive subjects with pre-vaccination concentration ≥20 EL.U./mL, an increase of at least two times the pre-vaccination concentration.

(For Study 004, analyses using the definitions described above for booster responses were not pre-specified and were performed *post-hoc*.)

- Anti-PT, anti-FHA and anti-PRN seropositivity rates, i.e., percentage of subjects with antibody concentrations ≥5 EL.U./mL before and one month after vaccination.
- Antibody Geometric Mean Concentrations (GMCs) to each antigen.

3.5.2. Criteria for Statistical Evaluation

The According To Protocol (ATP) cohort was the primary cohort for immunogenicity analyses in all studies. The ATP cohort for analysis of immunogenicity included all subjects for whom unbiased differential treatment effect on immunogenicity was likely (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol and having fulfilled the requirement for analysis) and for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

The following descriptive analyses were common to all studies:

For each *Boostrix* vaccine lot, pooled *Boostrix* vaccine lots and each treatment group, at each time-point that a blood-sample result was available:

- Seroprotection rates to diphtheria and tetanus (anti-D and anti-T antibody concentrations ≥0.1 IU/mL) with exact 95% confidence intervals (CIs) calculated per group.
- Percentage of subjects with anti-D antibody concentrations and anti-T antibody concentrations ≥1.0 IU/mL with exact 95% CIs calculated per group.
- Seropositivity rates to PT, FHA and PRN (antibody concentrations ≥5 EL.U./mL) with exact 95% CIs calculated per group.
- GMCs with 95% CIs tabulated for each antigen. Calculation of the GMCs was performed by taking the anti-log of the mean of the log-transformed antibody concentrations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.

In addition, for serology results one month after vaccination:

- Booster response rates to all vaccine antigens with exact 95% CIs calculated per group.
- Distributions of antibody concentrations against each antigen displayed using reverse cumulative distribution curves (RCCs).

3.5.2.1. Pivotal Study 001

In pivotal Study 001, criteria for evaluation of the four primary immunogenicity objectives were as follows:

1. *To demonstrate the lot-to-lot consistency of three production lots of Boostrix in terms of immunogenicity of each antigen:*

Criteria for evaluating consistency (one month post-vaccination): For all antigens and all pairs of lots, the two-sided 90% confidence interval (CI) on the GMC ratio between lots is within the [0.67; 1.5] interval.

2. *To demonstrate the non-inferiority of Boostrix compared to the Td vaccine in terms of immunogenicity, with respect to anti-D and anti-T seroprotection rate:*

Criteria for non-inferiority (one month post-vaccination): For both anti-D and anti-T seroprotection rates, the upper limit of the two-sided 95% CI for the treatment difference (Td group minus the pooled *Boostrix* group) in the percentage of subjects with seroprotective antibody concentrations is ≤10%.

3. *To demonstrate the non-inferiority of Boostrix compared to the Td vaccine in terms of immunogenicity, with respect to anti-D and anti-T booster responses:*

Criteria for non-inferiority (one month post-vaccination): For both anti-D and anti-T booster responses, the upper limit of the two-sided 95% CI for the treatment difference (Td group minus the pooled *Boostrix group*) in the percentage of subjects with booster response is ≤10%.

4. *To demonstrate that anti-PT, anti-FHA and anti-PRN booster responses occur in at least 80% of vaccinees administered Boostrix:*

Criteria (one month post-vaccination): For each of the pertussis antigens, the lower limit of the two-sided 95% CI for the percentage of subjects with a booster response is ≥80%.

In addition, antibody GMCs observed in pivotal study 001 were considered to be non-inferior to those observed in *Infanrix* infant immunogenicity Study 039 if the upper limit of the 95% CI on the ratio (*Infanrix* group divided by the pooled *Boostrix* group) on the GMCs is < 1.5.

3.6. Immunogenicity – Results

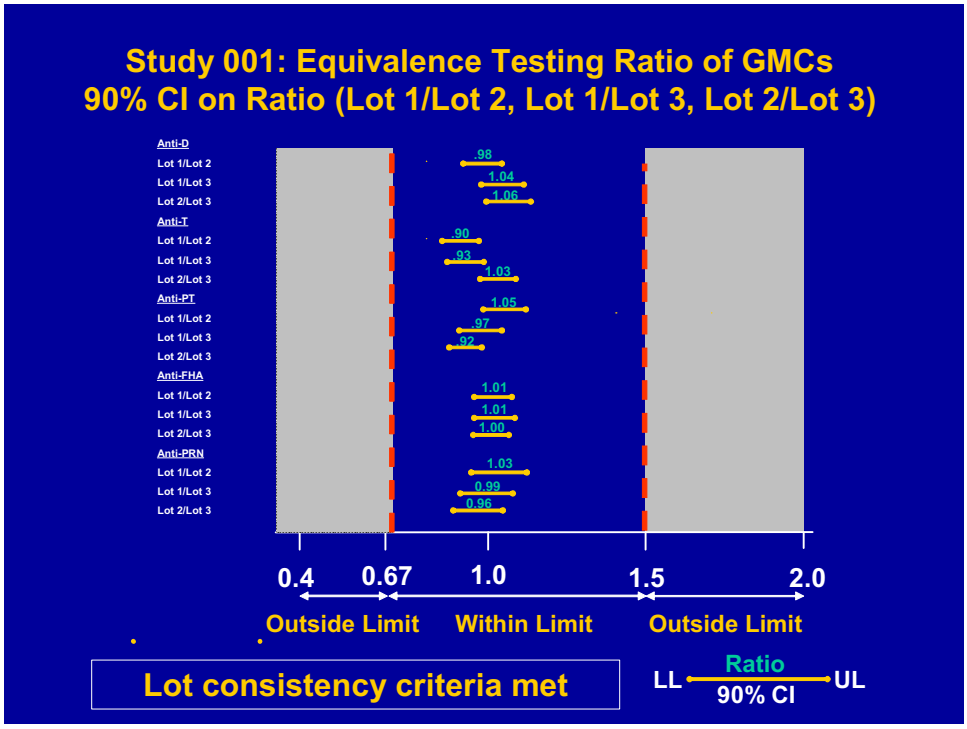
3.6.1. Pivotal Study 001

In order to demonstrate immunogenicity, safety and consistency of the manufacturing process, a randomized and controlled pivotal trial (001) was conducted encompassing a broad age range of US adolescents who had received five prior doses of DTP vaccine or four prior doses of DTP vaccine if the fourth dose was given after the fourth birthday. Subgroup analyses of immunogenicity and safety were performed according to age (subjects 10-14 and 15-18 years of age) and vaccination history (number of previous doses of DT-containing vaccine). The use of a control vaccine allowed the assessment of the candidate vaccine compared with a US-licensed Td vaccine. A total of 4,114 adolescents were vaccinated; approximately 75% were 10-14 years of age and 25% were 15-18 years of age. In the *Boostrix* group, 2800 (90.9%) of subjects met the criteria for inclusion in the ATP cohort for immunogenicity compared to 923 (89.2%) in the Td group.

3.6.1.1. Consistency of *Boostrix* production lots

Consistency of the immune response to three production lots of *Boostrix* was evaluated in Study 001 by computing for each pair of vaccine lots and each vaccine antigen the 90% CIs on GMC ratios, one month after vaccination using an analysis of covariance (ANCOVA) model on the logarithm$_{10}$ transformation of the antibody concentrations (see Figure 6).

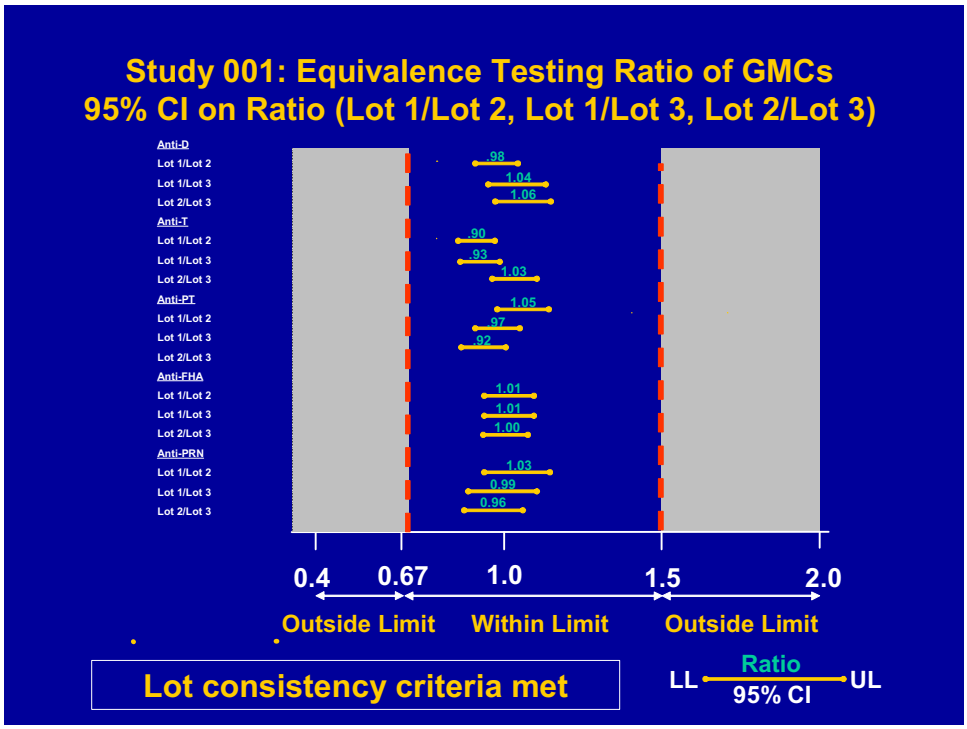
Figure 6 Study 001: Equivalence Testing Ratio of GMCs (90% CI)



Lot 1 = *Boostrix* Lot 1: 0.3 mg Al
Lot 2 = *Boostrix* Lot 2: 0.3 mg Al
Lot 3 = *Boostrix* Lot 3: 0.3 mg Al
Value above the bar is the point estimate of the ratio of GMC
90% CI = 90% Confidence Interval; LL = lower limit, UL = upper limit

Conclusion – primary objective 1: lot-to-lot consistency was demonstrated as evidenced by the 90% CI for the GMC ratio being within the pre-defined limits of [0.67; 1.5] for all antigens and all pairs of lots. FDA's current recommendations regarding manufacturing lot consistency include computing the 95% CI on GMC ratios (instead of 90% CI). *Post-hoc* analysis of lot-to-lot consistency was also demonstrated as evidenced by the 95% CI for the GMC ratio being within the limits of [0.67; 1.5] for all antigens and all pairs of lots (See Figure 7).

Figure 7 Study 001: Equivalence Testing Ratio of GMCs (95% CI)



Lot 1 = *Boostrix* Lot 1: 0.3 mg Al
Lot 2 = *Boostrix* Lot 2: 0.3 mg Al
Lot 3 = *Boostrix* Lot 3: 0.3 mg Al
Value above the bar is the point estimate of the ratio of GMC
95% CI = 95% Confidence Interval; LL = lower limit, UL = upper limit

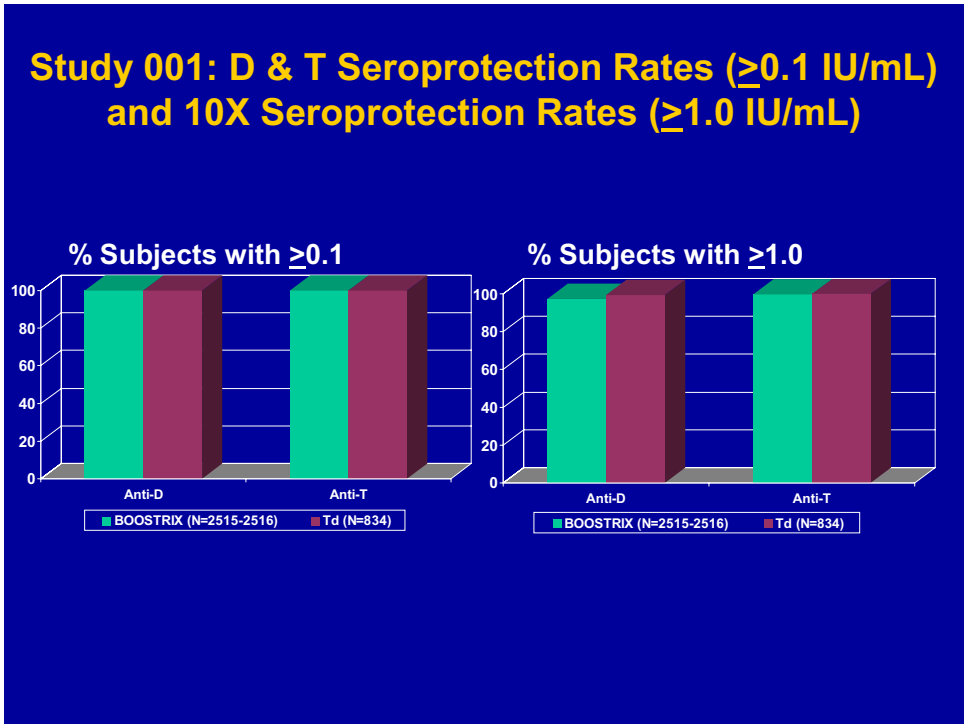
Since consistency with respect to immunogenicity among the three lots of *Boostrix* was demonstrated for all antigens, an analysis was performed on the pooled lots. Data for the pooled *Boostrix* lots compared to the Td group are presented in the following sections.

3.6.1.2. Response to Diphtheria and Tetanus

Because data were not available on the immunogenicity of MPHBL's Td vaccine prior to Study 001, and in order to assess the feasibility of demonstrating non-inferiority of pooled *Boostrix* lots vs. Td with respect to anti-D and anti-T booster responses, an interim analysis was done when approximately 400 subjects had completed Visit 2 (Day 30) to compare the *Boostrix* vaccine group and the Td vaccine group with respect to the anti-D and anti-T antibody concentrations ≥0.1 IU/mL and ≥1.0 IU/mL, booster response rates and GMC ratios. As these subjects were unblinded at the time of the interim analysis, immunogenicity data from subjects who contributed to the interim analysis were excluded from the final confirmatory analysis of diphtheria and tetanus responses for the comparison of *Boostrix* and Td vaccine groups.

Figure 8 presents the seroprotection rates to diphtheria and tetanus (antibody concentrations ≥0.1 IU/mL) and the percentage of subjects with anti-D and anti-T antibody concentrations ≥1.0 IU/mL one month after vaccination in the *Boostrix* and Td vaccine groups.

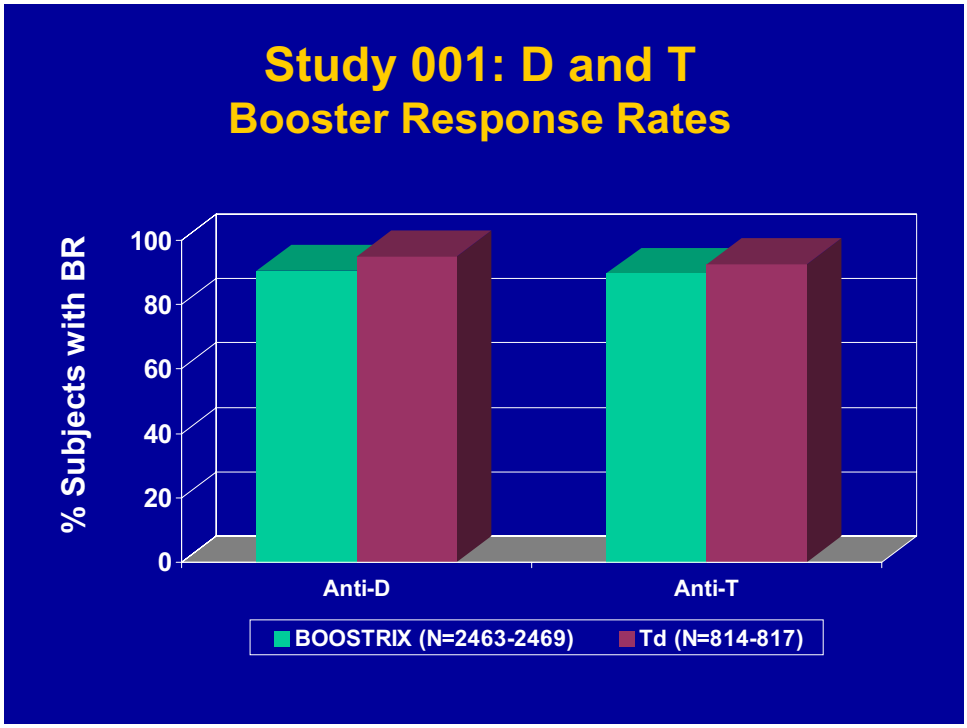
Figure 8 Study 001: D & T Seroprotection Rates (antibody concentration ≥ 0.1 IU/mL) and 10x Seroprotection Rates (antibody concentration ≥ 1.0 IU/mL)



Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects with available results

The anti-D and anti-T booster response rates in the *Boostrix* and the Td vaccine groups, one month after vaccination are presented in Figure 9.

Figure 9 Study 001: D and T Booster Response Rates



Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects with pre- and post -vaccination results available
Booster Response (See Immunogencity Endpoints, Section 3.5.1)

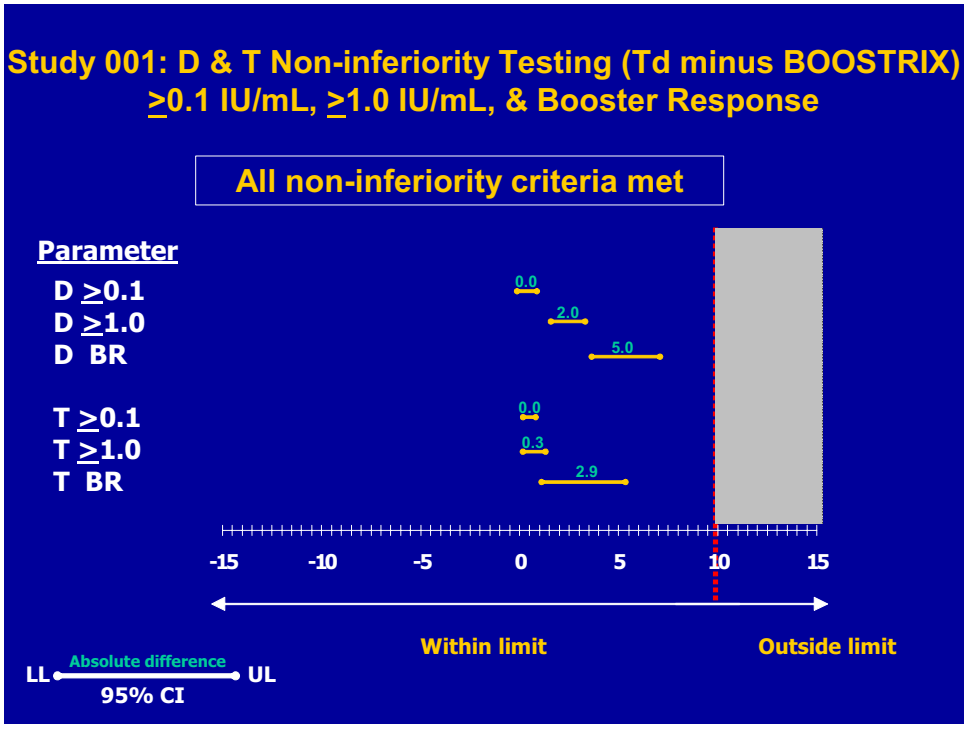
One month after vaccination, 99.9% of subjects in both vaccine groups had seroprotective antibody concentrations against diphtheria, and antibody concentrations ≥10 times the seroprotective level were elicited in 97.3% of the subjects in the *Boostrix* group and 99.3% in the Td group. Booster response rates to diphtheria were 90.6% in the *Boostrix* group and 95.9% in the Td group. Among the subjects who were seronegative prior to vaccination, 97.2% in the *Boostrix* group and all subjects in the Td group achieved a booster response.

One month after vaccination, all subjects in both vaccine groups had seroprotective antibody concentrations against tetanus, and antibody concentrations ≥10 times the seroprotective level were elicited in 99.5% of the subjects in the *Boostrix* group and 99.8% in the Td group. Booster response rates to tetanus were 89.7% in the *Boostrix* group and 92.5% in the Td group and all subjects in both vaccine groups who were seronegative prior to vaccination achieved a booster response.

The second and third primary immunogenicity objectives were to demonstrate non-inferiority of *Boostrix* compared to Td with respect to anti-D and anti-T seroprotection rates and booster responses, one month after vaccination. Non-inferiority would be

demonstrated if the upper limit of the treatment differences, Td minus *Boostrix*, was ≤10%. The non-inferiority results for pivotal Study 001 are summarized in Figure 10.

Figure 10 Study 001: Non-inferiority Testing D and T Seroprotection and Booster Response Rates

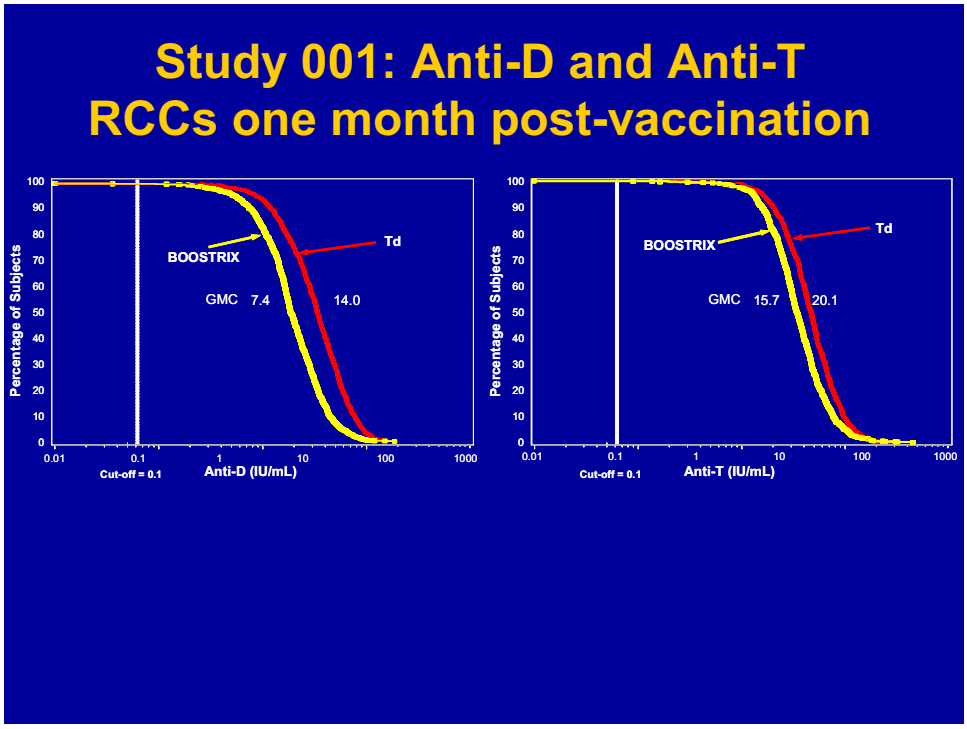


Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
D = Diphtheria parameter
T = Tetanus parameter
BR = Booster Response (see Immunogenicity Endpoints, Section 3.5.1)
Value above the bar is the point estimate of the treatment difference (Td minus *Boostrix*)
95% CI = 95% Confidence Interval; LL = lower limit, UL = upper limit

Conclusion - primary objectives 2 and 3: Non-inferiority of *Boostrix* compared to the Td vaccine in terms of seroprotection rates and booster response rates was demonstrated as the upper limit of the standardized asymptotic 95% CI for the difference between the Td group and the pooled *Boostrix* group was ≤10%. While not defined prospectively as a criterion for non-inferiority, the upper limit of the standardized asymptotic 95% CI for group difference in the percentages of subjects with anti-D and anti-T antibody concentrations ≥1.0 IU/mL (i.e., ≥10 times above the assay cut-off for seroprotection used in this study) was also ≤10%.

Figure 11 demonstrates through Reverse Cumulative Distribution Curves (RCCs) the anti-D and anti-T antibody concentrations achieved by all subjects one month after vaccination. RCC's are a graphical tool that provides a complete distribution of antibody data and allows a visual assessment of details of the distribution.

Figure 11 Study 001: Anti-D and anti-T Reverse Cumulative Curves, 1 Month Post-vaccination



Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
GMC = Geometric Mean Concentration

While the anti-D GMC was higher in the Td group (14.0) than *Boostrix group* (7.4), this difference does not appear to be clinically relevant as the distribution of antibody concentrations in each group parallel each other and the RCCs in each group are far to the right of (i.e., concentrations higher than) the seroprotective cut-off value. One month post-vaccination, subjects who received *Boostrix* achieved an anti-D GMC 74-fold higher than the seroprotective cut-off, and antibody concentrations ≥10 times the seroprotective level were elicited in 97.3% of subjects.

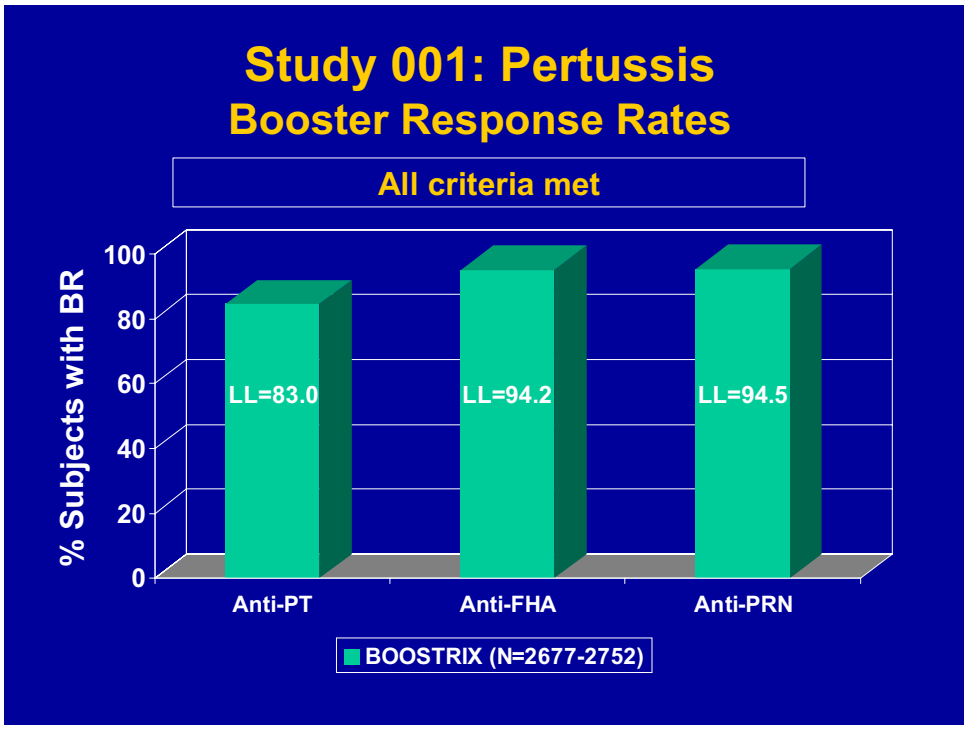
While the anti-T GMC was higher in the Td group (20.1) than *Boostrix* group (15.7), this difference does not appear to be clinically relevant as the distribution of antibody concentrations in each group parallel each other and the RCCs in each group are far to the right of (i.e., concentrations higher than) the seroprotective cut-off value. One month post-vaccination, subjects who received *Boostrix* achieved an anti-T GMC 157-fold higher than the seroprotective cut-off, and antibody concentrations ≥10 times the seroprotective level were elicited in 99.5% of subjects.

3.6.1.3. Response to Pertussis

The primary immunogenicity endpoint measured for pertussis was a booster response to the 3 pertussis antigens contained in *Boostrix* one month after vaccination. The pre-defined immunogenicity criterion was that for each of the pertussis antigens, the lower

limit of the two-sided 95% CI for the percentage of subjects with a booster response is ≥80%. Figure 12 presents the booster response rates to PT, FHA and PRN.

Figure 12 Study 001: Pertussis Booster Response Rates



Boostrix = GSK Biologicals' 0.3 mg AI formulation
BR = Booster Response (see Immunogenicity Endpoints, Section 3.5.1)
N = number of subjects with pre- and post -vaccination results available
LL = Lower Limit of two-sided 95% confidence Interval

Conclusion - primary objective 4: The lower limit of the exact two-sided 95% CI in the percentage of subjects with a booster response was ≥83.0% for each of the pertussis antigens, exceeding the pre-defined lower limit of 80% for demonstration of a booster response; therefore, all criteria were met.

Given the absence of recognized serologic correlates of protection against pertussis, the efficacy of *Boostrix* vaccine was evaluated by comparing the pertussis antibody responses achieved in pivotal Study 001 in adolescents to those measured in a previous immunogenicity portion (Study 039) of an efficacy study in infants, in which GSK's DTaP vaccine *Infanrix,* demonstrated 88.7% efficacy against WHO-defined typical pertussis, and 81.3% efficacy against a milder definition of pertussis in a German household contact study [Schmitt 1996a] [Schmitt ,1996b]. A NIH-sponsored double-blind, controlled trial in Italy has also demonstrated the efficacy of *Infanrix* against pertussis [Greco, 1996]. In the NIH-sponsored trial, *Infanrix* demonstrated 83.9% efficacy against WHO-defined typical pertussis.

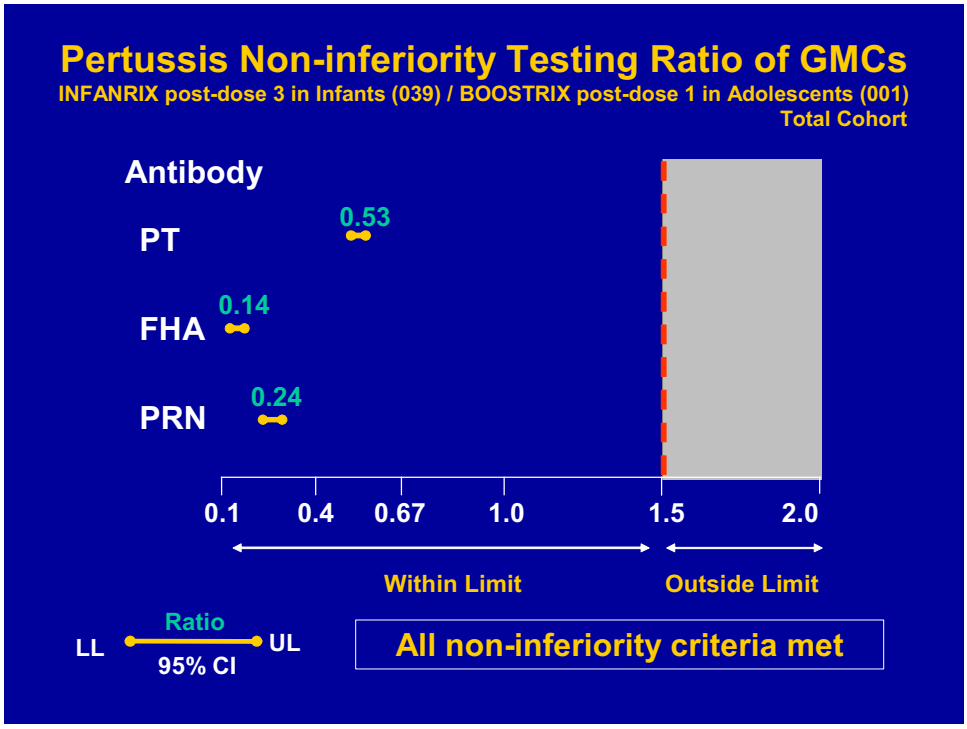
The antibody GMCs observed in *Boostrix* Study 001 were to be considered non-inferior to those observed in *Infanrix* Study 039 if the upper limits of the 95% CIs on the antibody

GMC ratio (*Infanrix* divided by *Boostrix)* were <1.5. Serum samples from the total cohorts from Studies 039 and 001 were tested using the same assay in the same laboratory in Rixensart, Belgium. In order to demonstrate that the serological method used for pertussis testing at GSK Biologicals' laboratory has been consistent over time, a subset of 100 serum samples from the total cohort in Study 039 were re-tested for antibodies to pertussis vaccine antigens. The results and additional analyses demonstrated that the serologic method used have been consistent over time for anti-PT, anti-FHA and anti-PRN testing. These samples were randomly selected from among samples with a sufficient volume remaining for testing, according to a Gibb's sampling (a sampling technique which ensures that the data distribution in the sub-sample is identical to the full distribution). Serologic samples from the total cohorts, rather than the ATP immunogenicity cohorts, were used when comparing the pertussis antibody responses achieved in Studies 001 and 039 because the criteria for the ATP immunogenicity cohort in Study 039 required that immunologic results be available at both the pre and post-vaccination timepoints; thus a large number of subjects were excluded from the Study 039 ATP cohort for immunogenicity. The BLA includes a reanalysis based on the ATP immunogenicity cohorts and all non-inferiority criteria were met for the ATP immunogenicity cohort when comparing the pertussis antibody responses achieved in Studies 001 and 039.

One month following primary vaccination of infants with *Infanrix* at three, four and five months of age in Study 039 (N=631-2884), the GMCs to PT, FHA and PRN were 45.7, 83.6 and 112.3, respectively. One month following vaccination of adolescents with *Boostrix* in Study 001 (N=2941-2979), the GMCs to PT, FHA and PRN were 86.9, 614.8, and 470.7, respectively. Antibody responses after *Boostrix* in adolescents compared to *Infanrix* in infants were 1.9 fold higher for PT, 7.3 fold higher for FHA and 4.2 fold higher for PRN.

Figure 13 shows the non-inferiority testing on the ratio of GMCs post-dose 3 following *Infanrix* in infants in Study 039 as compared to post-dose 1 following *Boostrix* in adolescents in Study 001.

Figure 13 Non-Inferiority Testing Ratio of GMCs (*Infanrix* Study 039 Post-Dose 3 divided by *Boostrix* Study 001), Total Cohort

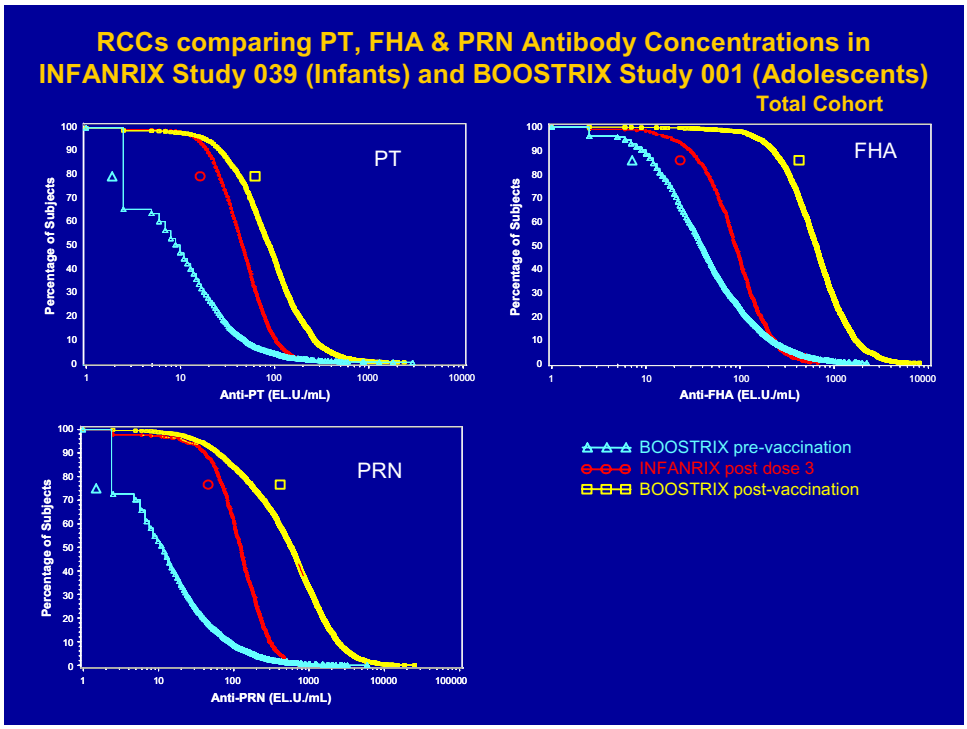


GMC = Geometric Mean Concentration
Boostrix = GSK Biologicals' 0.3 mg Al formulation
Infanrix = GSK Biologicals' US licensed Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine
Value above the bar is the point estimate of the ratio of GMC
95% CI = 95% Confidence Interval; LL = lower limit, UL = upper limit

The criteria for non-inferiority was met for all three antigens, as the upper limit of the 95% CI on the GMC ratio of *Infanrix* divided by *Boostrix* was <1.5. Antibody concentrations achieved in Study 001 were statistically higher than those achieved after a three-dose primary vaccination course with *Infanrix* in Study 039, as evidenced by the 95% CI on the GMC ratio for each of the three pertussis antigens not including "1".

The RCCs for anti-PT, anti-FHA and anti-PRN antibody concentrations from the total cohorts in Studies 039 and 001 are presented in Figure 14.

Figure 14 Reverse Cumulative Curves Comparing PT, FHA, and PRN Antibody Concentrations in INFANRIX Study 039 (Infants) and BOOSTRIX Study 001 (Adolescents), Total Cohort



RCC = reverse cumulative distribution curve
Boostrix = GSK Biologicals' 0.3 mg Al formulation
Infanrix = GSK Biologicals" US licensed Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine

The blue curves in Figure 14 represent the RCCs for study 001 adolescents before vaccination with *Boostrix* and show that for all 3 pertussis antigens, the RCCs are largely to the left of the red curves, which represent the RCCs achieved by infants after 3 doses of *Infanrix* in the immunogenicity portion of the infant efficacy trial. One month post-vaccination with *Boostrix,* RCCs for all 3 antigens (yellow curves) are shifted to the right of the curves from the immunogencity portion of the infant efficacy trial (red curves).

Based on the demonstrated efficacy with *Infanrix* in two clinical studies (the German infant household contact efficacy study [Schmitt 1996a] and the Italian NIH-sponsored efficacy study [Greco, 1996]), and on the demonstration that *Boostrix* achieves similar or higher pertussis antibody GMCs post-vaccination as the primary series of *Infanrix* in the infant household contact efficacy study, it is reasonable to assume that *Boostrix* will be efficacious in preventing pertussis disease in adolescents.

3.6.1.4. Evaluation of Immune Response to Boostrix in Specific Subpopulations

In Study 001, exploratory analyses were performed in subpopulations based on age at the time of booster vaccination with *Boostrix* (10-14 years of age or 15-18 years of age) and

vaccination history (four or five doses of DTP prior to enrollment in the study). The results demonstrated similar exploratory non-inferiority immunogenicity of *Boostrix* compared to Td in subpopulations based on age and vaccination history with respect to protective levels of antibodies to diphtheria or tetanus (≥0.1 IU/mL), anti-D and anti-T antibody concentrations 10times the cut-off for seroprotection (≥1.0 IU/mL), and with respect to seropositivity rates (antibody concentrations ≥5 EL.U./mL) and booster response rates to tetanus and pertussis antigens. With respect to diphtheria booster responses, similar exploratory non-inferiority immunogenicity of *Boostrix* compared to Td was demonstrated in the subpopulation of 10-14 year olds. However, in the subpopulation of 15-18 year olds, a diphtheria booster response was demonstrated in 87.1% of subjects who received *Boostrix* and 95.4% of subjects who received Td; the upper limit of the 95% CI for group difference in the booster response was 12.0%, marginally exceeding the 10% limit. Within each vaccine group, the antibody GMCs to each vaccine antigen in the subpopulations based on age and vaccination history were similar to those in the ATP Cohort as a whole.

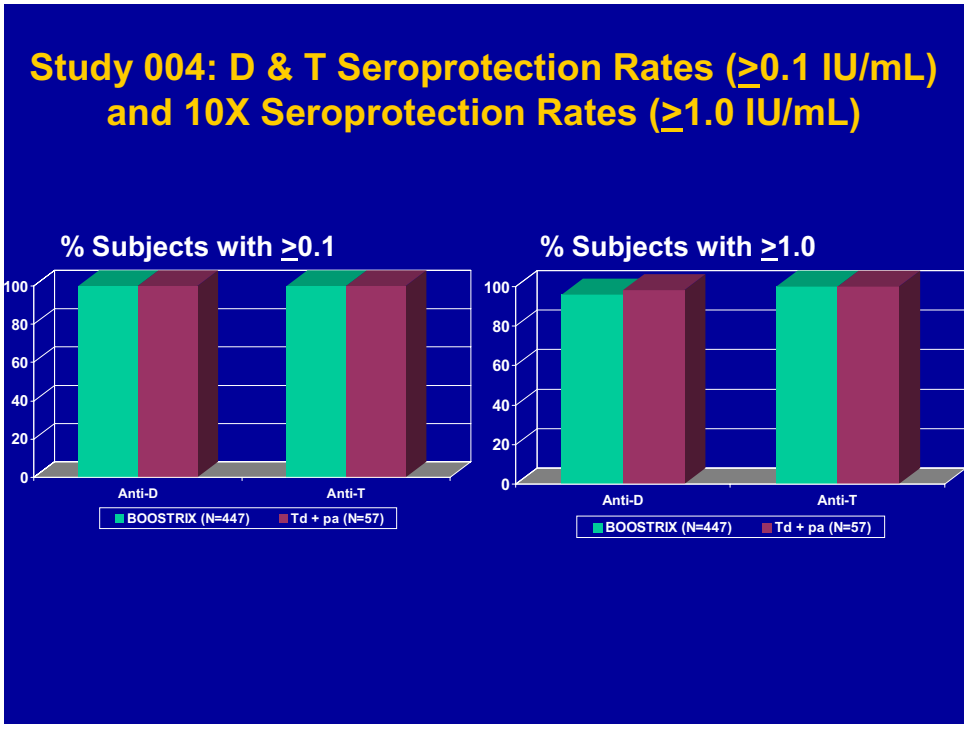
3.6.2. Supportive Study 004

Study 004 was a randomized and controlled trial in 510 adolescents 10-14 years of age which was conducted in Finland to assess the immunogenicity, safety and consistency of three manufacturing lots of the 0.5 mg Al *Boostrix* formulation compared to Lederle's US-licensed Td vaccine and GSK Biologicals' investigational pa vaccine. In this trial, 450 subjects received *Boostrix* and 60 subjects received Td followed one month later by pa (Td + pa). Subjects must have received four doses of DTPw in the first two years of life. Subjects were evenly distributed by age, gender and race between the two study groups. In the *Boostrix* group, 447 (99.3%) subjects met the criteria for inclusion in the ATP cohort for immunogenicity compared to 57 (95%) in the Td + pa group. Clinical Study 004, initiated in 1997, serves as a supportive trial. Note that while the study sample size is too small to meet today's more rigorous consistency standards, the data in this adolescent study met the consistency criteria pre-defined in the protocol and therefore the data presented in this briefing document are from the pooled *Boostrix* lots.

3.6.2.1. Response to Diphtheria and Tetanus

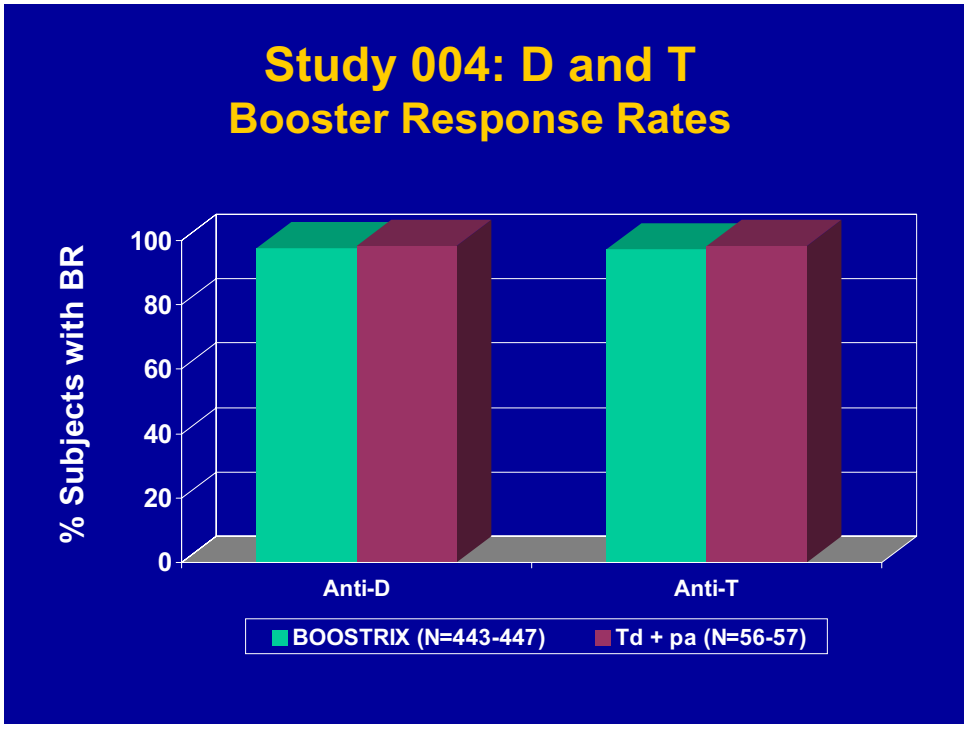
Figure 15 presents the seroprotection rates to diphtheria and tetanus (antibody concentrations ≥ 0.1 IU/mL) and the percentage of subjects with anti-D and anti-T antibody concentrations ≥1.0 IU/mL one month after vaccination in the *Boostrix* and the Td (+ pa) vaccine groups. Figure 16 presents the booster response rates to diphtheria and tetanus one month after vaccination in the two vaccine groups.

Figure 15 **Study 004: D & T Seroprotection Rates (antibody concentration ≥ 0.1 IU/mL) and 10 x Seroprotection Rates (antibody concentration ≥ 1.0 IU/mL)**



Boostrix = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Td = Lederle's tetanus-diphtheria vaccine (Lederject®)
pa = GSK Biologicals' investigational reduced antigen content acellular pertussis vaccine
N = number of subjects with available results

Figure 16 Study 004: D and T Booster Response Rates



Boostrix = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Td = Lederle's tetanus-diphtheria vaccine (Lederject®)
pa = GSK Biologicals' investigational reduced antigen content acellular pertussis vaccine
Booster Response (see Immunogenicity Endpoints, Section 3.5.1)
N = number of subjects with pre and post –vaccination results available

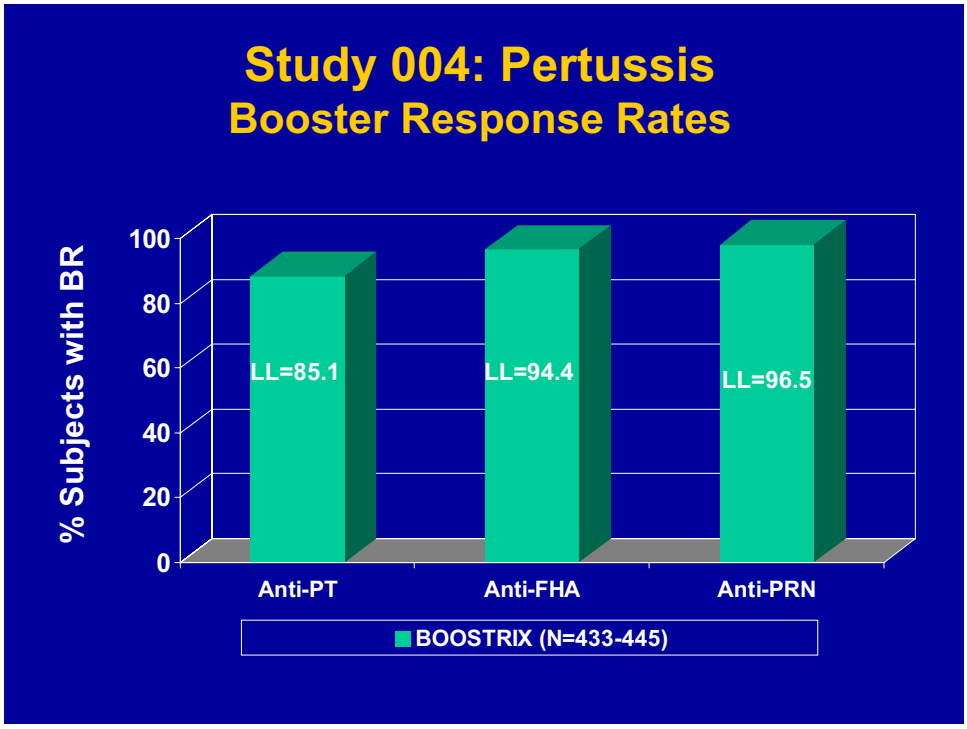
One month after vaccination, all subjects had seroprotective antibody concentrations against diphtheria, and 96.0% of the subjects in the *Boostrix* group vs. 98.2% of the subjects in the Td (+pa) group had antibody concentrations that were ≥10 times the ELISA cut-off for seroprotection. Anti-D antibody GMCs were 6.818 IU/mL following *Boostrix* vaccination and 8.061 IU/mL following Td (+ pa) vaccination. The difference in anti-D GMCs does not appear to be clinically relevant as 96.0% of subjects in the *Boostrix* group had antibody concentrations that were ≥10 times the assay cut-off for seroprotection. Booster responses were 97.7% in the *Boostrix* group and 98.2% in the Td (+ pa) group, and were similar [97.8% in the *Boostrix* group and 100% in the Td (+pa) group] for those subjects who were seronegative prior to vaccination.

One month after vaccination, all subjects had seroprotective antibody concentrations against tetanus and all subjects had antibody concentrations that were ≥10 times the assay cut-off for seroprotection. Anti-T antibody GMCs were 24.299 IU/mL following Boostrix vaccination and 37.665 IU/mL following Td (+ pa) vaccination. The difference in anti-T GMCs does not appear to be clinically relevant as all subjects had antibody concentrations that were ≥10 times the assay cut-off for seroprotection. Booster responses were 97.3% in the *Boostrix* group and 98.2% in the Td (+ pa) group and were similar (100% for both the *Boostrix* group and the Td (+ pa) group) for those subjects who were seronegative prior to vaccination.

3.6.2.2. Response to Pertussis

Results in the briefing document are presented for the subjects in the *Boostrix* group. Subjects in the Td + pa group received an investigational pa vaccine, and results from this group are presented in the BLA. Figure 17 presents the booster response rates to PT, FHA and PRN for the *Boostrix* group.

Figure 17 Study 004: Pertussis Booster Response Rates



Boostrix = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Td = Lederle's tetanus-diphtheria vaccine (Lederject®)
pa = GSK Biologicals' investigational reduced antigen content acellular pertussis vaccine
Booster Response (see Immunogenicity Endpoints, Section 3.5.1)
N = number of subjects with pre- and post –vaccination results available

Of the subjects in the *Boostrix* group, 88.5% had a booster response to PT, 96.6% had a booster response to FHA and 98.2% had a booster response to PRN. In the Td (+pa) group, 92.9% had a booster response to PT, 98.2% had a booster response to FHA and all had a booster response to PRN.

3.6.3. Persistence of Efficacy – Clinical Studies 017 and 030

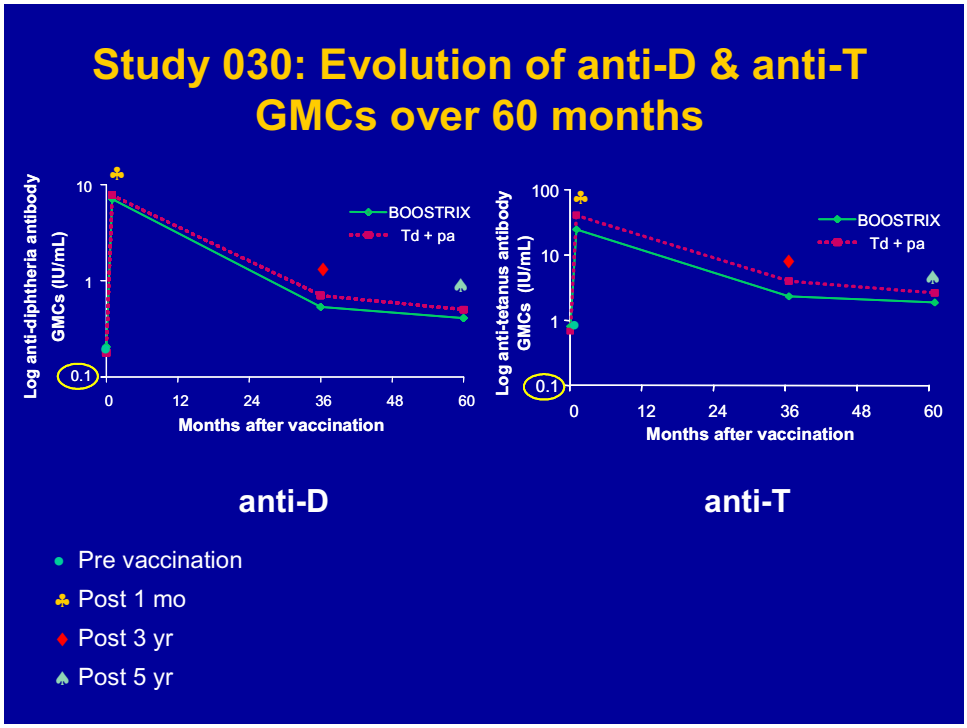
Long-term serological follow-up studies were conducted in subjects vaccinated in study 004. These Studies, 017 and 030, performed following immunization with *Boostrix* and conducted in an open fashion are supportive of the long-term efficacy of *Boostrix*. In Study 004, 510 adolescents 10-14 years of age were vaccinated with *Boostrix* formulated with 0.5 mg Al or Lederle's US-licensed Td vaccine. Two hundred and ninety-nine adolescents agreed to participate in Study 017 for follow-up serological testing three

years post vaccination and 303 subjects agreed to participate in Study 030 for follow-up serological testing five years post-vaccination.

3.6.3.1. Response to Diphtheria and Tetanus

Figure 18 shows the anti-D and anti-T antibody decay curves up to five years after vaccination from the subjects in Study 030.

Figure 18 Study 030: Evolution of anti-D and anti-T GMCs over 60 months



GMCs = Geometric Mean Concentrations
Boostrix = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Td = Lederle's tetanus-diphtheria vaccine (Lederject®)
pa = GSK Biologicals' investigational reduced antigen content acellular pertussis vaccine

At five years post-vaccination, all of the subjects in the Td (+ pa) and 99.2% of the subjects in the *Boostrix* group continued to have seroprotective anti-D antibody concentrations by ELISA or by the VERO cell neutralization assay. While declines in anti-D antibody GMCs of 12.5- to 13.2-fold in the *Boostrix* group and of 11.1- to 12.2-fold in the Td (+pa) group were observed from one month to three years post-vaccination, antibody GMCs leveled off and decreased only 1.3 to 1.4-fold in both vaccine groups between three and five years post-vaccination. At five years post-vaccination, antibody GMCs were still at least 2.0- to 2.8-fold higher than pre-vaccination antibody GMCs in both vaccine groups.

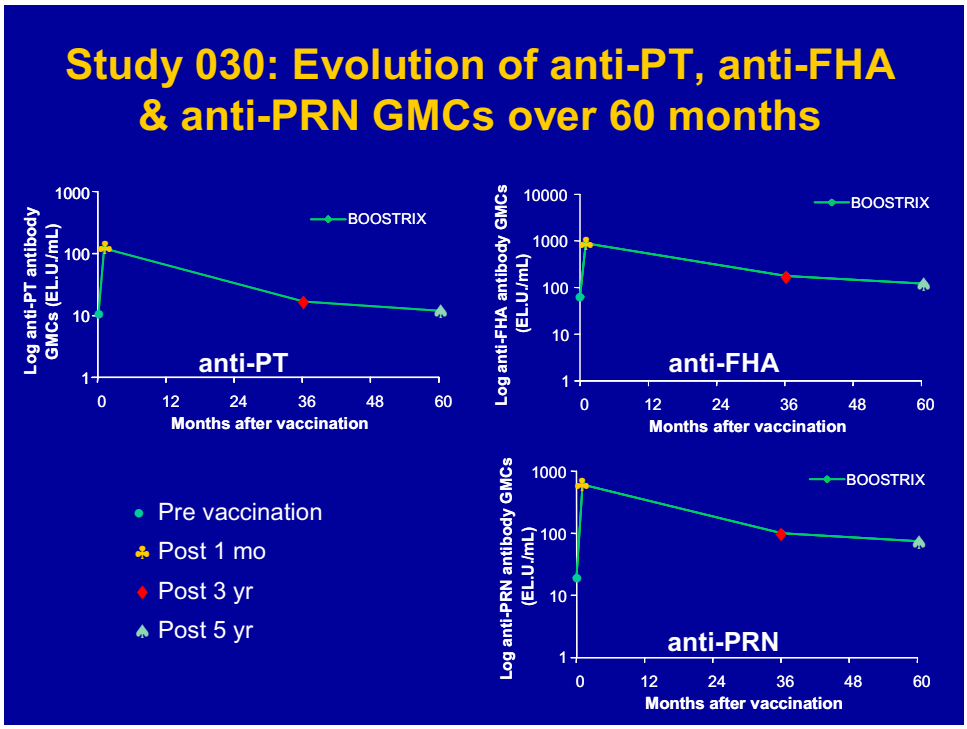
At three and five years post-vaccination, all subjects in both groups continued to have seroprotective anti-T antibody concentrations. While declines in anti-T antibody GMCs of more than 10-fold were observed in both vaccine groups from one month to three

years post-vaccination, antibody concentrations leveled off and decreased only 1.2- to 1.5-fold in both vaccine groups between three and five years post-vaccination and were still at least 3-fold higher than pre-vaccination antibody GMCs in both vaccine groups.

3.6.3.2. Response to Pertussis

Figure 19 shows the anti-PT, anti-FHA and anti-PRN antibody decay curves up to five years after vaccination from the subjects in the *Boostrix* group in Study 030.

Figure 19 Study 030: Evolution of anti-PT, anti-FHA and anti-PRN GMCs over 60 months:



GMCs = Geometric Mean Concentrations
Boostrix = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation

As previously stated, immunologic correlates of protection for pertussis have not been established. Antibody GMCs in the *Boostrix* group three years post-vaccination as compared to one month post-vaccination had declined approximately 7-fold for PT and 5-fold for FHA and PRN. From three to five years post-vaccination, antibody GMCs declined more than 1.3-fold for all three pertussis antigens. All pertussis antibody GMCs at the 5-year follow-up timepoint remained higher than pre-vaccination GMCs, although the anti-PT GMC approached the pre-vaccination GMC.

In addition to the antibody persistence data from *Boostrix* Study 030, follow-up data from Italian infants vaccinated with a three dose primary series of *Infanrix* without a booster dose in the second year of life in the NIH-sponsored efficacy trial demonstrated maintenance of a high level of efficacy against WHO-defined typical pertussis [vaccine efficacy = 86% (95% CI 79-91%)] to at least 6 years of age [Salmoso, 2001].

3.7. *Boostrix* Immunogenicity – Conclusions

Based on the immunogenicity data from these studies, it can be concluded that:

In the pivotal Study 001, manufacturing consistency, with respect to immunogenicity for all vaccine antigen components, was demonstrated between the three *Boostrix* vaccine lots.

In the pivotal study, one month after vaccination, *Boostrix* (containing 0.3 mg Al) was non-inferior to that of a US-licensed Td vaccine with respect to anti-D and anti-T seroprotection rates and booster response rates. In the pivotal Study 001, one month after vaccination, *Boostrix* elicited a booster response to the three pertussis antigens in at least 84.5% of subjects. The results of supportive study 004 show comparable immunogenicity of the diphtheria and tetanus components of *Boostrix,* containing 0.5 mg Al, as compared to a second US-licensed Td vaccine (different than that evaluated in Study 001). Booster response rates were elicited to the three pertussis antigens in at least 88.5% of subjects in this latter study.

The efficacy of *Boostrix* against pertussis was evaluated by comparing the pertussis antibody responses achieved in the pivotal Study 001 in adolescents to those observed with *Infanrix* following a 3-dose primary series in infants in immunogenicity Study 039, the trial that laid the groundwork for household contact study in which efficacy in infants was demonstrated. The antibody GMCs obtained in the pivotal study were shown to be non-inferior to those in Study 039 for all three pertussis antigens. In addition, antibody concentrations achieved in Study 001 were statistically higher than those achieved after a three-dose primary vaccination course with *Infanrix* in Study 039, as evidenced by the 95% CI on the GMC ratios for each of the three pertussis antigens not including "1".

The long-term (five years) follow-up of immunogenicity for *Boostrix* formulated with 0.5 mg Al, from Study 004, is supportive of long-term immunogenicity of the US formulation of *Boostrix*. Taken together, these data support the conclusion that the candidate vaccine is comparable to a US-licensed Td vaccine with respect to immunogenicity for the D and T components of the vaccine and will additionally afford protection against pertussis in adolescents.

3.8. Safety – Assessment and Objectives

The safety program for *Boostrix* was developed to provide an expanded safety database in adolescents and to compare the safety profile of *Boostrix* with that of US-licensed Td vaccines. The clinical safety experience with *Boostrix* in the US file included data on a total of 5,520 subjects of which 3,289 adolescents received the US formulation with 0.3 mg Al, and 2,231 subjects of all ages received *Boostrix* formulated with either 0.5 or 0.133 mg Al. Nine studies in the BLA were performed to support licensure outside of the US with the 0.5 mg Al formulation; these nine studies provide supportive safety data in the US license application on 1,343 of the previously mentioned 2,231 subjects of all ages. The solicited and unsolicited AE data from these nine additional studies were provided in safety synopsis format in the BLA and will not be presented in this briefing document with the exception of serious adverse events (see below).

The focus of the safety data presented in this briefing document is on the solicited and unsolicited adverse event data from pivotal Study 001 and supportive studies 004 and 029 and serious adverse event data from all of the studies included in the BLA.

The following categories of safety information were collected:

- Solicited local events (at the injection site): pain, redness, swelling, increase mid-upper arm circumference (Study 001 only): Days 0-14
- Solicited general events: fever, headache, fatigue, gastrointestinal (included nausea, vomiting , diarrhea, abdominal pain): Days 0-14
- Unsolicited AEs
    - Days 0-30
    - Day 31-month 6 (study 001 only)
- Serious adverse events (SAEs) (duration of study)

Definition and intensity rating scales for each type of event in pivotal Study 001 and supportive Studies 004 and 029 are summarized in Table 3.

Table 3 Studies 001, 004 and 029: Solicited local AE intensity grades

Event	Grade	Description		
		Study 001	Study 029	Study 004
Solicited Local Symptoms				
Pain at injection site	0	Absent	Same	Same
	1	Painful on touch	Same	Pain which was easily tolerated
	2	Painful when limb was moved	Same	Pain which caused sufficient discomfort to interfere with daily activities
	3	Spontaneously painful and/or prevented normal everyday activities	Spontaneously painful	Pain which prevented normal everyday activities and needed medical advice
Redness and swelling at injection site (greatest surface diameter in mm)	0	Absent	Same	Same
	1	>0 mm and ≤20 mm	Same	Same
	2	>20 mm and <50 mm	Same	Same
	3	≥50 mm	Same	Same
Increase in mid-upper-arm circumference	0	≤5 mm	Not applicable	Not applicable
	1	>5 and ≤20 mm	Not applicable	Not applicable
	2	>20 and ≤40 mm	Not applicable	Not applicable
	3	>40 mm	Not applicable	Not applicable
Solicited General Symptoms				
Fever* (oral or axillary) temperature in °C)	0	<37.5°C (< 99.5°F)	Same	Same
	1	≥37.5° and ≤38.0°C (≥ 99.5 and ≤ 100.4° F)	Same	Same
	2	>38.0° and ≤39.0°C (> 100.4 and ≤ 102.2° F)	Same	Same
	3	≥39.1°C (≥ 102.4° F)	Same	Same

Event	Grade	Description		
		Study 001	**Study 029**	**Study 004**
Headache and fatigue	0	Normal	Same	No (solicited)AE
	1	AE which was easily tolerated	Same	Same
	2	AE which interfered with normal activity	Same	AE which caused sufficient discomfort to interfere with daily activities
	3	AE which prevented normal activity	Same	AE which prevented normal everyday activities and needed medical advice
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Normal	Same	Not applicable
	1	AE which was easily tolerated	Same	Not applicable
	2	AE which interfered with normal activity	Same	Not applicable
	3	AE which prevented normal activity	Same	Not applicable
Malaise, dizziness and vomiting	0	Not applicable	Not applicable	No (solicited)AE
	1	Not applicable	Not applicable	AE which was easily tolerated
	2	Not applicable	Not applicable	AE which caused sufficient discomfort to interfere with daily activities
	3	Not applicable	Not applicable	AE which prevented normal everyday activities and needed medical advice

In pivotal Study 001, a co-primary endpoint was the comparison of *Boostrix* to a US-licensed Td vaccine with respect to the incidence of Grade 3 pain at the injection site. The criterion for non-inferiority was defined as the upper limit of the two-sided 95% CI for the difference in Grade 3 injection site pain (pooled *Boostrix* groups minus Td group) being less than or equal to the clinical limit of 4%.

With the exception of Grade 3 injection site pain in Study 001, which was a co-primary endpoint, comparisons between groups were exploratory. Two-sided Fisher's exact tests were used to compare the treatment groups and p-values less than 0.05 were used as an indicator that a difference between groups may exist. However, statistically significant findings should be interpreted with caution because, due to the multiplicity of endpoints, it is likely that some statistically significant findings occur by chance.

In Study 001, subjects were followed for an additional 5-month extended safety follow-up period for new onset of chronic illness(es) (e.g., diabetes, autoimmune diseases, asthma, allergies etc.), events that led to emergency room visits, and events that led to a physician's office visit that were not related to common illnesses (e.g., upper respiratory tract infection, sinusitis, pharyngitis, gastroenteritis, injury) or that were not routine visits for physical examinations or vaccinations. Any SAE and pregnancy that occurred during this period were also reported.

3.9. Safety results

Results for solicited local events, solicited general events, unsolicited adverse events and serious adverse events are summarized by study.

3.9.1. Pivotal Study 001

Pivotal Study 001 evaluated three production lots of *Boostrix* containing 0.3 mg Al compared to MPHBL's US-licensed Td vaccine as the control. The Total Vaccinated Cohort (N = 4,114) was the primary cohort for the analysis of safety and included all vaccinated subjects with available safety data.

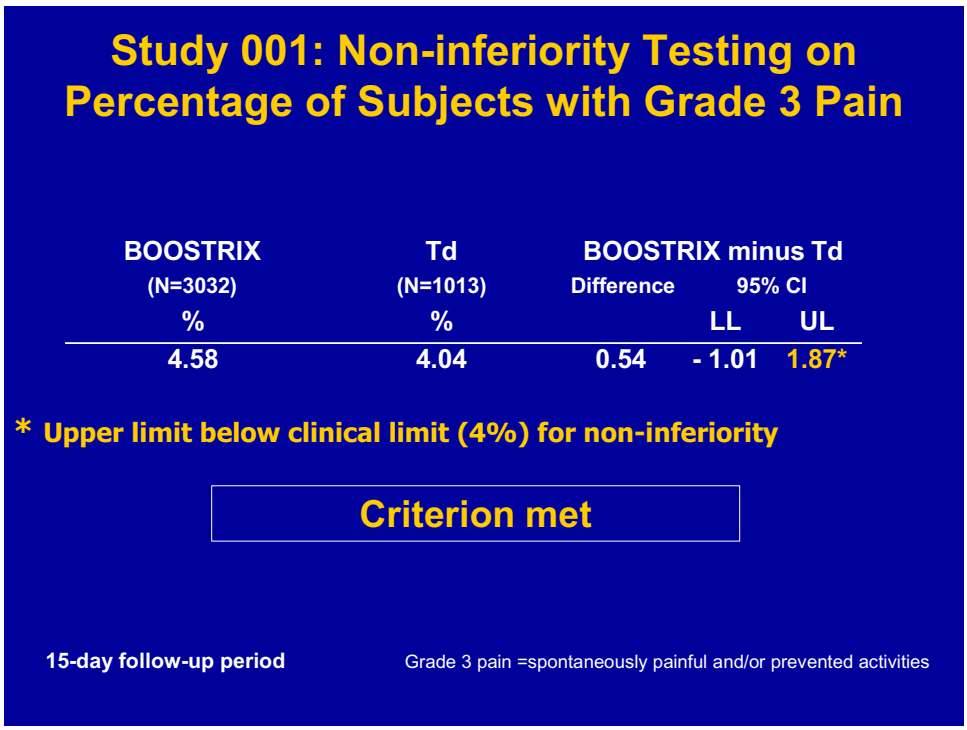
3.9.1.1. Adverse events by Boostrix lot

There was a similar incidence of any, local and general AEs (solicited and unsolicited) among the three lots of *Boostrix*. There was no statistical evidence of a difference between the three production lots in terms of safety (p value >0.05 for all comparisons by Fisher's exact test for the incidences of specific solicited AEs) with the exception of a >40 mm (Grade 3) increase in mid-upper arm circumference of the vaccinated arm within the 4-day reporting period (range 0.0% - 0.6%). The absolute value of the difference was small (range 0.0% - 0.6%) and is unlikely to be of clinical relevance. Details as to the percentages of subjects reporting AEs following each of the three *Boostrix* lots are provided in the BLA. Since there were no apparent clinically relevant differences among the three lots of *Boostrix* with respect to safety, an analysis was performed on the pooled lots of *Boostrix* compared to the Td vaccine group. The results of these comparisons are presented in the following sub-sections.

3.9.1.2. Solicited local adverse events

One of the primary objectives in Study 001 was to demonstrate the non-inferiority of *Boostrix* compared to MPHBL's US-licensed Td vaccine, in terms of safety, with respect to the incidence of Grade 3 pain at the injection site reported to occur within the 15-day follow-up period. Non-inferiority criterion for this primary objective was pre-specified to be met if the upper limit of the two-sided 95% CI for the difference in Grade 3 injection site pain (*Boostrix* group minus Td group) is ≤4%. Figure 20 presents the non-inferiority testing on the percentage of subjects who reported Grade 3 pain.

Figure 20 Study 001 – Non-Inferiority Testing on Percentage of Subjects with Grade 3 Pain



Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects with symptom sheets completed

The percentage of subjects experiencing Grade 3 injection site pain during the 15-day follow-up period was not statistically different between the two vaccine groups (4.58% vs. 4.04% in the *Boostrix* and Td vaccine groups, respectively). Non-inferiority for this primary objective was met since the upper limit of the two-sided 95% CI for the difference in Grade 3 injection site pain (*Boostrix* group minus Td group) was below the pre-defined clinical limit of 4%.

Figure 21 and Figure 22 present the incidence of any, Grade 2 or 3, and Grade 3 solicited local events occurring within the 4-day (Figure 21) and 15-day (Figure 22) post-vaccination period and an exploratory comparison of the incidences between the *Boostrix* group and the Td group.

Figure 21 Study 001: Incidence (%) of Solicited Local Events Within the 4-day Follow-up Period

Study 001: Incidence (%) of solicited local events
4-day follow-up period

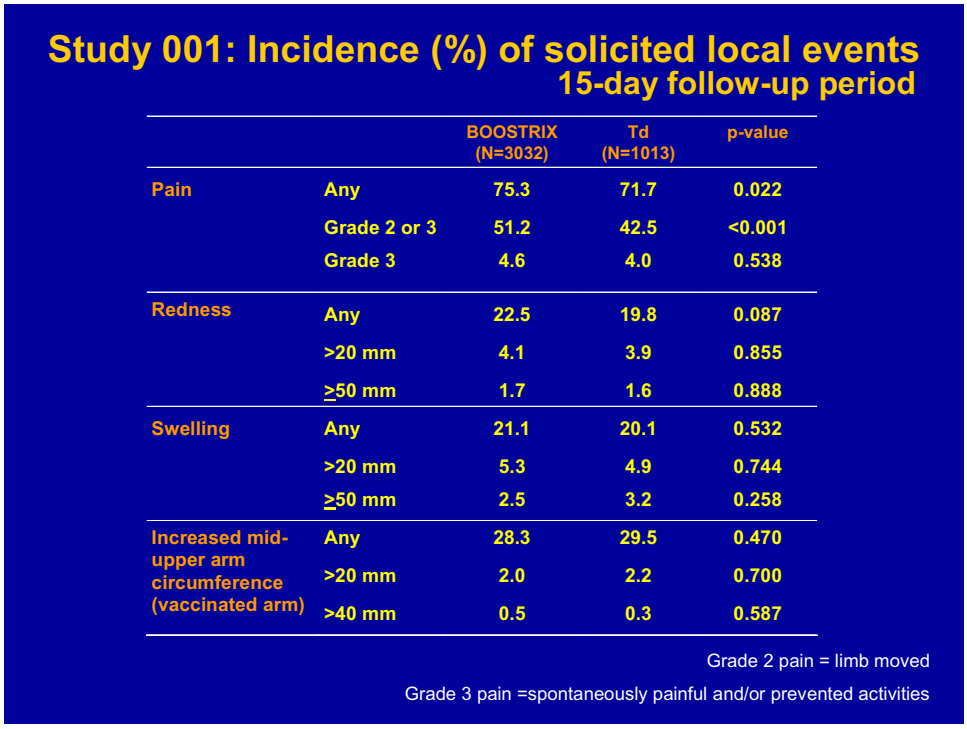
		BOOSTRIX (N=3032)	Td (N=1013)	p-value
Pain	Any	75.0	71.4	0.025
	Grade 2 or 3	50.7	42.2	<0.001
	Grade 3	4.5	3.7	0.332
Redness	Any	21.9	19.5	0.121
	>20 mm	4.0	3.8	0.780
	≥50 mm	1.6	1.5	0.885
Swelling	Any	20.2	19.8	0.821
	>20 mm	5.0	4.8	0.868
	≥50 mm	2.4	3.2	0.170
Increased mid-upper arm circumference (vaccinated arm)	Any	21.4	23.2	0.236
	>20 mm	1.6	1.5	1.000
	>40 mm	0.3	0.3	1.000

Grade 2 pain = limb moved

Grade 3 pain =spontaneously painful and/or prevented activities

Boostrix = GSK Biologicals' 0.3 mg AI formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects with symptom sheets completed
p-value = 2-sided Fisher's exact test

Figure 22 Study 001: Incidence (%) of Solicited Local Events Within the 15-day Follow-up Period



Study 001: Incidence (%) of solicited local events
15-day follow-up period

		BOOSTRIX (N=3032)	Td (N=1013)	p-value
Pain	Any	75.3	71.7	0.022
	Grade 2 or 3	51.2	42.5	<0.001
	Grade 3	4.6	4.0	0.538
Redness	Any	22.5	19.8	0.087
	>20 mm	4.1	3.9	0.855
	≥50 mm	1.7	1.6	0.888
Swelling	Any	21.1	20.1	0.532
	>20 mm	5.3	4.9	0.744
	≥50 mm	2.5	3.2	0.258
Increased mid-upper arm circumference (vaccinated arm)	Any	28.3	29.5	0.470
	>20 mm	2.0	2.2	0.700
	>40 mm	0.5	0.3	0.587

Grade 2 pain = limb moved

Grade 3 pain =spontaneously painful and/or prevented activities

Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects with symptom sheets completed
p-value = 2-sided Fisher's exact test

The most frequently reported solicited local AE, in both the 4-day and 15-day post-vaccination period, was pain in both the *Boostrix* and the Td vaccine groups. Subjects in the *Boostrix* group reported a statistically significant higher incidence of 'any' pain (75.0% vs.71.4% during the 4-day follow-up period and 75.3% vs.71.7% during the 15-day follow-up period) and Grade ≥2 pain (50.7% vs.42.2% during the 4-day follow-up period and 51.2% vs. 42.5% during the 15-day follow-up period) than subjects in the Td vaccine group. The rates of Grade 3 pain, however, were comparable between the *Boostrix* and the Td vaccine groups for both timeframes (4.5% vs. 3.7% in the 4-day follow-up period and 4.6% vs. 4.0% in the 15-day follow-up period). There were no statistically significant differences in both the 4-day and 15-day follow-up periods in the percentage of subjects in the *Boostrix* and the Td vaccine groups reporting redness and swelling of any intensity. The incidences of all Grade 3 solicited local events, including pain, were comparable between the two vaccine groups.

There were no significant differences between the *Boostrix* and the Td vaccine groups in the percentage of subjects reporting an increase from baseline in mid-upper arm circumference in the vaccinated arm. Increases in mid-upper arm circumference also were reported in the unvaccinated arm in a percentage of subjects in both the *Boostrix* and the Td vaccine groups (data not shown).

Details regarding recurrent and late-onset solicited local AEs as well as the number of days with injection site pain and the prevalence of injection site pain, the prevalence of increased mid-upper arm circumference in the vaccinated arm and the number of days with report of increased mid-upper arm circumference during the 15-day post-vaccination period are presented in the BLA. The percentages of subjects reporting recurrent and late onset solicited pain, redness and swelling were low and similar between the *Boostrix* and the Td vaccine groups. Among the events of pain, redness and swelling, the most commonly reported recurrent AE in both vaccine groups was pain (*Boostrix* = 8.1%; Td = 6.8%) whereas the most commonly reported late-onset AE, although at very low percentages, was swelling (*Boostrix* = 0.9%; Td = 0.3%).

3.9.1.3. Solicited general adverse events

Figure 23 and Figure 24 present the percentage of subjects reporting the occurrence of any, Grade 2 or 3 and Grade 3 solicited general events within the 4-day (Figure 23) and 15-day (Figure 24) post-vaccination period as well as the results of the exploratory comparison of the incidences in the *Boostrix* and the Td vaccine groups. Temperatures were measured by either the axillary or the oral (preferred) route.

Figure 23 Study 001: Incidence (%) of Solicited General Events Within the 4-day Follow-up Period

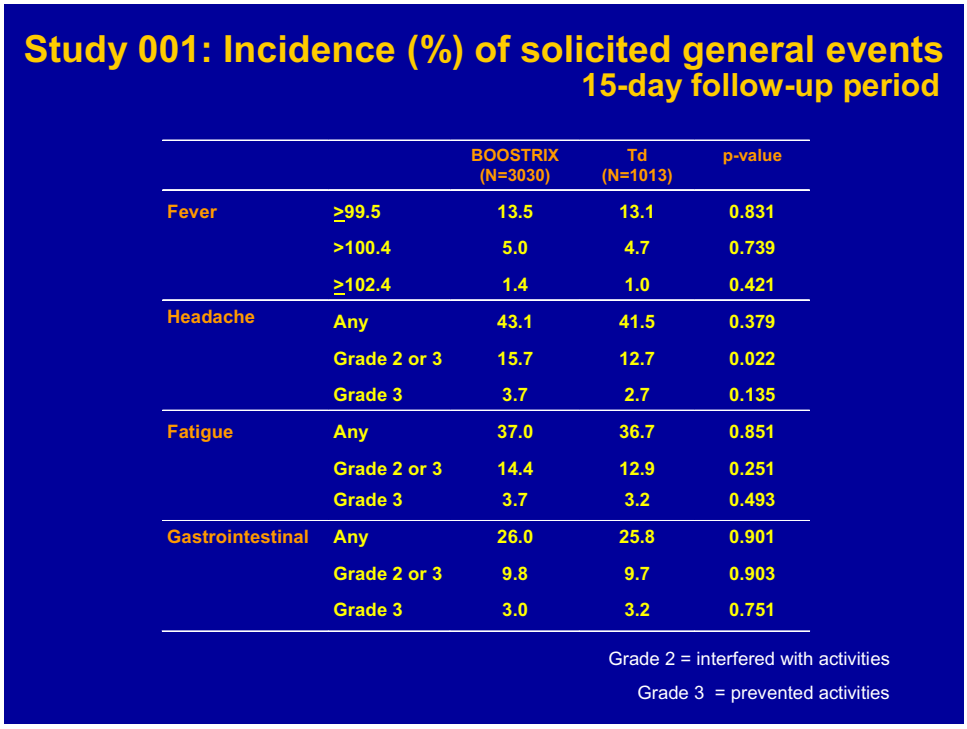
Study 001: Incidence (%) of solicited general events
4-day follow-up period

		BOOSTRIX (N=3030)	Td (N=1013)	p-value
Fever	≥99.5	6.5	5.4	0.259
	>100.4	1.8	1.5	0.578
	≥102.4	0.4	0.3	1.000
Headache	Any	33.1	30.9	0.906
	Grade 2 or 3	7.8	6.8	0.336
	Grade 3	1.4	1.2	0.752
Fatigue	Any	29.9	30.6	0.692
	Grade 2 or 3	8.8	8.6	0.898
	Grade 3	1.6	1.9	0.569
Gastrointestinal	Any	17.0	17.4	0.810
	Grade 2 or 3	4.9	4.9	0.933
	Grade 3	1.3	1.6	0.536

Grade 2 = interfered with activities
Grade 3 = prevented activities

Boostrix = GSK Biologicals' 0.3 mg AI formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects with symptom sheets completed
p-value = 2-sided Fisher's exact test

Figure 24 Study 001: Incidence (%) of Solicited General Events Within the 15-day Follow-up Period



Study 001: Incidence (%) of solicited general events
15-day follow-up period

		BOOSTRIX (N=3030)	Td (N=1013)	p-value
Fever	≥99.5	13.5	13.1	0.831
	>100.4	5.0	4.7	0.739
	≥102.4	1.4	1.0	0.421
Headache	Any	43.1	41.5	0.379
	Grade 2 or 3	15.7	12.7	0.022
	Grade 3	3.7	2.7	0.135
Fatigue	Any	37.0	36.7	0.851
	Grade 2 or 3	14.4	12.9	0.251
	Grade 3	3.7	3.2	0.493
Gastrointestinal	Any	26.0	25.8	0.901
	Grade 2 or 3	9.8	9.7	0.903
	Grade 3	3.0	3.2	0.751

Grade 2 = interfered with activities
Grade 3 = prevented activities

Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects with symptom sheets completed
p-value = 2-sided Fisher's exact test

In both groups, in both the 4-day and 15-day post-vaccination periods, the most frequently reported solicited general AEs were headache and fatigue. There were no statistically significant differences between the two vaccine groups for any solicited general AE, except for headache. In the 15-day post-vaccination period, a statistically significant difference was noted for the incidence of Grade 2 or 3 headache (but not headache of any intensity or Grade 3 headache) reported by 15.7% of subjects in the *Boostrix* group and by 12.7% of subjects in the Td group. The absolute difference (3%) was small and does not appear to be clinically relevant. In both the 4-day and 15-day post-vaccination periods, the incidences of Grade 3 solicited general events were comparable at a rate of <4% for the *Boostrix* and the Td vaccine groups.

Details regarding recurrent and late-onset solicited general AEs are presented in the BLA. Headache was the most commonly reported recurrent and late-onset event. Recurrent headache was reported in 18.5% and 17.7% of subjects and late-onset headaches were reported in 11.9% and 10.6% of subjects in the *Boostrix* and the Td vaccine groups, respectively.

3.9.1.4. Subgroup analyses of solicited local and general adverse events by age, gender, vaccination history and type of DTP vaccination

The incidence of any, Grade 2 or 3 and Grade 3 solicited local and general events during the initial 72-hour and the 15-day post-vaccination periods by age (subjects 10-14 years of age and 15-18 years of age), by gender, by vaccination history (<4, 4, 5 and >5 doses of a Td-containing vaccine, i.e., DTPw, DTaP, Td) and by type of DTP vaccine previously administered (all DTPw, mixed sequence of DTPw and DTaP, and unknown) for subjects who had previously received five doses of a DTP vaccine are presented in the BLA.

In these subgroup analyses, the difference between the *Boostrix* and Td vaccine groups was consistent with respect to what was observed for the overall Total Vaccinated Cohort. In these exploratory analyses, group differences were only observed for the following symptoms: Pain was higher in males (Grade 2 or 3), females (Grade 2 or 3) and Caucasians ('any' and Grade 2 or 3) in the *Boostrix* group than in the Td group; fatigue was higher in females ('any' fatigue) and Hispanics (Grade 2 or 3 and Grade 3) in the Td group; and headache was higher in males (Grade 2 or 3) and Caucasians (Grade 2 or 3) in the *Boostrix* group and was higher in Orientals (Grade 2 or 3) in the Td group. These differences are unlikely to be of clinical relevance and, therefore, these subgroup analyses support the conclusion of the overall analyses on the Total Vaccinated Cohort.

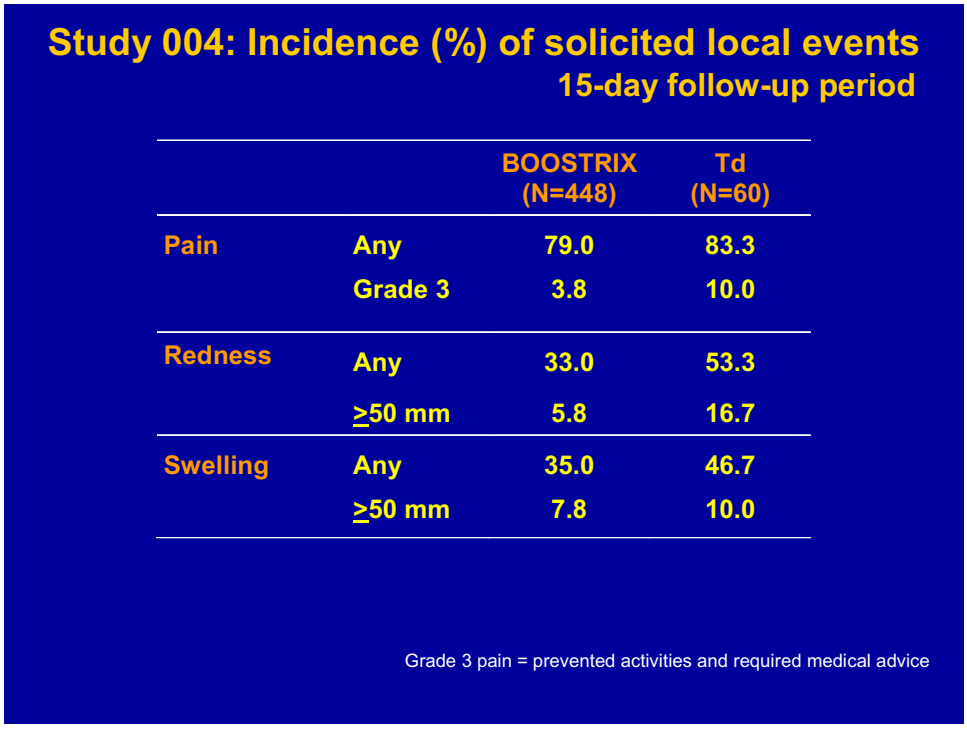
3.9.2. Supportive Study 004

In Study 004, three lots of *Boostrix* formulated with 0.5 mg Al were assessed and compared to Lederle's US-licensed Td vaccine as the control group. Subjects who were randomized to receive the Td vaccine were given open-label GSK Biologicals' investigational pa vaccine one month later. The ATP Safety Cohort (N=509) was the primary cohort for the analysis of safety and included all vaccinated subjects with available safety data who received at least one dose of study vaccine according to their random assignment. The three groups who received *Boostrix* were similar in terms of the incidence of solicited local and general AEs. Results of the pooled *Boostrix* groups for study 004 are presented in this briefing document. There were 509 vaccinated subjects who received 568 doses (449 Boostrix, 60 Td and 59 pa) of study vaccines and provided safety data during the 31-day period following vaccination. Safety data on the subjects receiving open-label pa are presented in the BLA and will not be presented in this briefing document.

3.9.2.1. Solicited local adverse events

Figure 25 shows the incidence of any and Grade 3 solicited local AEs (pain, redness and swelling) within the 15-day post-vaccination period.

Figure 25 Study 004: Incidence (%) of Solicited Local Events Within the 15-day Follow-up Period



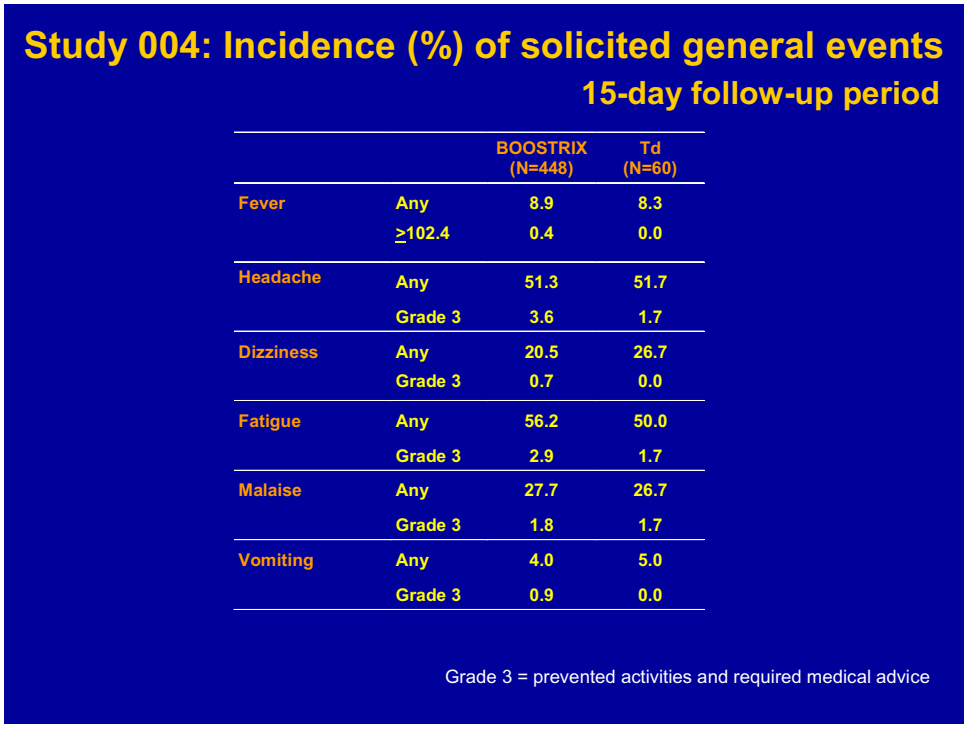
Boostrix = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Td = Lederle's tetanus-diphtheria vaccine (Lederject®)
N = number of subjects with symptom sheets completed

The most frequently reported solicited local AE was pain at the injection site. The point estimates for the incidence of pain, redness and swelling (any and Grade 3) were higher following the dose of the Td compared with *Boostrix*.

3.9.2.2. Solicited general adverse events

Figure 26 shows the incidence of any and Grade 3 solicited general AEs (fever, headache, dizziness, fatigue, malaise and vomiting) within the 15-day post-vaccination period.

Figure 26 Study 004: Incidence (%) of Solicited General Events Within the 15-day Follow-up Period



Boostrix = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Td = Lederle's tetanus-diphtheria vaccine (Lederject®)
N = number of subjects with symptom sheets completed

Overall, the incidences of solicited general AEs reported following the doses of *Boostrix* and Td vaccines were similar. The most frequently reported solicited general AEs following both vaccines were fatigue and headache, and the incidence of Grade 3 AEs was low in both groups (<4%).

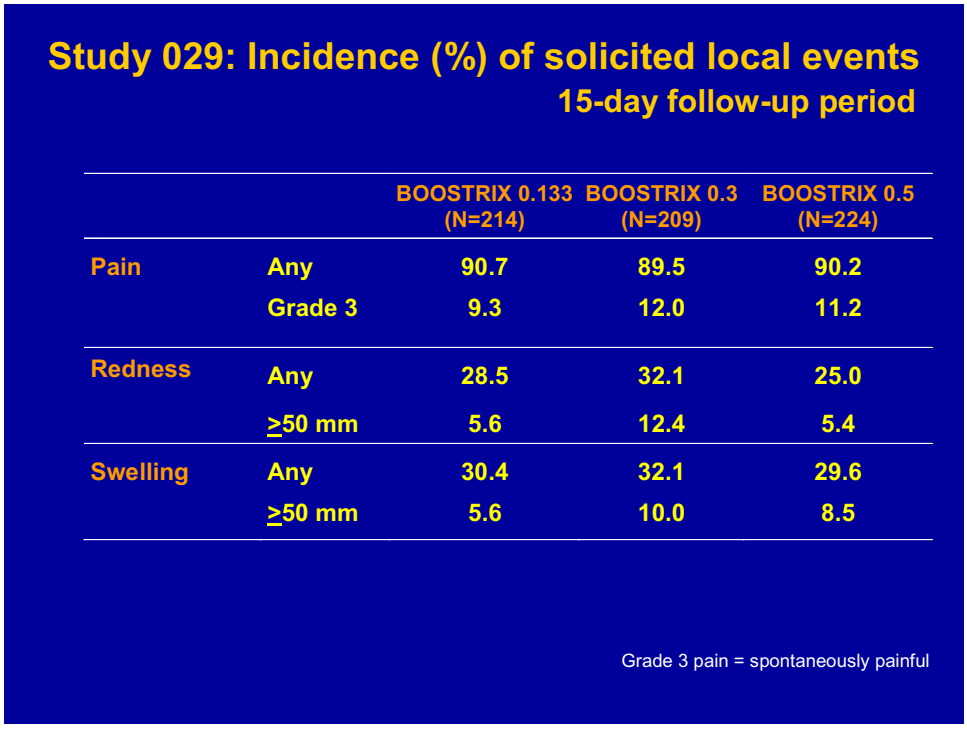
3.9.3. Supportive Study 029

Study 029 evaluated three different Al content formulations of *Boostrix:* 0.133 mg Al, 0.3 mg Al and 0.5 mg Al. The Total Cohort (N=647) was the primary cohort for the analysis of safety and included all vaccinated subjects with available safety data. The 0.3 mg formulation for US development was ultimately chosen from this study.

3.9.3.1. Solicited local adverse events

Figure 27 presents the percentage of subjects reporting any and Grade 3 solicited local AEs (pain, redness, and swelling) with an onset during the 15-day post-vaccination period.

Figure 27 Study 029: Incidence (%) of Solicited Local Events Within the 15-day Follow-up Period



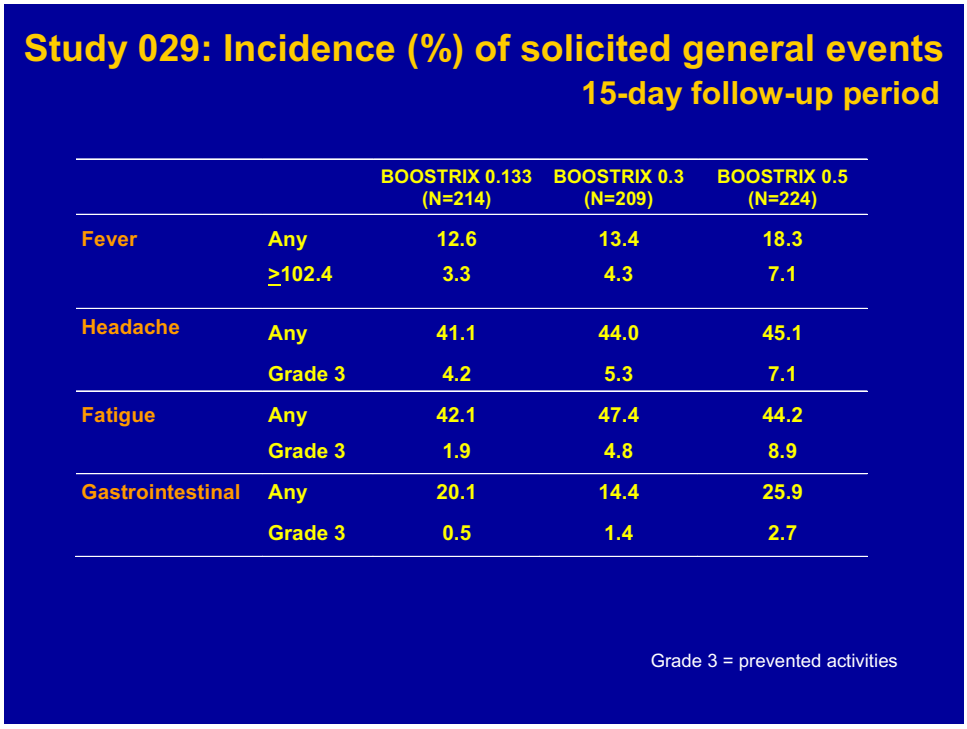
Boostrix = GSK Biologicals' 0.133 mg Al, 0.3 mg Al and 0.5 mg Al formulations
N = number of subjects with symptom sheets completed

The most frequently reported solicited local AE was injection site pain and the incidence was similar across the three groups. The incidences of redness and swelling also were similar between the three groups.

3.9.3.2. Solicited general adverse events

The incidence of solicited general AEs (fever, headache, fatigue, gastrointestinal) reported during the 15-day post-vaccination period is presented in Figure 28.

Figure 28 Study 029: Incidence (%) of Solicited General Events Within the 15-day Follow-up Period



Boostrix = GSK Biologicals' 0.133 mg Al, 0.3 mg Al and 0.5 mg Al formulations
N = number of subjects with symptom sheets completed

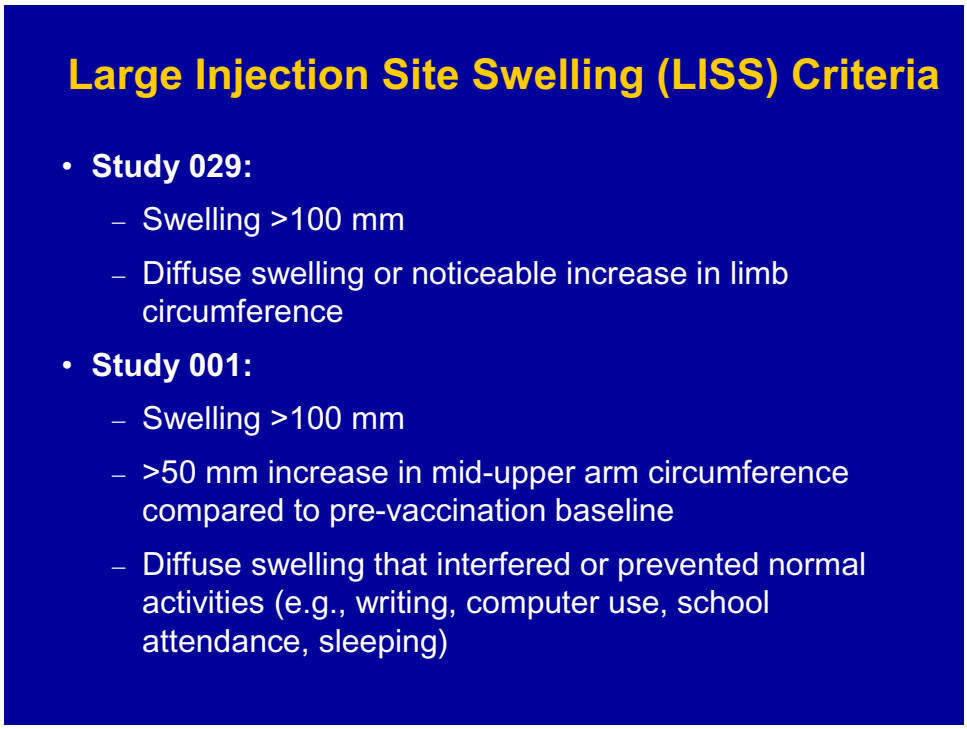
Headache and fatigue were the most frequently reported solicited general AEs and the incidences were similar across the three groups.

3.9.4. Large injection site swelling (LISS)

Large swelling reactions involving the entire vaccinated limb are known to occur following a variety of vaccines including DTPw, DTaP, Td and Hib vaccines [Woo, 2003]. For example, Margaret Rennels from the Center for Vaccine Development in Baltimore evaluated several clinical studies retrospectively and reported that entire proximal limb swelling occurs in 2% to 6% of children, primed in infancy with DTaP vaccines, given booster doses of DTaP vaccines. In addition to the solicited local AE of swelling at the injection site, data concerning large injection site swelling were actively collected in Studies 001 and 029. In Study 001, the mid-upper arm circumference of both the vaccinated and the unvaccinated arms was measured and the measurements were recorded daily on subject Diary Cards during the 15-day post-vaccination period. Mid-upper arm circumference was not collected in Study 029. In both studies, subjects or subjects' parents/guardian who observed any extensive or noticeable swelling of the injected limb were requested to contact study personnel and to present to the investigator for evaluation. The investigator was instructed to record detailed information concerning the AE (including a narrative description of the swelling, the greatest diameter and percentage of upper arm involved in the swelling and associated signs and symptoms including functional impairment and pruritus). It is important to note that most subjects

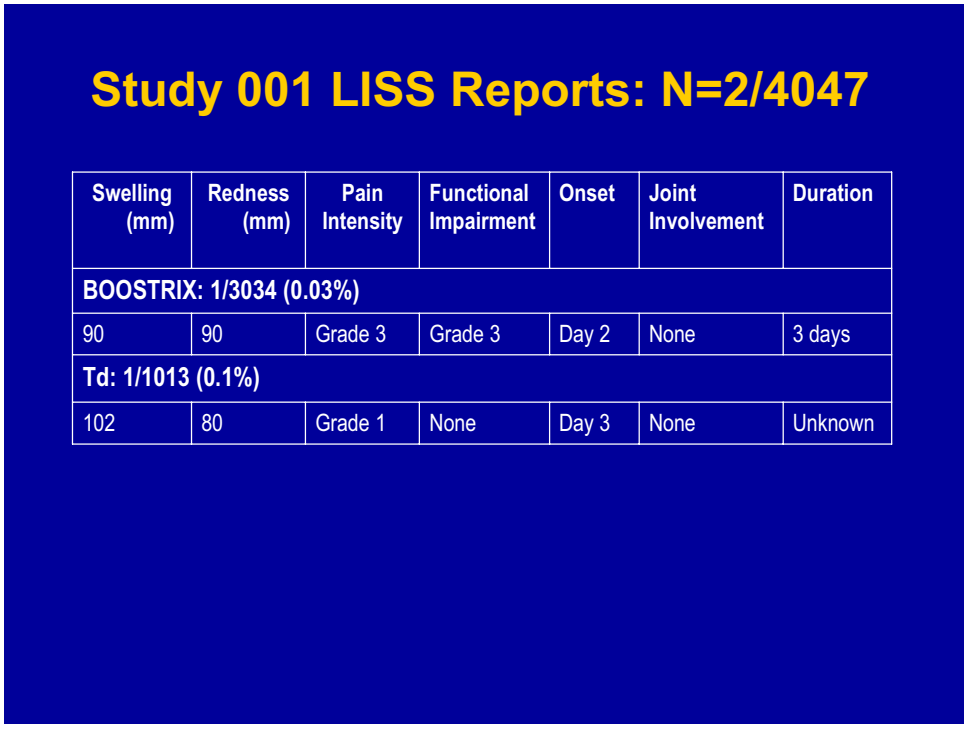
in Studies 001 and 029 were primed with at least 3 doses of whole-cell DTP. The criteria defining a large injection site swelling in Studies 001 and 029 are outlined on Figure 29.

Figure 29 Large Injection Site Swelling (LISS) Criteria



In Study 001, two subjects, one in the *Boostrix* group (subject had previously received five doses of DTP, type unspecified) and one in the Td vaccine group (subject had previously received DTPw x 3 and DTaP x 2), reported an episode of large injection site swelling. Both events of LISS had an onset within three days, had no joint involvement, were associated with pain and local redness, and resolved without sequelae. Additional details regarding both events of injection site swelling from Study 001 are summarized in Figure 30.

Figure 30 Study 001: Large Injection Site Swellings Reports



Swelling (mm)	Redness (mm)	Pain Intensity	Functional Impairment	Onset	Joint Involvement	Duration
BOOSTRIX: 1/3034 (0.03%)						
90	90	Grade 3	Grade 3	Day 2	None	3 days
Td: 1/1013 (0.1%)						
102	80	Grade 1	None	Day 3	None	Unknown

Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
Pain Intensity Grade 1 = painful on touch
Pain Intensity Grade 3 = spontaneously painful and/or prevented activities
Functional Impairment Grade 3 = prevented activities

In Study 029, five subjects reported an episode of large injection site swelling. One subject was vaccinated with the *Boostrix* 0.5 mg Al formulation and four subjects with the 0.3 mg Al formulation. In all cases, the investigators classified the swellings as large local swelling without involvement of the adjacent joints. All five events of LISS had an onset within two days, had no joint involvement, were associated with pain and local redness, and resolved without sequelae. Additional details regarding all five events of injection site swelling from Study 029 are summarized in Figure 31.

Figure 31 Study 029: Large Injection Site Swelling Reports

Study 029 LISS Reports: N=5/647 (0.8%)

Swelling (mm)	Redness (mm)	Pain Intensity	Functional Impairment	Onset	Joint Involvement	Duration
BOOSTRIX 0.3 mg Al						
125	125	Grade 2	Grade 2	Day 2	None	4 days
110	110	Grade 3	Grade 3	Day 2	None	2 days
110	100	Grade 2	Grade 2	Day 2	None	2 days
127	125	Grade 3	Grade 3	Day 1	None	3 days
BOOSTRIX 0.5 mg Al						
120	120	Grade 2	Grade 2	Day 2	None	2 days

Boostrix 0.3 mg Al = GSK Biologicals' 0.3 mg Al formulation
Boostrix 0.5 mg Al = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
Pain Intensity Grade 2 = painful when limb moved
Pain Intensity Grade 3 = spontaneously painful
Functional Impairment Grade 2 = interferes with activities
Functional Impairment Grade 3 = prevents activities

These 7 large injection site swelling events in Studies 001 and 029 do not signal a new or unexpected safety issue. The overall frequency of LISS following *Boostrix* was low in these two studies (0.03 – 0.8 %) despite active surveillance.

Of interest will be the incidence of large injection site swelling events in adolescents who will be vaccinated with *Boostrix* who have been primed throughout life with all acellular-pertussis containing vaccines. DTaP vaccines were first licensed in the US for use in infants in late 1996, and therefore the cohort of US adolescents primed entirely with DTaP vaccine will not be evaluable until at least 2007.

Post-approval, a study report will be submitted to the FDA on a cohort of approximately 300 German adolescents recently enrolled in a clinical study where they received a 6th consecutive dose of acellular-pertussis containing vaccine.

3.10. Unsolicited Adverse Events

3.10.1. Pivotal Clinical Study 001

3.10.1.1. Day 0-30

Unsolicited AEs were coded using the World Health Organization (WHO) Dictionary for Adverse Reaction Terminology in pivotal Study 001. Figure 30 presents those unsolicited AEs which were reported to occur in at least 1% of subjects. The sample size of 3000 subjects, vaccinated with *Boostrix* in Study 001, allowed for a conclusion that an adverse event that was not observed had an incidence rate of <0.1% with a 5% risk of error.

Figure 32 Study 001: Unsolicited AEs Reported in at Least 1% of Subjects (Day 0 - 30)

Study 001: Unsolicited AEs Reported in at Least 1% of Subjects, Day 0-30

WHO Preferred Term	BOOSTRIX (N=3034) %	Td (N=1013) %
At least one AE	25.4	24.5
Pharyngitis	4.6	4.3
URI	4.3	4.8
Rhinitis	2.7	0.7
Injury	2.2	1.8
Coughing	1.8	1.6
Injection site reaction	1.7	1.6
Pain	1.6	1.1
Dysmenorrhea	1.2	0.7

Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects with documented doses (reported by means of a symptom sheet or by other means)

In the *Boostrix* group, 771 of 3034 subjects (25.4%) reported at least one unsolicited AE within the 31 days post-vaccination and in the Td vaccine group, 248 of 1013 subjects (24.5%) reported at least one unsolicited AE. The most frequently reported unsolicited AEs in both groups were pharyngitis (4.6% of subjects in the *Boostrix* group and 4.3% of subjects in the Td vaccine group) and upper respiratory infections (4.3% and 4.8%, respectively).

Grade 3 unsolicited AEs were reported by 64 (2.1%) of the subjects in the *Boostrix* group and by 19 (1.9%) of subjects in the Td vaccine group. The most frequently reported Grade 3 unsolicited event was pharyngitis (0.5%) in the *Boostrix* group and viral infection (0.3%) in the Td vaccine group. Further details regarding the percentages of subjects reporting the occurrence of any and Grade 3 unsolicited AEs are presented in the BLA.

3.10.1.2. Day 31 - Month 6

From day 31 through month 6 (the extended safety follow-up phase), the percentages of subjects reporting the occurrence of a SAE, a new onset of chronic illness, and/or an AE that resulted in an emergency room visit, or resulted in a physician's office visit that were not related to routine visits for physical examinations or common illnesses were recorded. Of the 4114 adolescents vaccinated, extended safety follow-up data was collected on 3005 in the *Boostrix* group and 1003 in Td group. The percentages of subjects reporting the occurrence of an AE during the extended safety follow-up phase, categorized by AE type (at least 1 adverse event, chronic illness, emergency room visit, physician office visit, SAE), are presented in Figure 33.

Figure 33 Study 001: Unsolicited AEs Day 31 – Month 6

Study 001: Unsolicited AEs Day 31 - Month 6

Category	BOOSTRIX (N=3005) %	Td (N=1003) %
At least one AE	5.5	4.3
Onset chronic illness	0.7	0.9
Emergency Room Visit	3.4	2.5
Physician Office Visit	1.7	1.6
SAE	0.5	0.2

Boostrix = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine
N = number of subjects in extended safety follow-up cohort

The percentages of subjects reporting the occurrence of AEs, regardless of type, were similar between the two groups with 5.5% in the *Boostrix* group compared to 4.3% in the

Td group. The absolute difference between groups in the frequency of AEs in any specific category was small (≤0.9%).

3.10.2. Supportive Study 004

Unsolicited AEs were coded using the World Health Organization (WHO) Dictionary for Adverse Reaction Terminology in study 004. Within 31 days (Days 0-30) following vaccination, there were 198 unsolicited AEs reported by 120 subjects who received *Boostrix* (27%), 18 subjects who received Td (30%) and 11 subjects who received the pa vaccine (19%). Unsolicited AE rates were similar between the *Boostrix* and Td groups. The most frequently reported AEs in the *Boostrix* group were upper respiratory tract infections, pharyngitis and rhinitis. Further details are presented in the BLA.

3.10.3. Supportive Study 029

Unsolicited AEs were coded using the WHO Dictionary for Adverse Reaction Terminology in Study 029. Unsolicited AE reporting was similar among the three *Boostrix* groups. Following the booster dose, 207 of the 647 subjects reported at least one unsolicited AE (29.4%, 34.4% and 32.1% in the 0.133 mg, 0.3 mg and 0.5 mg Al groups, respectively). The most frequently reported unsolicited AE for all three Al formulations was upper respiratory tract infections (6.1%, 8.6% and 5.4% in the 0.133 mg, 0.3 mg and 0.5 mg Al groups, respectively). Further details are presented in the BLA.

3.11. Serious Adverse Events and Other Significant Adverse Events

In Study 001, in the month after vaccination with *Boostrix* or Td, no serious adverse events were reported in the 4,114 vaccinated subjects. In Study 004, in the month after vaccination with *Boostrix* or Td, 2 serious adverse events were reported in the 510 vaccinated subjects. In Study 029, in the month after vaccination with *Boostrix*, 3 serious adverse events were reported in the 648 vaccinated subjects. In the additional 9 safety studies included as safety synopses in the BLA, 3 SAEs were reported in the 1,343 subjects vaccinated with *Boostrix* and in two subjects vaccinated with a comparator. All SAEs were reported by the investigator as unrelated to vaccination.

Serious adverse events reported to occur within 31 days (Day 0 – 30) after vaccination in any of the BLA studies are summarized in Figure 34.

Figure 34 Serious Adverse Events (All Studies in BLA): Day 0 – 30

All Studies: Serious Adverse Events Day 0-30

Pivotal Study 001: None

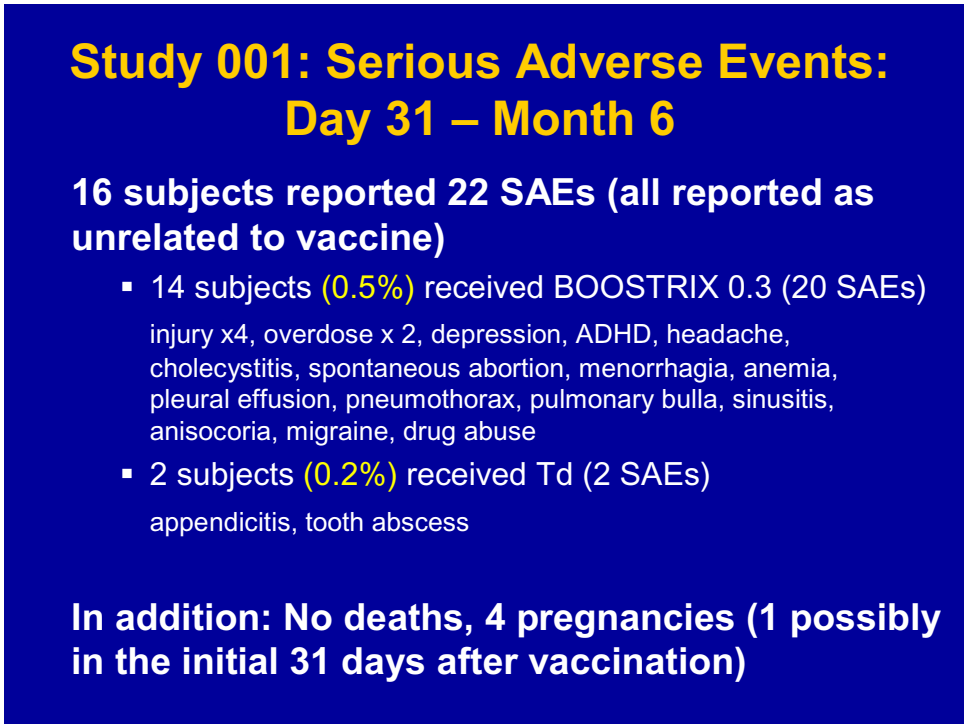
Supportive studies: 10 subjects reported 10 SAEs

Study	Onset	Age/Sex	Vaccines administered	SAE	Related to vaccine
004	20 d	11/F	BOOSTRIX 0.5	Diabetes Mellitus	No
004	23 d	11/F	BOOSTRIX 0.5	Appendicitis	No
029	21 d	13/M	BOOSTRIX 0.5	Cerebral concussion 2° vasovagal syncope and fall	No
029	37 d	11/F	BOOSTRIX 0.5	Diabetic coma	No
029	28 d	14/F	BOOSTRIX 0.3	Alcohol intoxication	No
01	0 d	12/F	BOOSTRIX 0.5	Syncope	No
02	7 d	49/F	BOOSTRIX 0.5	Uveitis	No
02	3 d	44/M	pa	Chest pain	No
118	29 d	6/F	BOOSTRIX 0.5	Adenoidectomy	No
118	24 d	6/M	Td	Burn	No

Boostrix 0.3 = GSK Biologicals' 0.3 mg Al formulation
Boostrix 0.5 = GSK Biologicals' 0.5 mg Al non-US *Boostrix* formulation
pa = GSK Biologicals' investigational reduced antigen content acellular pertussis vaccine
Td = Chiron-Behring's combined diphtheria and tetanus vaccine (Td-pur®)

In Study 001, all subjects were followed for an additional 5 month extended safety follow-up phase. As summarized in Figure 35, over this extended safety follow-up period, 16 subjects reported 22 SAEs; all were reported by the investigator as unrelated to vaccination; 14 or 0.5% of the subjects received *Boostrix* (20 SAEs were reported in this group) and 2 or 0.2% of the subjects received Td (2 SAEs were reported in this group).

Figure 35 Study 001: Serious Adverse Events: Day 31- Month 6



Boostrix 0.3 = GSK Biologicals' 0.3 mg Al formulation
Td = Massachusetts Public Health Biologic Laboratories' tetanus-diphtheria vaccine

There were no deaths reported in any of the clinical trials. In Study 001, there was one pregnancy that may have occurred during the initial 31-day period following vaccination. This subject received Td, was vaccinated 9 April 2003 and her last menstrual period began 11 April 2003. She delivered a healthy female infant by normal vaginal delivery on 29 Jan 2004, one day after her estimated date of delivery. Three pregnancies occurred in the extended safety follow-up phase of Study 001. The outcome for one of these pregnancies was a spontaneous abortion approximately two months after the last menstrual period. The outcomes of the other two pregnancies were healthy newborns.

3.12. *Boostrix* Safety - Conclusions

Based on the safety data from these studies, it can be concluded that:

The clinical safety experience with *Boostrix* in the US file is derived from data on 5,520 subjects, of which 3,289 adolescents received the US formulation with 0.3 mg Al and 2,231 subjects of all ages received *Boostrix* formulated with either 0.5 or 0.133 mg Al. Based on the safety and reactogenicity data from pivotal Study 001, it can be concluded that *Boostrix* is not inferior to US-licensed Td vaccine with respect to the incidence of Grade 3 pain at the injection site. The overall safety profile of *Boostrix* is comparable to US-licensed Td vaccines, and *Boostrix* is safe and well-tolerated among adolescents 10-18 years of age.

4. BENEFITS AND RISKS CONCLUSIONS

In pivotal Study 001, one month after vaccination, seroprotection rates against diphtheria and tetanus achieved by *Boostrix* were high. Non-inferiority of *Boostrix* compared to a US-licensed Td vaccine was demonstrated with respect to anti-D and anti-T seroprotection rates and with respect to anti-D and anti-T booster responses. Although long-term serological data following vaccination with the specific US formulation of *Boostrix* are not available, follow-up studies performed with the non-US 0.5 mg Al *Boostrix* formulation and a US-licensed Td vaccine demonstrate that 99.2% of the *Boostrix* and 100% of the Td vaccinees remained seroprotected against diphtheria, and that 100% of the *Boostrix* and Td vaccinees remained seroprotected against tetanus five years after booster vaccination. These data can be considered to provide a strong indication of the long-term anti-D and anti-T immunogenicity of the candidate vaccine because the 0.5 mg Al and 0.3 mg Al formulations produced similar immune responses in a head-to-head study (Study 029, data provided in BLA). Efficacy against diphtheria and tetanus will not be compromised when vaccinating subjects 10-18 years of age with *Boostrix* compared to US-licensed Td vaccines.

No safety issues were identified during the clinical development of *Boostrix.* The sample size of 3,080 US adolescent subjects who received *Boostrix* in pivotal Study 001 provided 90% power (with an alpha of 0.05) to detect any AEs that occurred at a frequency of 1/1000 or greater. In pivotal Study 001, the AE profile of *Boostrix,* throughout the 31-day period following vaccination and the additional five-month extended safety follow-up phase, was comparable to that of a US-licensed Td vaccine. In pivotal Study 001, large injection site swelling occurred in one subject (0.03%) vaccinated with *Boostrix* and in one subject (0.1%) vaccinated with the US-licensed Td vaccine. In both subjects, there was no involvement of the elbow or shoulder and both events resolved without sequelae. Large local injection site reactions after repeat vaccination with DTaP, DTPw, Td and other vaccines have been well described [Rennels 2003; Woo, 2003]. These events do not signal a new or unexpected safety issue. Based on the results in Study 001, the incidence of large injection site reactions after vaccinations with *Boostrix* is anticipated to be on the order of 0.03% – 0.8% in adolescents primed with either all whole-cell DTP or a combination of DTPw and DTaP. A sizeable cohort of adolescents in the US who have been primed throughout life with acellular pertussis-containing vaccines will not be evaluable until at least 2007.

Additional clinical trial experience with GSK Biologicals' non-US licensed 0.5 mg Al *Boostrix* formulation demonstrates no specific safety issues and supports the safety profile of the candidate vaccine as reported in the clinical studies in the BLA. Safety will not be compromised when vaccinating subjects 10-18 years of age with *Boostrix* compared to US-licensed Td vaccines.

Data on the safety and immunogenicity of *Boostrix* during pregnancy or lactation are not available. Given that the intended population for this vaccine includes women of child-bearing potential, a reproductive toxicology study was performed and no evidence of teratogenicity was observed. It is not known whether *Boostrix* can cause fetal harm when administered to a pregnant woman or if *Boostrix* can affect reproductive capacity. It is generally accepted that inactivated vaccines pose no risk to the pregnant or lactating woman [CDC, 2002b]. In the absence of supportive data, *Boostrix* should only be administered to pregnant women when clearly needed and when the possible benefit outweighs the potential risk. GSK Biologicals plans to establish a pregnancy registry post-licensure.

Boostrix has not been studied in immunosuppressed individuals or those with chronic disease. According to current guidelines, *Boostrix* may be used in these circumstances, however the immune response to vaccination may be reduced [CDC, 2002b; Loutan ,1997].

Pertussis disease is common among adolescents and adults and has important implications for clinical practice. *Boostrix* offers the opportunity to extend pertussis protection to older populations. In pivotal Study 001, anti-PT, anti-FHA and anti-PRN booster responses exceeded the pre-defined lower limit for a demonstration of a booster response. Antibody GMCs for anti-PT, anti-FHA and anti-PRN after vaccination with *Boostrix* were at least as high as or higher than those achieved by infants following primary immunization with *Infanrix* in a cohort in which efficacy against pertussis was subsequently demonstrated. Therefore, it is anticipated that *Boostrix* will be efficacious in preventing pertussis disease in adolescents. Although long-term serological follow-up data after vaccination with the US formulation of *Boostrix* are not available, data from Study 030 with the 0.5 mg Al non-US formulation are available and demonstrate five years after vaccination that GMCs to all pertussis antigens remain higher than pre-vaccination GMCs, although the anti-PT GMC approaches the pre-vaccination GMC. In addition, follow-up data from Italian infants vaccinated with a 3-dose primary series of *Infanrix* without a booster dose in the second year of life in an NIH-sponsored efficacy trial demonstrated *Infanrix* efficacy against WHO-defined typical pertussis to be 86% (95% CI 79-91%) to at least 6 years [Salmoso, 2001]. These data can be considered to provide an indication of the long-term anti-pertussis protection likely to be afforded by *Boostrix*.

The data presented and the balance of risks and benefits support the use of *Boostrix* to confer protection against diphtheria, tetanus and pertussis diseases with an acceptable safety and reactogenicity profile that is comparable to a US-licensed Td vaccine. By combining acellular pertussis antigens with the recommended adolescent Td booster vaccine, *Boostrix* will offer adolescents clear benefit providing needed protection against pertussis with no additional injection. For younger adolescents, an additional office visit

for the immunization is not necessary if coupled with the ACIP-recommended routine 11-12-year pre-adolescent assessment. In addition to the direct benefit to the vaccinee, the use of *Boostrix* may additionally reduce circulation of *B. pertussis* in the population and, therefore, also reduce the chance that susceptible persons are in contact with *B. pertussis* and become infected. The risk-benefit ratio is favorable for the intended population. The additional availability of *Boostrix* for individuals 10-18 years of age would add value to the current standard of medical care.

5. REFERENCES

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