Vaccines and Related Biological Products Advisory Committee

Meeting Date: March 15, 2005

FDA Clinical Briefing Document
for
Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine, Adsorbed (Tdap, ADACEL™)
Aventis Pasteur, Limited.

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1. INTRODUCTION

1.1. Product Description

ADACEL™ is the proposed trade name of Tdap vaccine, a reduced antigen preparation (less diphtheria toxoid and pertussis toxoid) of DAPTACEL®, the DTaP manufactured by Aventis Pasteur Limited and licensed in the U.S. for the first four doses of the primary series.

A summary of the compositions of diphtheria, tetanus and pertussis containing vaccines used in the clinical trials is shown in Table 1.1.

Table 1.1. Compositions of Tetanus, Diphtheria and Pertussis-Containing Vaccines Produced by Aventis Pasteur Limited

Antigen/Component	ADACEL™ (Tdap)	DAPTACEL®[1] (DTaP)	HCPDT[2]	Td[3]
Tetanus toxoid	5Lf	5 Lf	5 Lf	5 Lf
Diphtheria toxoid	2 Lf	15 Lf	15 Lf	2 Lf
PT	2.5 ug	10 ug	20 ug	-
FHA	5 ug	5 ug	20 ug	-
PRN	3 ug	3 ug	3 ug	-
FIM 2/3	5 ug	5 ug	5 ug	-
Al phosphate[4]	1.5 mg	1.5 mg	1.5 mg	1.5 mg
Other Ingredients				
2-phenoxyethanol	0.6% ± 0.1% (v/v)	0.6% ± 0.1% (v/v)	0.6% ± 0.1% (v/v)	-
Thimerosal	-	-	-	0.01%
Water for injection				

[1]DTaP – formulation evaluated in the Sweden I Efficacy Trial, and licensed in the U.S. for the primary series.
[2]HCPDT – higher antigen content vaccine, evaluated in the Sweden II Efficacy Trial.
[3]Produced by Aventis Pasteur Inc and licensed in the U.S.
[4]Aluminum = 0.33 mg

1.2. Indication Sought

The proposed indication for ADACEL™ is for the active immunization for prevention of diphtheria, tetanus and pertussis in adolescents and adults aged 11 through 64 years as a booster. The dosing schedule is one dose administered intramuscularly.

1.3. Regulatory History

1.3.1. Pertussis Vaccines: Demonstration of Efficacy in Adolescents and Adults - VRBPAC 1997

During deliberations in 1997, the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) considered performing a study to evaluate the efficacy of acellular pertussis vaccines (ACVs) in adolescents and adults to be a daunting task. No generally accepted serologic markers of protection for pertussis have been identified, which could facilitate the use of an immunologic correlate for evaluating efficacy of ACVs. VRBPAC suggested that an acceptable approach for evaluation of efficacy would be comparison of the immune responses following administration of an ACV in older age groups with the immune responses observed in infants following a primary series in trials, in which efficacy of the ACV had been demonstrated (e.g., Sweden I and II Efficacy Trials).

1.3.2. ADACEL™ BLA

The Biologics License Application (BLA) for this product was received by CBER on 13-Aug-04.

1.4. Basis for Licensure

The proposed clinical basis for licensure of ADACEL™ for adolescents and adults in the U.S. is:

- Demonstration of non-inferiority of the safety profile and immune responses of tetanus and diphtheria, as compared to a U.S.-licensed Td vaccine (Study Td506).

- Demonstration of non-inferiority of the immune responses to the pertussis antigens as compared to the immune responses observed in the Sweden I Efficacy Trial. The bridging of the serologic responses to the pertussis antigens elicited by Tdap in adolescents and adults (Td506) as compared to those following DTaP (DAPTACEL®) in infants in Sweden I Efficacy trial as measured in the ADACEL™ Serology Bridging Study.
- Demonstration of booster responses to all of the vaccine antigens in the Tdap.
- Demonstration of consistency of manufacture based on safety and immunogenicity of three consecutively produced Tdap vaccine lots (Study Td505).

In addition, concomitant administration data of Tdap with influenza vaccine in adults (Td502) and with hepatitis B vaccine in adolescents (Td501) have been provided.

Additional Supportive Trials

Abbreviated study reports containing data from three historical trials, which formed the basis of licensure for ADACEL™ in adolescents and adults in Canada and Germany, have also been submitted as supportive for the BLA. The data from these trials were used as follows:

- To provide 962 subjects (324 adolescents and 638 adults) to the safety database,
- For sample size calculations for studies Td501, Td502, Td505 and Td506, and
- To define the antibody cut-off values for booster response rates for diphtheria and tetanus.

2. BACKGROUND AND EPIDEMIOLOGY

2.1. Pertussis

Bordetella pertussis is increasingly recognized as a cause of chronic cough in adolescent and adults, and these older age groups are often implicated as the reservoir of infection for infants and children. In the United States, a 5 dose series of pertussis vaccinations (combined with diphtheria and tetanus toxoids) are administered to infants and children, with the 5th dose being given at 4-6 years of age. Whole-cell pertussis vaccines (WCV) were not given to anyone over 7 years because of concerns of adverse reactions, though waning vaccine immunity has been demonstrated. Waning vaccine-induced immunity from WCVs may be a contributor to the increase in pertussis cases reported in older children, adolescents and adults. With ACVs demonstrating less reactogenicity (as well as proven immunogenicity and efficacy) and the increasing recognition of pertussis in adolescents and adults, evaluation of ACVs in older age groups was undertaken.

2.2. Diphtheria

Diphtheria is caused by *Corynebacterium. diphtheriae*. This acute respiratory infection is characterized by formation of pharyngeal pseudomembranes, which may progress to airway obstruction. Routine immunizations in the U.S. have resulted in high levels of immunity in the population. Diphtheria toxoids (generally combined with tetanus toxoids) vaccinations are recommended by the Advisory Committee on Immunization Practices (ACIP) every 5-10 years after completion of the 5-dose series at 4-6 years of age.

2.3. Tetanus

Tetanus, caused by *Clostridium tetani*, is a severe acute infection characterized by painful muscle contractions. The organism is ubiquitous, though the disease has been controlled primarily due to routine immunization practices. In the U.S. and Canada, there are only 2-3 cases annually, mostly in people that have not received appropriate booster doses. Tetanus boosters are recommended by the ACIP every 5-10 years to maintain immunity.

3. SUMMARY TABLE OF ADACEL™ CLINICAL TRIALS

The BLA included safety and immunogenicity data from four clinical studies performed under U.S. IND, three study synopses (with safety data) from historical trials, and one supportive laboratory study.

Table 3.1a. Summary of Clinical Trials for ADACEL™ BLA

Study Number	Study Objectives	Age Range (Years)	Vaccine Groups	Number Enrolled	Trial Site
Pivotal					
Td506	1a. Tdap vs. Td for comparisons of dip and tet 1b. Tdap vs. DTaP (Sweden I Trial) for comparisons of pertussis antibodies	Adolescents (11-17) Adults (18-64)	Tdap, N=2936 Td, N=1365	Total=4480	U.S.
Td505	Evaluation of safety and immunogenicity to assess lot consistency	11-17	Tdap (lot 1) Tdap (lot 2) Tdap (lot 3)	Total =1811	U.S.
Non-Pivotal					
Td502	Safety and immunogenicity of Tdap with influenza vaccine	19-64	A; Tdap + Flu B: Tdap, Flu	Total=720 A= 359 B= 361	Canada
Td501	Safety and immunogenicity of Tdap with Hepatitis B vaccine	11-14	A: Tdap + Hep B B: Tdap, Hep B	Total = 410 A = 206 B = 204	Canada
Supportive					
TC9704	Evaluation of lot consistency to support licensure in Canada	12-54	Tdap (lot 1) Tdap (lot 2) Tdap (lot 3) Td + ap[1] ap + Td	Total=755 Tdap = 453	Canada
TD9707	Safety and immunogenicity of Tdap, or Td +ap or Td followed by ap	12-60	Tdap Td + ap Tdap, ap	Total=1214 Tdap=374	Canada
TD9805	Safety and immunogenicity of Tdap with Hepatitis B vaccine	11-14	Tdap + Hep B vs. Tdap, Hep B	Total=272	Canada
Lab Study					
Serology Bridging Study	Comparison of pertussis antibodies: Tdap (Td505) and DTaP (Sweden I)	Sweden I (2-7 mo) Td505 (11-17 yrs)	Sweden I - DTaP at 2,4 and 6 mo Td505 – 1 dose of Tdap	Paired Sera Sweden I, N=80 Td505, N=1056	CIP – CA[2]

[2]CIP-CA = Clinical Immunology Platform-Canada (Aventis Pasteur Ltd, in Toronto, Canada).
[1]ap=reduced antigen content acellular pertussis vaccine

The total number of individuals exposed to study vaccines (Tdap and Td) in clinical trials in the BLA is shown on Table 3.1b.

Table 3.1b. Summary of Number of Subjects Evaluated in ADACEL™ Clinical Trials.

			ITTS[1]		PPI[2]	
Trials	**Enrolled and Randomized**	**Completed**	**Tdap**	**Td**	**Tdap**	**Td**
Pivotal and Non-Pivotal						
Td506	4480	4320	2936	1365	1270	1026
Td505	1811	1791	1806	0	1056	0
Td502	720	696	696	0	678	0
Td501	410	392	403	0	312	0
Total	7421	7199	5841	1365	3316	1026
Supportive[3]						
TC9704	449	-	449	-	-	-
TD9707	244	-	244	-	-	-
TD9805	269	-	269	-	-	-
Total	962	-	962	-	-	-
ALL	8383		6803			

[1]ITTS – Study participants enrolled in the Intent-to-Treat Safety population (defined in each protocol)
[2]PPI – Study participants enrolled in the Per Protocol Immunogenicity population (defined in each protocol)
[3]Supportive trials contributed individuals to the safety database.

PIVOTAL TRIALS

Td506: Safety and Immunogenicity of Tetanus and Diphtheria Toxoids Adsorbed, Combined with Component Pertussis (Tdap) Vaccine Compared to Tetanus and Diphtheria Toxoids Adsorbed (Td) in Adolescents and Adults 11 to 64 Years of Age.

1. SUMMARY

Td506 was a multi-center, Phase 3, randomized, modified double blind, controlled trial evaluating Tdap vaccine in adolescents and adults, 11-64 years of age. The sponsor called this "modified" double blind because of the difference in presentation of the vaccines (single vs. multi-dose vials) so the personnel administering the vaccines were different from those collecting the safety data.

The Tdap vaccine was compared with a U.S. licensed Td (manufactured by Aventis Pasteur, Inc, Swiftwater, PA) to evaluate safety and to assess immunogenicity of diphtheria (dip) and tetanus (tet). Additionally, the immune responses to the pertussis antigens following Tdap were compared with responses of infants following a three dose primary series of DAPTACEL® from the Sweden I Efficacy Trial. A subset of 80 pairs of sera from Sweden I were assayed in 2002 (Serology Bridging Study described on page 44), and the antibody values were used for comparisons with those obtained in Td506. Booster responses to all of the vaccine antigens following Tdap were also evaluated.

The study met its primary objectives and the results are discussed below.

2. HYPOTHESIS AND OBJECTIVES

2.1. Primary Objectives

2.1.1. To assess the immunogenicity of the dip and tet of the Tdap vaccine compared to the licensed Td vaccine when given as a booster dose.

2.1.2. To assess the immunogenicity of the pertussis antigens of the Tdap vaccine when given as a booster dose compared to the immune responses from the historical controls from the Sweden I Efficacy Trial (DAPTACEL®).

2.2. Primary Hypotheses

The following hypotheses will be addressed for adolescents 11 to 17 years of age and adults 18 to 64 years of age, separately.

2.2.1. The anti-diphtheria toxin and anti-tetanus toxin responses for participants who receive Tdap Vaccine will be non-inferior to responses observed in recipients who receive Td Vaccine upon completion of a booster vaccination, assessed as the comparison of seroprotection rates at the $\geq$ 0.1 IU/mL level using the difference in rates between the groups.

2.2.2. The anti-diphtheria and anti-tetanus toxin booster responses for participants who receive Tdap Vaccine will be non-inferior to the booster responses elicited by the licensed Td vaccine; a booster response is defined as a four-fold response for participants with a pre-vaccination titer equal to or below the pre-defined cut-off level and a two-fold response for participants with pre-vaccination titers above the cut-off levels. The cut-off levels are: 2.56 IU/mL for diphtheria and 2.7 IU/mL for tetanus.

2.2.3. The anti-pertussis [PT, FHA, FIM and PRN] responses upon completion of a booster vaccination for participants who receive Tdap will be non-inferior to responses observed in recipients 1 month after completing a primary series of DAPTACEL® (Sweden I Efficacy trial) at 2, 4 and 6 months of age, assessed as the comparison of geometric mean concentration (GMCs) using the ratio of GMCs of Tdap vaccine and DAPTACEL®.

2.2.4. The anti-pertussis [PT, FHA, FIM and PRN] booster responses upon completion of a booster vaccination for participants who receive Tdap Vaccine will be comparable to acceptable boosting responses defined from the data observed in the supportive trials with Tdap Vaccine (81.2% for PT, 77.6% for FHA, 82.4% for FIM, 86.4% for PRN); a booster response is defined as a four-fold response for participants with a pre-vaccination titer equal to or below the pre-defined cut-off levels and a two-fold response for participants with pre-vaccination titers above the cut-off level. The cut-off levels are: for PT 85 EU/mL, for FHA 170 EU/mL, for FIM 285 EU/mL, for PRN 115 EU/mL, respectively (values defined based upon historical trials with Tdap).

Per the primary hypotheses for diphtheria and tetanus, the non-inferiority of Tdap vaccine to Td vaccine will be concluded if the lower limits of the 2-sided 95% CI of the difference in post-vaccination seroprotection rates (at the level of $\geq$ 0.1 IU/ml) and booster rates between the 2 groups are above –10%.

Per the primary hypothesis for the pertussis antigens, the non-inferiority of the Tdap vaccine to DAPTACEL (in the Sweden I Efficacy Trial) will be concluded if the lower limit (LL) of the 2-sided 95% CI of the post-vac GMCs ratio between the two vaccine groups is above 0.67.

2.3. Secondary Objective

To assess the erythema, swelling, pain and fever rates during Days 0-14 after the Tdap dose compared to the licensed Td vaccine when given as a booster.

2.4. Secondary Hypothesis

The following hypothesis was addressed for adolescents 11 to 17 years of age and adults 18-64 years of age, separately:

The erythema, swelling, pain and fever rates Days 0-14 after the Tdap dose will be non-inferior to the rates of these events after the licensed Td when given as a booster.

Per the secondary hypothesis, for erythema, swelling, pain and fever, the non-inferiority of Tdap vaccine to Td vaccine will be concluded if the upper limit (UL) of the 2-sided 95% CI of the differences in the event rates between the two groups is below 10%.

2.5. Observational Objective

To assess the safety profile of Tdap as compared to licensed Td for other solicited adverse events not evaluated in the secondary hypothesis and for unsolicited adverse events after the booster vaccination.

A summary of the study endpoints is shown in Table 2.1.

Table 2.1. Summary of Study Td506 Endpoints

Antigen	Endpoint	Criteria
Diphtheria	% booster % ≥0.1 IU/ml	95% CI δ < 10% 95% CI δ < 10%
Tetanus	% booster % ≥0.1 IU/mL	95% CI δ < 10% 95% CI δ < 10%
PT	GMC % booster*	90% CI ratio Tdap/Sweden I ≥ 0.67 95% CI > 80.8% (85 EU/ml)
FHA	GMC % booster*	90% CI ratio Tdap/Sweden I ≥ 0.67 95% CI > 79.5% (170 EU/ml)
Pertactin	GMC % booster*	90% CI ratio Tdap/Sweden 1 ≥ 0.67 95% CI > 86.2% (115 EU/ml)
Fim	GMC % booster*	90% CI ratio Tdap/Sweden 1 ≥0.67 95% CI > 81.7% (285 EU/ml)
Safety	Erythema, swelling, pain and fever	95% CI δ < 10%

*Booster response = 4-fold rise for values below and 2-fold rise for values above the pre-defined cutoff levels (for diphtheria: cut-off value = 2.56 IU/ml and for tetanus cut-off value =2.7 IU/ml)

3. STUDY DESIGN

Each subject received one injection of study vaccine (Tdap or Td) intramuscularly (IM). Five age categories were stratified across the 11-64 year age cohort (11-13y, 14-17y, 18-28y, 29-48y, and 49-64 years). Vaccine distribution within each age group was in a 3:2 ratio for adolescents and 3:1 for adults.

Safety Monitoring

- Immediate Adverse Events (AEs) – AEs that occurred within 30 minutes after vaccination
- Solicited local and systemic AEs - AEs (listed in Table Td506-3a.) were queried from Day 0-14 post-vaccination and recorded on diary cards.
- Unsolicited AEs:
    - Day 0-14 - Any AE that represented a change in health status or was considered to be associated with the vaccine, according to the participant, was collected.
    - Day 14-28 (Visit 2) - Any AE that elicited medical attention was to be reported.
    - After Visit 2 - Any AE that elicited a visit to a physician's office, an ER visit or hospitalization was queried at the 6 month follow-up call.
- Serious adverse events (SAEs) – were defined consistently with 21 CFR 312 including 1) death, 2) immediately life-threatening, 3) results in persistent or significant disability, 4) results in or prolongs an existing hospitalization, and 5) is a congenital anomaly or birth defect. Additionally, an important medical event may have been considered an SAE based upon medical judgment if it jeopardized the participant and may have required medical intervention to prevent one the listed outcomes. SAEs were actively queried at each study contact throughout the study period.

Solicited AEs

Solicited events included local injection site events (erythema, pain, swelling) and the systemic events of fever, chills, nausea, vomiting, diarrhea, generalized body aches/muscle weakness, tiredness/decreased

energy, and sore and/or swollen joints. The intensity of these events was classified as "mild," "moderate," "severe," as defined on Table Td506-3a. Two additional categories ("any," and "moderate and severe") were considered in the analyses. Rash was recorded as present or not present.

Table Td506-3a. Rating System for Local and Systemic Events

Adverse Event	Mild	Moderate	Severe
Erythema[1]	<10 mm	10-34 mm	≥ 35 mm
Swelling[1]	<10 mm	10-34 mm	≥ 35 mm
Fever[2]	≥ 38°C to ≤ 38.7 °C ≥ 100.4°F to ≤ 101.9 °F	≥ 38.8°C to ≤ 39.4 °C ≥ 102°F to ≤ 103 °F	≥ 39.5°C ≥ 103.1°F
Any of the Following: **Pain at site** **Chills** **Headache** **Generalized bodyache (and/or muscle weakness)** **Tiredness (and/or ↓ energy)** **Nausea** **Vomiting** **Diarrhea** **Sore and/or swollen joints** **Lymph node swelling**	Noticeable but did not Interfere with activities	Interfered with activities, but did not require medical care or absenteeism	Incapacitating, Unable to perform usual activities, may have/or required medical care or absenteeism
Rash[3]			
Limb Swelling[4]			

[1]Participant or parent was to record measurement daily.
[2]Temperatures were taken orally.
[3]A "rash" was intended to capture vaccine reactions and excluded obvious other rashes, e.g, poison ivy.
[4]Limb circumference was measured at baseline and daily from Day 0-14.

Unsolicited Adverse Event Monitoring
Unsolicited AEs were evaluated for three time periods post-vaccination: Days 0-14, Days 14-28 and Day 28 until the 6-month phone call. Events were classified and coded using MedRA Systems Organ Class (SOC) and preferred terms.

Immunogenicity Monitoring
Serum samples were obtained from the immunogenicity cohort on Day 0 (prior to vaccination) and Day 35 ± 7 days. Subjects from whom bleeds were obtained were randomized between the groups and within the entire age cohort throughout the trial.

Laboratory Methods
The Clinical Immunology Platform at Aventis Pasteur Inc. (CIP-US) performed the assays for diphtheria and tetanus antibodies. Seroneutralization assays were performed for dip antibodies (IUs/ml) and ELISA for tetanus antibodies with values in EUs/ml converted to IUs/ml. The CIP in Toronto, Canada (CIP-CA) performed the ELISA assays for pertussis antibodies, with results in EUs/ml. The assay methodologies were submitted for review and were considered acceptable for this application by CBER.

4. RESULTS

4.1. Study Population and Follow-up

4.1.1. Disposition of Participants

A total of 4480 participants were enrolled and randomized: 2053 were in the 11-17y age group (Tdap n=1225; Td n=818) and 2427 were in the 18-64 y age group (Tdap n=1807; Td n=600). A total of 4461 randomized participants were vaccinated.

4.1.2. Analysis Populations

Three analysis populations were used in this study:

- Intent-to-treat safety (ITTS) population – included all participants who were randomized and received a dose of study vaccine, Tdap or Td
- Intent-to-treat immunogenicity (ITTI) population – consisted of a subset of participants who were randomized and bled for immunogenicity analyses
- Per-protocol population immunogenicity – included all ITTI participants who had no major protocol violations (i.e. violations that might impact upon their immunologic responses, e.g. late phone calls for safety checks).

4.1.3. Demographic Characteristics

Adolescent Participants (11-17 years)

The mean ages for the adolescent study groups were 13.8 years for both the Tdap and Td vaccinees. In both vaccine groups, gender (50.1% female) and ethnic origins (~85% Caucasian, 9.3% Black, 2% Hispanic and 1% other) were similar.

Adult Participants (18-64 years)

The mean ages for the adult study groups were 39.3 years for the Tdap vaccine and 39.5 years for the Td vaccine group. A higher percentage of females (64%) than males was enrolled, and this was seen in both the Tdap and Td groups. The ethnic origins for adult enrollees were similar to those of the adolescent participants.

4.1.4. Vaccination History

A total of 76% of adolescents and 1.1% of adults reported a history of 5 previous doses of dip-tet-pertussis containing vaccines, and there were no differences between the Tdap and Td groups. The date of their last dip and/or tet vaccine was unknown for 46.6% of the adult subjects, and was between 5 and 9 years prior for 21.8% of adults.

4.2. IMMUNOGENICITY RESULTS

All analyses were performed on the ITTI and the PPI populations, though the PPI population was used for the primary analyses. A summary of the immunogenicity results for adolescent and adult Tdap and Td PPI groups is provided in Table Td506-4.2a.

The immunogenicity objectives were met for both adolescent and adult age groups.

Table Td506-4.2a. Summary of Immunogenicity Endpoints at One-Month Post-Vaccination

	Adolescents (11-17 years)				Adults (18-64 years)			
	Tdap		Td		Tdap		Td	
	n/N	%	n/N	%	n/N	%	n/N	%
Seroprotection ≥ 0.1 IU/ml								
Diphtheria	526/527	99.8	515/516	99.8	697/741	94.1	482/507	95.1
Tetanus	527/527	100	516/516	100	742/742	100	508/509	99.8
Booster Response Rates								
Diphtheria	501/527	95.1	489/515	95	646/739	87.4	422/506	83.4
Tetanus	483/527	91.7	471/516	91.3	468/742	63.1	340/509	66.8
PT	482/524	92	-	-	624/739	84.4	-	-
FHA	450/526	85.6	-	-	611/739	82.7	-	-
FIM	499/526	94.9	-	-	635/739	85.9	-	-
PRN	496/525	94.5	-	-	693/739	93.8	-	-
GMCs	**N**	**Post-GMC**	**N**	**Post-GMC**	**N**	**Post-GMC**	**N**	**Post-GMC**
Diphtheria(IU/ml)	527	8.5	516	7.1	741	2.5	507	2.4
Tetanus (IU/ml)	527	12.9	516	14.4	742	7.7	509	8.2
PT (EU/ml)	524	309.3	515	15.6	741	178.8	508	13.2
FHA (EU/ml)	526	214.8	515	20.9	741	192.9	507	19.3
FIM (EU/ml)	526	1792.4	515	28.8	741	852.7	507	31.7
PRN (EU/ml)	526	344.5	515	11.7	741	341.9	507	11.7

Adapted from Aventis Pasteur eBLA Table 5.8, page 90.
n, % = number and percent of participants with the specified seroprotection levels and booster response.
N = number of participants evaluated.
GMC = Geometric mean concentration, calculated excluding missing observations.

4.2.1. Diphtheria and Tetanus Results

4.2.1.1. Seroprotection Rates

Pre-vaccination rates for seroprotection for dip and tet were comparable between the Tdap and Td groups in both age groups.

For diphtheria, 1-month post-vac, seroprotection rates were 99.8% for adolescents in both Tdap and Td groups, and for adults the rates were 94.1% for Tdap and 95.1% for Td groups. With review of seroprotection across the adult age substrata (18-28, 29-48, and 49-64 years), rates declined with increasing age (Tdap: 98.9%, 97.5%, and 85.4% and Td: 100%, 97.2%, and 88.7% respectively).

For tetanus, 100% of adolescent and 99.8% of adults achieved seroprotective levels post-vaccination. Seroprotection rates of 100% were observed across all of the age substrata (11-13, 14-17, 18-28, 29-48 and 49-64 years), except one adult in the 49-64 year group.

4.2.1.2. Comparison of Seroprotection Rates (Primary Objective)

Non-inferiority of Tdap compared to Td for both dip and tet was demonstrated, with the lower limit (LL) of the 95% CI for the difference in seroprotection rates > -10%. See Table Td506-4.2b.

Table Td506-4.2b. Diphtheria and Tetanus: Comparison of Seroprotection Rates[1] between Tdap and Td Groups at One-Month Post-Vaccination

Antigen	Age in Years	Seroprotection Rate				
		Tdap Rate %	Td Rate %	Diff %	LCL	UCL
Diphtheria	11-17	99.8	99.8	0	-0.53	0.54
	18-64	94.1	95.4	-1.01	-3.55	1.53
Tetanus	11-17	100	100	0	0	0
	18-64	100	99.8	0.2	-0.19	0.58

Adapted from Aventis Pasteur eBLA, Tables 5.9 - 5.12, pages 94 - 98.
[1] Seroprotection defined ≥ 0.1 IU/ml for dip and tet.
Diff % = Difference between Tdap and Td groups
LCL, UCL = Lower and upper limits of the 2-sided 95% CI for the difference in proportions.
In 11-17 year group, Tdap (PPI = 527) and Td (PPI=516)
In 18-64 year group, Tdap (PPI=743) and Td (PPI=510)

4.2.1.3. Booster Response Rates

Booster response rates for dip and tet were similar between the Tdap and Td groups in both the adolescent and adult groups. Rates for dip were 95.1% for Tdap and 95% for Td for 11-17 year, and 87.4% for Tdap and 83.4% for Td for the 18-64 year group. Booster response rates for tetanus were 91.7% for Tdap and 91.3% for Td for the 11-17 year group and 63.1% in the Tdap and 66.8% in the Td adult groups.

4.2.1.4. Comparison of Booster Response Rates (Primary Objective)

For both dip and tet, non-inferiority of booster response rates was observed between the Tdap and Td groups (the difference in the rates LL of 95% CI > -10%) in adolescents and adults,

Table Td506 4.2c. Diphtheria and Tetanus: Comparison of Booster Rates[2] Between Tdap and Td Groups at One-Month Post-Vaccination

Antigen	Age in Years	Booster Response Rates				
		Tdap Rate %	Td Rate %	Diff %	LCL	UCL
Diphtheria	11-17	95.1	95.0	0.11	-2.53	2.76
	18-64	87.4	83.4	4.02	-0.01	8.04
Tetanus	11-17	91.7	91.3	0.37	-3.02	3.76
	18-64	63.1	66.8	-3.72	-9.09	1.64

Adapted from Aventis Pasteur eBLA, Tables 5.9 - 5.12, pages 94 - 98.
[1]Booster Responses defined: for diphtheria: 4-fold rises if pre-vac titers were ≤ 2.56 IU/ml or 2-fold rises if pre-vac titer were >2.56 IU/ml and for tetanus: 4-fold rises if pre-vac titers were ≤ 2.7 IU/ml or 2-fold rises if pre-titers were >2.7 IU/ml
Diff % = Difference between Tdap and Td groups
LCL, UCL = Lower and upper limits of the 2-sided 95% CI for the difference in proportions.
In 11-17 year group, Tdap (PPI = 527) and Td (PPI=516)
In 18-64 year group, Tdap (PPI=743) and Td (PPI=510)

4.2.1.5. Additional Analyses for Diphtheria and Tetanus

4.2.1.5.1. Seroprotection ≥ 1.0 IU/ml

For diphtheria, 98.7% of Tdap and 98.4% of Td groups in the adolescent age group and 78% of Tdap and 79% of the Td group in the adult age group achieved seroprotective levels of ≥ 1.0 IU/ml post-vaccination.

For tetanus, 99.6% of Tdap and 99.4% of Td in the adolescent group and 97.8% of Tdap and 98.2% of the Td group in the adult age group achieved seroprotective levels of ≥ 1.0 IU/ml post-vaccination.

4.2.1.5.2. Geometric Mean Concentrations (GMCs)

Robust rises in GMCs from pre- to post-vaccination were observed for both dip and tet, and post-vac GMCs are shown on Table Td506-4.2a. Pre-vaccination GMCs for dip and tet were similar between the Tdap and Td groups in both age groups, *data not shown*.

4.2.1.5.3. Comparison of GMCs

Statistical comparisons of dip and tet GMCs using 90% CI for the GMC ratios for both antigens between Tdap and Td showed non-inferiority of Tdap vaccine compared to Td vaccine (LL of 90% CI of the GMC ratio was above 0.67) for adolescents and adults. Non-inferiority was also demonstrated for comparisons using the 95% CIs.

4.2.2. Pertussis Results

4.2.2.1. GMCs in Tdap Recipients

Generally, adolescents achieved higher GMC ratios pre-to-post vaccination titers for the pertussis antigens than those observed in adults, though robust increases post-vaccination were observed across the entire study cohort 11-64 years. Responses to PT and FIM varied across the five age subgroups and consistently decreased with age. However, responses to FHA and PRN were less variable and showed no pattern of decrease across the age subgroups. The post-vaccination GMCs are shown on Table Td506-4.2a. For the Td group, no remarkable rises in pertussis GMCs were observed.

4.2.2.2. Comparisons of GMCs to Sweden I GMCs (Primary Hypothesis)

One-month post-vaccination GMCs were consistently higher among Tdap recipients in Td506 (adolescents and adults) than those observed in infants following three doses of the primary series with DTaP (DAPTACEL®) in Sweden I Efficacy Trial.

Non-inferiority of the responses of adolescents and adults compared to those from the Sweden I trial was demonstrated: the lower limit of the 95% CI for the ratio of GMCs for all of the pertussis antibodies was above 0.67 (Table Td506-4.2d).

Reverse cumulative distribution curves showed that the pertussis antibodies in Td506 (for pre and post-vaccination levels) in both adolescent and adult participants were consistently higher than those in the Sweden I participants (Figures Td506 5.2-5.8 in Appendix 1).

Table Td506-4.2d. Pertussis Antigens: Comparison of GMCs between ADACEL Recipients in Td506 (Adolescent and Adult Groups) and DTaP Recipients in Sweden I Efficacy Trial

Antigen (EU/ml)	Time[1]	Tdap in Td506		DTaP in Sweden I		Tdap vs. DTaP	
		M	GMC	M	GMC	GMC Ratio	95% CI
ADOLESCENTS							
PT	Pre	527	14.5	80	5.2	2.8	2.06, 3.70
	Post	524	309.3	80	86.6	3.6	2.83, 4.52
FHA	Pre	527	19.5	80	5.2	3.7	2.81, 4.99
	Post	526	214.8	80	39.9	5.4	4.46, 6.49
FIM	Pre	527	25.8	80	13.3	1.9	1.52, 2.5
	Post	526	1792.4	80	341.1	5.3	3.90, 7.09
PRN	Pre	526	10.0	80	2.2	4.7	3.46, 6.3
	Post	526	344.5	80	108.1	3.2	2.48, 4.10
ADULTS							
PT	Pre	741	12.5	80	5.2	2.4	1.80, 3.18
	Post	741	178.8	80	86.6	2.1	1.58, 2.70
FHA	Pre	741	18.1	80	5.2	3.5	2.68, 4.52
	Post	741	192.9	80	39.9	4.8	3.94, 5.92
FIM	Pre	741	28.6	80	13.3	2.2	1.63, 2.84
	Post	741	852.7	80	341.1	2.5	1.77, 3.54
PRN	Pre	741	8.5	80	2.2	3.9	2.89, 5.36
	Post	741	341.9	80	108.1	3.2	2.25, 4.44

Adapted from Aventis Pasteur eBLA Table 5.16 and 5.17, pages 105-106.
Adolescents = 11-17 years; Adults = 18-64 years
DTaP = DAPTACEL (See Table 1.1 for composition)
[1]Time = pre or post vaccination
M= number of participants evaluated, excluding missing observations, used for calculating GMCs; for Sweden 1 Efficacy trial, in a subset of sera (N=80) evaluated in Serology Bridging Study.
GMC Ratio = ratio of Tdap and DTaP GMCs
95% CI = 95% Confidence Intervals

4.2.2.3. Booster Responses (Co-Primary Objective)

For each pertussis antigen, the LL of the 95% CI for the booster rate is above the pre-defined acceptable rate (as defined from the historical trials) for both adolescent and adult Tdap recipients. In addition, the Tdap vaccine elicited booster responses to each of the pertussis antigens in $\geq$ 80% of adolescent and adult recipients, shown in Table Td506-4.2e.

For the Td group, no remarkable booster responses to the pertussis antigens were seen.

Table Td506 4.2e. Booster Response Rates to Pertussis Antigens for Adolescent and Adult Tdap Recipients in Td506

		1 Month Post-Vaccination					
Antigen (EU/ml)	**Age (Years)**	**M[1]**	**n**	**%**	**LCL**	**UCL**	**Pre-Defined Acceptable Rate[2]**
PT	11-17	524	482	92	89.3	94.2	81.2
	18-64	739	624	84.4	81.6	87.0	
FHA	11-17	526	450	85.6	82.3	88.4	77.6
	18-64	739	611	82.7	79.8	85.3	
FIM	11-17	526	499	94.9	92.6	96.6	82.4
	18-64	739	635	85.9	83.2	88.4	
PRN	11-17	525	496	94.5	92.2	96.3	86.4
	18-64	739	693	93.8	91.8	95.4	

Adapted from Aventis Pasteur eBLA Table 5.18, page 116.
[1] M= number of participants used for calculating the percent. Participants missing observations and participants not evaluated are not included (M=N-missing).
Total possible participants: for 11-17 years, N=527; for 18-64 year, N=743.
[2]The values were the same for the adolescents and adult populations.
n, % = Number and percent (n/M) of participants with booster response, defined as post/pre-titer $\geq$ 4-fold for pre-titers $\leq$ 85 for PT, $\leq$ 170 for FHA, $\leq$ 285 for FIM and $\leq$ 115 for PRN **OR** $\geq$ 2-fold for pre-titers above the specified value for each antigen.

4.3. SAFTEY RESULTS

Clinical safety data were analyzed using the ITTS population. Overall, the safety profiles in both adolescents and adults were comparable between the Tdap and Td groups. An overview of safety results is provided in Table Td506-4.3a.

Table Td506-4.3a. Overview of Safety: Number and Percentage of Participants with Any Solicited Events, Immediate Adverse Events, Unsolicited Adverse Events or Serious Adverse Events in Adolescents and Adults

	Adolescents				Adults			
	Tdap		Td		Tdap		Td	
Type of Adverse Event	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Immediate AE	6/1184	0.5	5/792	0.63	4/1752	0.23	1/573	0.2
Any Solicited Local Reactions (Days 0-14)	952/1184	80.4	586/792	74.0	1199/1752	68.4	384/573	67.0
Any Solicited Systemic Events (Days 0-14)	776/1184	65.5	483/792	61.0	881/1752	50.3	273/573	47.6
Solicited Reactions (Days 0-14)								
Erythema	244/1175	20.8	155/787	19.7	420/1698	24.7	121/561	21.6
Swelling	246/1175	20.9	144/787	18.3	356/1698	21.0	97/561	17.3
Pain	914/1175	77.8	559/787	71.0	1115/1698	65.7	353/561	62.9
Fever ($\geq$ 38°C/100.4°F)	58/1170	4.9	21/783	2.7	24/1688	1.4	6/551	1.1
Solicited Reactions (Days 0-3)								
Erythema	239/1175	20.3	152/787	19.3	392/1698	23.1	117/561	20.9
Swelling	245/1175	20.9	136/787	17.3	336/1698	19.8	92/561	16.4
Pain	912/1175	77.6	555/787	70.5	1086/1698	64.0	346/561	61.7
Fever ($\geq$ 38°C/100.4°F)	34/1170	2.9	12/782	1.5	14/1685	0.8	2/551	0.4
Unsolicited AEs (Days 0-28)	301/1184	25.4	202/792	25.5	375/1752	21.40	120/573	20.9
Unsolicited AEs (> Day 28)	474/1184	40.0	289/792	36.5	391/1752	22.31	106/573	18.5
Serious AEs	11/1184	0.9	8/792	1.0	33/752	1.9	11/573	1.9

Adapted from Aventis Pasteur eBLA, Tables 5.19 and 5.20 pages 118 – 119.
n= number of participants reporting the event.
For adolescents, Tdap Vaccine (N=1184) and Td Vaccine (N=792).
For adults, Tdap Vaccine (N=1752) and Td Vaccine (N=573).

4.3.1. Immediate Adverse Events

Sixteen participants experienced 24 immediate AEs: 10 Tdap (6 adolescents + 4 adults) and 6 Td (5 adolescents + 1 adult) vaccinees. All 16 subjects recovered without sequelae. No anaphylaxis events were reported. Fourteen of the 24 events were classified under nervous system, e.g. syncope, vasovagal event, etc.

4.3.2. Solicited Local Reactions

4.3.2.1. Solicited Local Reactions – Adolescents

The majority of adolescent participants reported at least one solicited local AE from Days 0-14; 80.4% of Tdap and 74% of Td vaccinees. The frequency and intensity of solicited local AEs were comparable between the Tdap and Td groups. The occurrence of solicited AEs was highest from Days 0-3, and declined from Days 4-14 for both vaccine groups.

Pain was the most frequent local reaction reported by both vaccine groups from Days 0-14 and at all time points. From Days 0-14, pain was reported by 77.8% of Tdap and 71.0% of Td recipients.

The rates of erythema were higher in the younger age group (11-13 years, Tdap=24.5% and Td=21.0%) compared to the older age group (14-17 years, Tdap=17% and Td=18.3%). A trend for higher rates of swelling was also seen in the younger subjects but no appreciable difference was observed for pain. No formal statistical comparisons between age strata were planned or performed.

Other Local AEs

The occurrence of "any" axillary lymph node swelling was reported 6.6% of Tdap and 5.3% of Td recipients. Late onset local AEs were uncommon ($\leq$ 1%) and similar for the two vaccine groups.

Rates of recurrence (defined as onset from Days 0-3 and re-occurrence prior to Day 14) for erythema, swelling and pain were comparable between the two vaccine groups, with each event occurring between 5 and 10% of the Tdap and Td groups.

Changes in limb circumference from baseline were comparable between the two vaccine groups, with the mean change of 1.3 cm for the Tdap group and 1.4 for the Td group.

4.3.2.2. Solicited Local Reactions – Adults

The patterns of local AEs in the adult population were similar to those in the adolescent participants, though a trend for decreased frequency of events in the older age groups was seen. The majority of adult participants reported at least one solicited local AE from Days 0-14; 68.4% of Tdap and 67.0% of Td vaccines, results shown on Table Td506-4.3a. The frequency and intensity of solicited local AEs were comparable between the Tdap and Td groups at all time points evaluated.

Pain was the most frequent local reaction reported by both vaccine groups (65.7% of Tdap and 62.9% of Td recipients) from Days 0-14 and at all time points evaluated.

Other Local AEs

The occurrence of "any" axillary lymph node swelling was reported by 6.5% of Tdap and 4.1% of Td recipients. Late onset local AEs were uncommon ($\leq$ 1.7%) and similar for the two vaccine groups.

Rates of recurrence for erythema, swelling and pain were comparable between the Tdap and Td recipients, with 5 to 6% of each group reporting recurrence of each of these AEs.

Changes in limb circumference from baseline were comparable between the two vaccine groups, with the mean change of 1.5 cm for the Tdap group and 1.3 for the Td group.

4.3.2.3. Comparison of Erythema, Swelling and Pain Rates – Secondary Hypothesis for Adolescents and Adults

Pain was more frequent in the adolescent group for "any" intensity following Tdap, with the upper limit of the 95% CI = 10.72% for the difference in the rates between Tdap and Td groups. Non-inferiority was demonstrated for "moderate and severe" intensity for pain in adolescents, and for pain of "any" and "moderate and severe" intensities for the adults.

Non-inferiority was demonstrated for "any" and "moderate and severe" erythema and swelling for both the adolescent and adult groups.

4.3.3. Solicited Systemic Reactions

A summary of the solicited systemic event rates is shown in Table Td506-4.3b.

Table Td506-4.3b. Overview of Solicited Systemic Adverse Events: Number and Percentage of Adolescent and Adult Participants with "Any" Solicited Systemic Event from Days 0-14

	Adolescents				Adults			
	Tdap		Td		Tdap		Td	
Type of Adverse Event	n/N	%	n/N	%	n/N	%	n/N	%
Any Solicited Systemic Events	952/1184	80.4	586/792	74.0	1199/1752	68.4	384/573	67.0
(Days 0-14)	776/1184	65.5	483/792	61.0	881/1752	50.3	273/573	47.6
Solicited Reactions (Day0-14)								
Fever (≥ 38°C/100.4°F)	58/1170	5.0	21/783	2.7	24/1688	1.4	6/551	1.1
Headache	514/1175	43.7	318/787	40.4	575/1698	33.9	191/560	34.1
Generalized Body Aches	357/1175	30.4	235/787	29.9	371/1697	21.9	105/560	18.8
Tiredness/Decreased Energy	355/1175	30.2	215/787	27.3	413/1698	24.3	116/560	20.7
Chills	177/1175	15.1	99/787	12.6	138/1698	8.1	37/560	6.6
Nausea	156/1175	13.3	97/787	12.3	156/1698	9.2	44/560	7.9
Vomiting	54/1175	4.6	22/787	2.8	51/1698	3.0	10/560	1.8
Diarrhea	121/1175	10.3	80/787	10.2	175/1697	10.3	63/560	11.3
Sore and/or Swollen Joints	133/1175	11.3	92/787	11.7	155/1697	9.1	39/560	7.0
Presence of Rash	32/1174	2.7	6/787	2.0	34/1697	2.0	13/560	2.3
Solicited Reactions (Days 0-3)								
Fever (≥ 38°C/100.4°F)	34/1170	2.9	12/782	1.5	14/1685	0.8	2/551	0.4
Serious AEs	11/1184	0.9	8/792	1.0	33/752	1.9	11/573	1.9

Adapted from Aventis Pasteur eBLA, Tables 5.36 – 5.45 and 5.46-5.55, pages 142-162.
n/N= Number of participants with the event/number of participants reporting (excluding subjects without observations).
% - Percent value is based on the number evaluated (excluding missing observations, n1).
Days 0–3, Days 0–14: Maximum intensity of events reported during the time period.
Presence of Rash - includes the number of participants reporting rash.

4.3.3.1. Solicited Systemic AEs - Adolescents

In adolescents, 65.5% of Tdap and 61% of Td recipients experienced at least one solicited systemic AE from Days 0-14. The frequency and maximum intensity of each of the solicited systemic AEs were comparable between the Tdap and Td groups at all time points evaluated.

Fever (above 38°C) was reported by 5.0% of Tdap and 2.7% of Td recipients from Days 0-14, and the rates of fever were similar in the Days 0-3 and Days 0-14 time periods. The rate of fever > 39.5°C was 0.17% in Tdap and 0.13% in the Td group.

From Days 0-14, headache was the most common systemic AE reported in both groups; 43.74% in Tdap and 40.41% in the Td group. Sore and/or swollen joints occurred in 11.3% of Tdap group and 11.7% of Td group.

Most of the systemic AEs were reported as "mild" in intensity. Less than 2% of each group scored any individual AE as "severe."

4.3.3.2. Solicited Systemic AEs - Adults

As observed with local AEs, reports of systemic AEs were less frequent in adults than in adolescents. In adults, 50.3% of Tdap and 47.6% of Td recipients experienced a solicited systemic AE from Days 0-14. The frequency and maximum intensity of each of the solicited systemic AEs were comparable between the Tdap and Td groups for all time points.

Fever (above 38^{o}C) was reported by 1.4% of Tdap and 1.1% of Td recipients from Days 0-14. Fever $\geq$ 39.5^{o}C occurred in 0.24% in Tdap and 0.18% in the Td group.

From Day 0-14, headache was the most common systemic AE reported in both groups, occurring in 33.9% in Tdap and 34.1% in the Td group.

Most of the systemic AEs were reported as "mild" in intensity. There was similar occurrence of solicited systemic AEs across the Days 0-14 period in both the Tdap and Td groups.

4.3.3.3. Comparison of Fever Rates in Adolescents and Adults (Secondary Hypothesis)

The rate of fever during Days 0-14 after Tdap was non-inferior to the rate after Td in both adolescents and adults, with the upper limit of the 95% CI being < 10% for the differences in fever rates for "any" and "moderate and severe" intensities.

Additionally, no differences in the rates of any of the other systemic AEs for adolescent or adults were apparent (exploratory analysis).

4.3.4. Additional Safety Analyses

To explore additional areas of interest including gender differences, the potential relationship between antibody responses and AEs, as well as limb circumference size, were evaluated. Formal statistical comparisons were not planned or performed.

4.3.4.1. Rates of AEs by Gender

Rates of AEs were evaluated by gender and for subgroups of adolescents and adults. Generally, the rates of solicited AEs occurred at a higher rate in females in both vaccine groups, and this was more pronounced in adults than adolescents.

4.3.4.2. Solicited Local AEs in Relationship to Pre- or Post-Vaccination Antibodies

To address the concern that there is increased reactogenicity observed with higher antibody levels, exploratory analyses were presented for participants with "severe" erythema or swelling ($\geq$35 mm) or "severe" pain and pre- or post-vaccination antibodies to diphtheria, tetanus, and PT. No associations of these antibodies and severe local AEs were evident.

4.3.4.3. Limb Circumference and Injection Site Swelling

There was no apparent relationship between limb circumference increases ($\geq$ 3cm) and the size of local injection site swelling, as identified upon exploratory review of these two parameters for all 14-day observations for participants who had at least one recording of limb circumference increase $\geq$ 3 cm.

4.3.5. Unsolicited Adverse Events (AEs)

Between Days 0 and 28 an unsolicited AE of any System Organ Classification (SOC) was reported for 25.4% of Tdap and 25.5% of Td recipients in the adolescent age group and 21.4% of Tdap and 20.9% of Td recipients in the adult population. The most frequently reported events

were classified as "Infectious and Infestations" with nasopharyngitis and pharyngitis being the most common. There were no apparent differences between the Tdap and Td groups.

4.3.5.1. Pregnancy

Thirty women (a total of 31 pregnancies) became pregnant during the study period. Outcome was known for 29 of the 31 pregnancies, and 19 of these 29 resulted in healthy full term infants. There were 5 spontaneous abortions (Tdap n=4 and Td n=1), 1 therapeutic abortion, and 4 premature infants (all otherwise healthy). No congenital abnormalities were reported.

4.3.6. Serious Adverse Events (SAEs)

A total of 83 SAEs were reported in 66 participants over the entire study period for all randomized participants. Seventy-nine (79) of the 83 SAEs were reported in 63 of 4301 (1.5%) participants; of these 44/2976 (1.5%) were in Tdap recipients and 19/1365 (1.4%) were in Td recipients. Twenty-four of the SAEs occurred in adolescents and 55 occurred in adult participants. Most of the events were hospitalizations. No deaths were reported.

Two SAEs in adults following Tdap were neuropathic events and appeared plausibly associated with receipt of the Tdap vaccine. These events included one hospitalization for severe migraine with unilateral facial paralysis in a 26 year old female on the day of Tdap vaccination. The subject had elevated BP (160/100) at the time of vaccination and a history of headaches. She recovered without sequelae. Another hospitalization occurred for a 49 year old female 12 days post-Tdap for symptoms of dysaesthesia in her neck and left arm. She was evaluated for possible myocardial infarction, and was diagnosed with nerve compression, which was treated with neurontin and celebrex. Although she did not return for the follow-up evaluations, she reported that all symptoms had resolved. No other neuropathic SAEs were reported.

Three seizure events reported, two in adolescent male Tdap recipients with pre-existing histories of seizure disorders and one seizure event that occurred 22 days after Tdap in a 55 year old female with a history of migraines and hypertension. This subject did not have a history of seizures, and the event reportedly resolved without sequelae. Two new-onset diabetes mellitus diagnoses were reported as SAEs; one in an 11 year old male 105 days after Td and one as an incidental finding in a 56 year old male admitted to the hospital after trauma who was also found to have a suprasellar mass and hyperglycemia.

5. ASSESSMENT of Td506

The primary and secondary objectives for this trial were met. Non-inferiority was demonstrated for the safety and immunogenicity profiles of Tdap as compared to U.S. licensed Td, in both adolescents and adults. Only one parameter, for safety ("any pain" in adolescents), slightly exceeded the 10% limit for the 2-sided 95% CI. Although this difference was statistically significant, it is not likely clinically meaningful. No differences between the groups were observed for moderate and severe pain.

The immune responses to the pertussis antigens following one dose of Tdap in both adolescents and adults were found to be non-inferior to those observed following three doses of DTaP in infants in the Sweden I Efficacy Trial, where efficacy of DTaP was estimated at 85% against *B. pertussis* infection associated with 21 days of cough.

This study shows that the Tdap in adolescents and adults has a safety profile that is similar to that of a U.S. licensed Td, and that Tdap elicits immune responses in adolescents and adults that are non-inferior to those observed following DTaP in infants, which has proven efficacy.

Td505: Safety and Immunogenicity of Three Lots of Tetanus and Diphtheria Toxoids Adsorbed, Combined with Component Pertussis (Tdap) Vaccine in Adolescents 11 to 17 Years of Age.

6. SUMMARY

Td505 was a Phase 3, randomized, double-blind, multi-center trial designed to assess lot consistency as measured by the safety and immunogenicity of 3 lots of Tdap when given as a booster dose to adolescents 11-17years of age. Participants in the trial were stratified into 2 age groups, 11 to < 14 years and ≥ 14 to ≤ 18 years. Adolescents were chosen for this evaluation of lot consistency because this population was more uniform in age and previous immunizations against diphtheria, tetanus and pertussis.

As the primary objective, the immunogenicity of the 3 lots of Tdap vaccine in a subset of participants was compared to assess the consistency of manufacturing. Safety assessment was the secondary objective, and parameters measured were similar to those in Td506.

This study met its objective of demonstrating lot consistency as measured by safety and immunogenicity, with the exception of a single immune parameter (post-vaccination FIM GMC ratio between Lot Tdap2 and Tdap3, upper limit of the 90% CI = 1.55, exceeding the 1.5 limit), among multiple comparisons. Additionally, the immunogenicity results were evaluated as part of the Serology Bridging Study (described on page 44). This study also contributed approximately 1800 adolescent subjects to the safety database for the BLA.

7. HYPOTHESES AND OBJECTIVES

7.1. Primary Objective and Hypothesis

7.1.1. Primary Objective

To assess the lot consistency of the Tdap vaccine manufacturing process through evaluation of the immune responses elicited by 3 lots when given as a booster dose.

7.1.2. Primary Hypothesis

The anti-pertussis (PT, FHA, FIM, and PRN), anti-dip, and anti-tet antibody responses will be similar in recipients of each of 3 Tdap lots upon completion of a booster vaccination.

The statistical criterion for concluding consistency in the serology responses among the 3 lots that supports the primary hypothesis was based upon the comparisons of seroprotection rates (≥ 0.1 IU/ml) for dip and tet and the comparisons of GMCs for pertussis antigens. Comparisons of the booster rates and GMCs for diphtheria and tetanus were also performed, per CBER's request.

The following criteria were used to establish consistency of Lots 1, 2, and 3: if the 2-sided 95% CI of the difference in post-vaccination seroprotection rates and booster rates between each 2 lots (Lots 1 and 2, Lots 1 and 3, and Lots 2 and 3) were within the interval (-10%, 10%), and the 2-sided 90% CI for Lot 1/Lot 2, Lot 1/Lot 3 and Lot 2/Lot3 post-vac GMC ratios were within the interval (0.67, 1.5), it was concluded that the lots were consistent.

7.2. Secondary Objective and Hypothesis

7.2.1. Secondary Objective

To assess the erythema, swelling, pain and fever rates elicited by 3 lots of Tdap vaccine during Days 0-14 after the vaccine is given as a booster dose.

7.2.2. Secondary Hypothesis

The erythema, swelling, pain and fever rates will be similar between the 3 lots of Tdap when given as a booster dose.

An analysis was performed on adverse events (AEs) during Days 0-14 that were rated as either "any" or "moderate and severe" intensity. If the 2-sided 95% CI on the difference between Lots 1, 2 and 3 (Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3) in rates of erythema, swelling, pain, and fever were within the interval (-10%, 10%), this was evidence of consistency of safety among the 3 lots with respect to each event.

7.3. Observational Objective

To assess the safety profile of Tdap by comparing between lots the proportions of other solicited AEs not evaluated in the secondary objective and the proportions of unsolicited AEs after completing the booster dose.

8. STUDY DESIGN

Participants were randomized to one of 3 vaccine groups (3 lots of Tdap). Each participant had 2 study visits. At Visit 1 on Day 0, each participant received one IM dose of Tdap and then returned for Visit 2 on Day 35 ($\pm$ 7 days, range 28-42 days) for safety check and immunogenicity assessments (subset).

Safety Monitoring – Safety monitoring was performed similarly to Td506, though no 6-month follow-up checks were performed. Serious adverse events (SAEs) were collected throughout the study period.

Immunogenicity Monitoring - Blood samples were obtained from a randomly selected subset of subjects prior to vaccination on Visit 1 (Day 0) and again at Visit 2 (Day 28 – 42) for immunogenicity analyses.

9. STUDY PROCEDURES

General study procedures, including statistical methodology, were followed similarly to those of Td506.

9.1. Definition of Populations

Three analysis populations were used in this study:

- Intent-to-treat safety (ITTS) population – included all participants who were randomized and received a Tdap vaccine. Participants who were randomized to receive one lot of Tdap but received another lot were included into the lot that they actually received.
- Intent-to-treat immunogenicity (ITTI) population – consisted of a subset of participants who were randomized and vaccinated, and bled for immunogenicity analyses.
- Per-protocol population immunogenicity – included all ITTI participants who had no major protocol violations (i.e. violations that might impact upon their immunologic responses).

10. RESULTS

10.1. Disposition of Participants

A total of 1811 subjects were enrolled and randomized, 603 subjects each in Tdap1 and Tdap 3, and 605 subjects in Tdap2. Twenty participants of the 1811 (1.2%) discontinued early from the trial, and this was balanced between the 3 lots of Tdap.

10.2. Demographic Characteristics

The number of participants in the two age strata (11-13yrs and 14-17yrs) was similar. Age (median =14 years), gender (48.4% were female) and ethnic origins [Caucasian (84.6%), Black (8.9%), and Hispanic (2%)] were similar for the 3 lots.

10.2.1. Vaccination History

All but one participant (1/1806, 99.9%) in the ITTS had received 5 doses of dip-tet-pertussis vaccine prior to study enrollment. Twenty participants had received more than 5 doses of dip-tet-pertussis vaccines.

10.3. Immunogenicity Results

The PPI is considered as the primary analysis and the discussion focuses on this population. A summary of the immungoenicity results in provided in Table Td505 10.3a.

Table Td505 10.3a Summary of Immunogenicity Results for the PPI Population

	Tdap1		Tdap2		Tdap3		Total	
	n/N	%	n/N	%	n/N	%	n/N	%
Seroprotection ≥ 0.1 IU/ml								
Diphtheria	351/351	100%	347/349	99.4%	352/353	99.7%	1050/1053	99.7%
Tetanus	351/351	100%	350/350	100%	353/353	100%	1054/1054	100%
Booster Response Rates								
Diphtheria	337/351	96%	334/349	95.7%	335/353	94.9%	1006/1053	95.5%
Tetanus	324/350	92.6%	327349	93.7%	324/353	91.8%	975/1052	92.7%
4-Fold Response Rates								
PT	323/351	92%	304/348	87.4%	310/352	88.1%	937/1051	89.2%
FHA	303/351	86.3%	281/347	81%	283/351	80.4%	867/1050	82.6%
FIM	327/350	93.4%	322/348	92.5%	330/352	93.8%	979/1050	93.2%
PRN	335/351	95.4%	324/348	93.1%	330/352	93.8%	989/1051	94.1%
GMCs	**N**	**GMC**	**N**	**GMC**	**N**	**GMC**	**N**	**GMC**
Diphtheria (IU/ml)	351	7.7	349	7.2	353	7.5	1053	7.5
Tetanus (IU/ml)	351	16.3	350	16.7	353	17.2	1054	16.7
PT (EU/ml)	351	343.7	349	347.4	353	323.9	1053	338.1
FHA (EU/ml)	351	285.1	349	265.0	353	247.8	1053	265.5
FIM (EU/ml)	351	1901.6	349	2025.4	353	1528.8	1053	1804.8
PRN (EU/ml)	351	366.1	349	394.7	353	343.2	1053	367.3

Adapted from Aventis Pasteur eBLA, Table 5.5 of Td505 page 69
n, % = number and percent of participants who achieved the specified levels for seroprotection, booster response, and four-fold response rates.
N = number of participants evaluated.
GMC = Geometric Mean concentration, calculated excluding missing observations.
Tdap1 (N=351), Tdap2 (350), Tdap3 (N=355) administered at Day 0.

10.3.1. Diphtheria and Tetanus

10.3.1.1. Seroprotection Rates

Pre-vaccination seroprotection rates were high for both dip (73.8% to 76.9% for the 3 lots) and tet (98%-99.2% for the 3 lots). At 1-month post-vac titers ≥ 0.1 IU/ml, were achieved by 100% of participants for tet, and ≥ 99.4% for dip. Non-inferiority of the dip and tet responses between lots was demonstrated.

10.3.1.2. Booster Response Rates

Over 92% of all participants achieved booster responses for dip and tet. Responses for the younger age subgroup of 11-13 years and the older subgroup of 14-17 years were similar. Consistency was demonstrated between any two lots for dip and tet booster response rates, d*ata not shown.*

10.3.1.3. Geometric Mean Concentrations and Comparisons Between Lots

Geometric mean concentrations (GMCs) and comparisons of GMCs are shown on Table Td505-10.3b. Consistency between any two lots was demonstrated for both dip and tet, based upon the GMC ratio criteria [90% CIs were within the interval (0.67, 1.5)]. Consistency was also demonstrated using 95% CI for the comparisons.

10.4. Pertussis Antigens

10.4.1. Geometric Mean Concentrations and Comparison Between Lots

The GMC comparisons are shown on Table Td505-10.3b. For PT, FHA and PRN, the 90% CI for the post-vac GMC ratios between any two groups were with the interval (0.67, 1.5). For FIM, the GMC ratio between Lots 2 and 3 had an upper limit of 1.55, but the other FIM GMC ratios between the other lots were within the pre-specified interval. The post-vac GMCs to each of the 4 antigens were generally lower for Tdap 3 than for Tdap1 and Tdap2. The comparisons of the GMC ratios using 95% CI were also with the interval (0.67, 1.5) for all comparisons, except FIM between Tdap2 and Tdap3.

Table Td505-10.3b. Diphtheria, Tetanus and Pertussis Antigens: Comparison of GMCs for the PPI Population

		Post-Vaccination				
Antigen	**Groups**	**GMC1**	**GMC2**	**GMC Ratio**	**LCL**	**UCL**
Diphtheria	Tdap1 vs. Tdap2	7.74	7.16	1.08	0.96	1.22
	Tdap1 vs. Tdap3	7.74	7.52	1.03	0.91	1.16
	Tdap2 vs. Tdap3	7.16	7.52	0.95	0.85	1.07
Tetanus	Tdap1 vs. Tdap2	16.27	16.72	0.97	0.91	1.04
	Tdap1 vs. Tdap3	16.27	17.22	0.95	0.88	1.01
	Tdap2 vs. Tdap3	12.72	17.22	0.97	0.91	1.04
PT	Tdap1 vs. Tdap2	343.65	347.36	0.99	0.87	1.13
	Tdap1 vs. Tdap3	343.65	323.89	1.06	0.93	1.21
	Tdap2 vs. Tdap3	347.36	323.89	1.07	0.94	1.22
FHA	Tdap1 vs. Tdap2	285.10	264.98	1.08	0.98	1.19
	Tdap1 vs. Tdap3	285.10	247.76	1.15	1.04	1.27
	Tdap2 vs. Tdap3	264.98	247.76	1.07	0.97	1.18
FIM	Tdap1 vs. Tdap2	1901.6	2025.38	0.94	0.80	1.10
	Tdap1 vs. Tdap3	1901.6	1528.75	1.24	1.06	1.45
	Tdap2 vs. Tdap3	2025.38	1528.75	1.32	1.13	**1.55**
PRN	Tdap1 vs. Tdap2	366.14	394.69	0.93	0.81	1.07
	Tdap1 vs. Tdap3	366.14	343.21	1.07	0.93	1.23
	Tdap2 vs. Tdap3	394.69	343.21	1.15	1.0	1.32

Adapted from Aventis Pasteur eBLA, Tables 5.10 - 5.13, Td505 pages 79-82.
GMC1, GMC2 = GMCs for the 1st and 2nd group respectively in the comparison.
GMC Ratio = ratio of GMCs between the two groups.
LCL, UCL = lower and upper limits of the 2-sided 90% CI for the GMCs ratio for the 2 groups.
Tdap1 (PPI=351), Tdap2 (PPI=350) and Tdap3 (PPI=355).

10.4.2. Four-Fold Response Rates

Most participants achieved $\geq$ 4-fold rise to each of the pertussis antigens: $\geq$ 87.4% for PT, $\geq$ 80.4% for FHA, $\geq$ 92.5% for FIM and $\geq$ 93.1% for PRN. Rates were similar in each of the 3 lots. No differences in the 11-13 year and 14-17 year age groups were appreciable, though no formal statistical testing was performed.

10.5. Safety

Clinical safety data were summarized and analyzed using the ITTS population. An overview of the safety results is shown in Table Td505-10.5a. Rates of solicited and unsolicited adverse events (AEs) were generally comparable between the study groups. Statistical testing of the secondary hypothesis

showed that all objectives were met for pain, erythema, swelling, and fever of "any" and "moderate and severe" intensities.

Table Td505-10.5a Overview of Safety: Number and Percentage of Participants with Any Solicited Events, Immediate Adverse Events (AE), Unsolicited Adverse Events or Serious Adverse Events (ITTS Population)

	Tdap1		Tdap2		Tdap3		Total	
Type of Adverse Event	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Immediate AE (within 30 min)	6/600	1.00	4/604	0.7	3/602	0.5	13/1806	0.7
Any Solicited Local Reactions (Days 0-14)	500/600	83.3	499/604	82.6	501/602	83.2	1500/1806	83.1
Any Solicited Systemic Events (Days 0-14)	388/600	64.7	403/604	66.7	396/602	65.8	1187/1806	65.7
Solicited Reactions (Day0-14)*								
Erythema	141/596	23.7	145/599	24.2	150/598	25.1	436/1793	24.3
Swelling	125/596	21.0	133/599	22.2	146/598	24.4	404/1793	22.5
Pain	481/596	80.7	472/599	78.8	480/598	80.3	1433/1793	79.9
Fever (≥ 38°C/100.4°F)	39/595	6.6	25/599	4.2	29/596	4.9	93/1790	5.2
Headache	269/600	45.1	266/604	44.4	258/602	43.1	793/1806	44.2
Tiredness	180/600	30.2	203/604	33.9	179/602	29.9	562/1806	31.3
Generalized Body Aches	185/600	31.0	178/604	29.7	182/602	30.4	545/1806	30.4
Sore/Swollen Joints	79/600	13.7	94/604	15.7	78/602	13.1	251/1806	14.0
Solicited Reactions (Days 0-3)*								
Fever (≥ 38°C/100.4°F)	19/595	3.2	16/599	2.7	18/596	3.0	53/1790	3.0
Unsolicited AEs (Days 0-28)	141/600	23.5	141/604	23.3	142/602	23.6	424/1806	23.5
Serious AEs	1/600	0.2	2/604	0.3	1/602	0.2	4/1806	0.2

Adapted from Aventis Pasteur eBLA Tables 5.15, Td505 page 86.
*Selected systemic event of "any" fever.
n, %= number and percentage of participants reporting the event
Tdap1 (N=600), Tdap2 (N=604), Tdap3 (N=602)
Total number of participants (ITTS population) was 1806.

10.5.1. Immediate Reactions

Thirteen subjects (Tdap1 n=6, Tdap2 n=4, Tdap3 n=3) reported 15 immediate AEs. No anaphylaxis events were reported. The most common (n=5) classification was for "nervous system", e.g., dizziness, syncope and hypoasthesia.

10.5.2. Solicited AEs

AEs were monitored, including diary cards, definitions and intensities, similarly to Td506.

10.5.2.1. Solicited Local AEs

A summary of the local AEs is shown in Table Td505-10.5a A total of 83.1% (1500/1806) of all participants reported at least one solicited AEs from Day 0-14. Pain was the most frequently reported local AE occurring in ~80% of all subjects. Rates of erythema, swelling, pain and underarm lymph node swelling were similar in the 3 groups.

Intensity

Most solicited AEs were considered to be "mild" at all time points for the 3 vaccine groups, with the exception of swelling, where the rates of mild, moderate and severe were similar (rates of 6.04% to 9.7% in all subjects from Day 0-14).

No subjects reported severe lymph node swelling from Day 0-3. Two participants reported severe lymph node swelling at Days 4-14, one each in Tdap1 and Tdap3. For limb circumference, about two-thirds of participants reported changes of < 1 cm.

10.5.2.2. Comparison of Erythema, Swelling, and Pain Rates – Secondary Hypothesis

Rates of these AEs were compared for "any" and "moderate and severe" intensities for Days 0-14, using 95% CI on the difference in rates between any 2 lots. Consistency was to be concluded if the 95% CIs were within the interval (-10%, 10%). Consistency between the lots was demonstrated for "any" and "moderate and severe" for erythema, swelling, and pain.

10.5.2.3. Solicited Systemic AEs

A total of 65.7% of all participants experienced at least one solicited systemic AE from Day 0-14. The rates of events at all time periods were similar between the lots. The rates of selected systemic AEs are shown in Table Td505-10.5a.

Sore and/or swollen joints occurred in 13.07% to 15.69% of participants in each group from Day 0-14. Rash occurred in $\leq$ 4.4% of all participants from Day 0-14, and rates were similar between the groups.

10.5.2.4. Comparison of Fever Rates

Consistency was demonstrated as measured by fever scored as "any" and "moderate & severe" intensity from Day 0-14, using the pre-defined criteria of the 95% CI for the differences in fever rate between any 2 lots were within the interval (-10%, 10%).

Additionally, there were no apparent differences in the rates of any of the other systemic AEs, though formal statistical comparisons were not performed.

10.5.2.5. Additional Doses of DTP and Reactogenicity

No obvious differences were noted in the reactogenicity profiles (based upon review of erythema, swelling, pain and fever) for the 25 participants with protocol violations for vaccine history (20 had received > 5 doses of a dip- and tet-containing vaccine and 5 participants had received the last dose within the previous 5 years).

10.5.2.6. Rates of AEs by Age and Gender

Rates of erythema, swelling, pain and fever were analyzed by age subgroup (11-13 years and 14-17 years) and gender. This observational evaluation showed a trend for higher rates of these events from Days 0-14 in the younger age group and in females; no formal statistical comparisons between the age groups were planned or performed.

10.5.3. Unsolicited AEs

A total of 424 participants (23.5% of 1806) reported 624 unsolicited AEs, and the number of events was similar for the 3 groups. Events were reported most frequently in the SOC of "Infections and Infestations" (185 events in 168 subjects) and "Respiratory, Thoracic, Mediastinal Disorders" (169 events in 127 participants). Nasopharyngitis was the most frequently reported event, occurring in ~3-4% of each group.

There were no reports of whole arm swelling, seizures, new onset diabetes, or other autoimmune diseases during the study period.

10.5.4. SAEs

Four participants experienced 4 SAEs: three cases of appendicitis (one in each study group with onset from Day 7 through 37 post-vaccination) and one suicide in the Tdap2 group on Day 70 post-vaccination. None of these events were considered to be related to study vaccine.

11. ASSESSMENT of Td505

The primary and secondary objectives for this trial were met. Consistency of manufacturing was demonstrated; no important differences were observed for safety and immunogenicity of the three

production lots when given to adolescents 11-17 years of age. Of note, the serum samples from this trial were assayed simultaneously with the serum samples from infants in the Sweden I Efficacy Trial. These results are discussed in the Summary for the Serology Bridging Study. Additionally, this study provided approximately 1800 adolescent participants to the safety database of the BLA.

Among the multiple statistical comparisons performed to assess lot consistency, and only one parameter (comparison of GMC ratio for anti-FIM between Lots 2 and 3 was 1.55), was outside the pre-defined interval. Although statistically significant, this difference was small. The antibody concentrations achieved for the pertussis antigens, including FIM, exceeded the levels reported from the Sweden I Efficacy trial (See Serology Bridging Study). For dip and tet for all participants, the rates of seroprotective levels ($\geq$ 0.1 IU/ml) were high (over 99%) and similar between groups.

The safety objective of the study was evaluated by comparing rates of erythema, swelling, pain and fever between the recipients of each of the 3 lots. As an observational objective, the rates of solicited events, and unsolicited AEs were found to be similar between the 3 lots, also supporting consistency of manufacturing. During the one month study period, no unexpected SAEs or new onset of serious medical conditions were observed. No safety concerns were identified for Tdap vaccination in the adolescent study population.

NON-PIVOTAL (CONCOMITANT ADMINISTRATION) TRIALS

Td502: Safety and Immunogenicity of Tetanus and Diphtheria Toxoids Adsorbed, Combined with Component Pertussis (Tdap) Vaccine Given Concurrently with Influenza Vaccine Compared to Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Given 4-6 Weeks After Influenza Vaccine in Adults 19 to 64 Years of Age.

12. SUMMARY

Td502 was a multi-center, open-labeled, randomized, controlled study designed to measure the safety and immune responses generated by Tdap vaccine and influenza vaccine given concurrently or separately in 720 adults, 19-64 years of age.

Participants were divided into 2 vaccine groups. In Group A, subjects received Tdap and influenza vaccines concurrently and in Group B, subjects received the influenza vaccine at the first visit, then 4-6 weeks later received the Tdap vaccine. The primary objective was assessment of immunogenicity and the secondary objective was assessment of safety measures. Assessments were performed similar to Td506.

Non-inferiority was not demonstrated for the safety profiles and for the immune responses parameters measured when the Tdap and influenza vaccines were given concurrently compared to separately. Non-inferiority was demonstrated for immunogenicity for diphtheria, influenza, PT, FHA and FIM, but not for tetanus booster responses or PRN antibodies GMCs. For safety, non-inferiority was not demonstrated for pain at the injection site of "any" and "moderate and severe intensity", though non-inferiority was demonstrated for the rates of erythema, swelling, and fever.

13. HYPOTHESIS AND OBJECTIVES

13.1. Primary Objective

To determine whether the concurrent administration of Tdap vaccine and influenza vaccine, in adults 19-64 years of age, induces antibody responses similar to those observed when each vaccine is given 4-6 weeks apart.

13.2. Primary Hypothesis

The dip and tet antitoxin antibodies and pertussis antibody responses (PT, FHA, FIM and PRN) measured 4-6 weeks after the booster dose of Tdap given concurrently with influenza vaccine are

non-inferior to those obtained when each vaccine is given 4-6 weeks apart. Comparisons of booster rates and of GMCs for both dip and tet were added to the primary analyses after the study was started. The following criteria were used to establish non-inferiority of Group A (concomitant administration, Tdap + Flu) compared to Group B (separate administration, Flu, Tdap):

- If the upper limit of the 2-sided 95% CI for the differences between Groups B and A (B minus A) is seroprotection rates ($\geq$ 0.1 IU/ml) and booster response rates for both dip and tet were < 10%, then it was concluded that the dip and tet antibody responses in Group A were non-inferior to those in Group B.
- If the lower limit of the 2-sided 90% CI for the ratio of post-booster GMCs for dip and tet between Groups A and B (GMCA/GMCB) was greater than 0.67, then it was concluded that the response in Group A was non-inferior to the response in Group B with respect to GMCs.

If the lower limit of the 2-sided 90% CI for the ratio of the post-booster GMCs for the pertussis antigens between Groups A and B (GMCA/GMCB), was greater than 0.67, then it was concluded that the responses in Group A was non-inferior to those in Group B.

For each of the three influenza antigens, with respect to both seroprotection rates (defined by the sponsor as post-vaccination HAI titers $\geq$ 1:40 IU/ml) and seroconversion rates (defined as $\geq$ 4-fold responses), if the upper limit of the 2-sided 95% CI for the difference between Group B and Group A (B minus A) was less than 10%, then it was concluded that the response in Group A was non-inferior to the response in Group B.

13.3. Secondary Objective

To determine whether the safety, in adults 19-64 years of age, of a booster dose of Tdap given concurrently with the influenza vaccine is comparable to the safety of a booster dose of Tdap given ~4-6 weeks after the influenza vaccine.

13.4. Secondary Hypothesis

The safety in terms of fever, erythema, pain and swelling rates during Days 0-14 following a booster dose of Tdap administered concurrently with influenza vaccine is non-inferior to that in subjects who receive a booster dose of Tdap vaccine ~ 4-6 weeks after influenza vaccine. Safety in terms of other local and systemic solicited and unsolicited adverse events, including serious adverse events is comparable between the study groups.

The non-inferiority analysis was performed on adverse events (AEs) that are rated as either "any" or "moderate & severe" reported for Days 0-14. If the upper limit of the 2-sided 95% CI on the difference between Groups A and B (A minus B) in erythema, pain, swelling and fever was < 10%, it was concluded that the safety of Group A was non-inferior to the safety of Group B with respect to erythema, pain, swelling and fever.

Safety in terms of other local and systemic solicited reactions as well as unsolicited AEs, including immediate AEs and SAEs, is comparable between the study groups.

14. STUDY DESIGN

This was a multi-center, open-labeled, randomized, controlled non-pivotal study designed to measure the safety and immune responses generated by Tdap vaccine and influenza vaccine given concurrently or separately in adults.

14.1. Safety Monitoring

Safety monitoring was performed after the receipt of the Tdap vaccine. No active monitoring was performed following receipt of the influenza vaccine.

14.2. Immungoenicity

Sera were obtained prior and 4-6 weeks after Tdap, as well as 4-6 weeks after the influenza vaccine.

14.3. Laboratory Methods

The diphtheria, tetanus and pertussis assays were performed as described in Td506. The influenza antibodies were measured using hemagglutination inhibition assays (HAI), which were performed by ---------- . The HAI methodology was reviewed and considered acceptable by CBER.

15. PRODUCT DESCRIPTION

15.1. Tdap

As described above.

15.2. Influenza (Fluzone®)

Fluzone® is the U.S. licensed influenza vaccine produced by Aventis. Each 0.5 ml dose contains 15 ug of the three influenza strains (A/H1N1, A/H3N2, and B) recommended by the U.S. Public Health Service. This study was performed in 2000, and the strains were A/Panama/2007/99 (A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (A/New Caledonia/20/99 (H1N1)-like), and B/Yamanashi/166/98 (B/Bejing/184/93 – like strain).

16. STUDY PROCEDURES

General study procedures, including statistical methodology, were followed similarly to those of Td506.

16.1. Definition of Populations

The analysis populations were defined as:

- Intent-to-treat (ITT) – included all participants who were randomized and received the study vaccine. The ITT included 696 individuals (excluded 24 who did not receive Tdap vaccine).
- Per-Protocol (PP) – included participants who received Tdap vaccine and underwent blood draws according to the protocol schedule and did not have any protocol violations that might influence the immunologic response. The PP population included 678 participants (354 in Group A and 324 in Group B).

17. RESULTS

A total of 720 individuals were enrolled in the study from 27-Oct-00 through 25-Apr-01. This included 359 individuals randomized to Groups A (Tdap + flu) and 361 to Group B (flu, Tdap). A total of 96.7% of subjects completed the trial, with 99.2% in Group A and 94.2% of Group B completing the study.

17.1. Early Discontinuations

Twenty-four of the 720 (3.3%) participants discontinued prior to completion of the trial; 3 were from Group A and 21 from Group B. All 24 withdrew after enrollment but prior to vaccination with Tdap. The sponsor states that the discrepancy in withdrawals is likely accounted for by the difference in vaccination schedules for Group A and B. In Group A, both vaccines were received at Visit 1, and in Group B the participants only received flu vaccine at Visit 1 and then had to return 4-6 weeks later for the Tdap vaccine.

17.2. Demographics and Baseline Characteristics

Age and demographic characteristics of Group A and Group B were comparable. The majority of participants were Caucasian (93.1%), 2.2% were Black, 1.1% were Asian, 1.3% Hispanic and 2.3% were “other”. There were more (59.6%) females than males. About 50% of each group was 30-49 years, 30.5% were 19-29 years, and 18.1% were 50-64 years of age.

17.3. Vaccination History

By reported history, ~69% of participants reported prior receipt of five doses of DPT- containing vaccines. About 35.5% of participants reported previous dose of dip and tet vaccine in the 5-15 years prior to study participation, and 36% of participants did not know when they had received a previous dose of dip and tet vaccine.

17.4. Immunogenicity

Blood samples were obtained from all subjects at Visit 1 prior to vaccination (Day 0). For Group A, a second sample was obtained at Visit 2 (4-6 weeks after receipt of Tdap and flu vaccines). For Group B a second sample was taken at Visit 2 (for influenza HAI) and a third sample at Visit 3 (4-6 weeks after Tdap vaccine). All immunogenicity analyses were performed on both the ITT and PP populations, and the PP population was used for the primary analyses.

17.4.1. Overall Immunogenicity Results

A summary of immunogenicity results is shown in Table Td502 – 17.4a.

Table Td502 – 17.4a. Summary of Primary Immunogenicity Results

	Group A		Group B	
	Tdap + Flu		Flu, Tdap	
Immune Responses	**n/N**	**%**	**n/N**	**%**
Seroprotection (≥ 0.1 IU/ml)				
Diphtheria	305/354	86.2	282/324	87.0
Tetanus	353/354	99.7	318/324	98.1
Booster Response Rates				
Diphtheria	308/354	87.0	281/323	87.0
Tetanus	278/353	78.8	269/323	83.3
Seroprotection (HAI ≥ 1:40 IU/ml)*				
A/Panama/2007/99 (H3/N2)	295/341	86.5	261/294	88.8
A/New Caledonia/20/99 (H1N1)	184/341	54.0	138/294	46.9
B/Yamanashi/166/98	275/341	80.6	237/295	80.3
4-Fold Response Rates*				
A/Panama/2007/99 (H3/N2)	237/341	69.5	204/294	69.4
A/New Caledonia/20/99 (H1N1)	233/341	68.3	199/294	67.7
B/Yamanashi/166/98	214/341	62.8	192/295	65.1
GMCs – Post-Vaccination	**N**	**GMC**	**N**	**GMC**
Diphtheria (IU/ml)	354	0.7	324	0.7
Tetanus (IU/ml)	354	6.9	324	7.3
PT (EU/ml)	352	186.4	322	234.5
FHA (EU/ml)	354	200.6	323	242.2
FIM (EU/ml)	354	925.8	323	1136.3
PRN (EU/ml)	354	191.7	323	260.3

Adapted from Aventis Pasteur eBLA, Table 5.5 in Td502, page 73.
n, % = number and percent of participants who achieved the specified levels for seroprotection, booster response and seroconversion rates.
N = number of participants evaluated.
GMCs = geometric mean concentration (4-6 weeks post-vaccination), excluding subjects with missing observations.
*Influenza strains: A/H3N2 = A/Panama/2007/99, A/H1N1 = A/New Caledonia/20/99, and B = B/Yamanashi/166/98.

17.4.2. Diphtheria and Tetanus

17.4.2.1. Seroprotection Rates

The pre-vaccination seroprotection rates (antibody levels ≥ 0.1 IU/ml) were low for dip (36.4% for Group A and 32.5% for Group B), and at post-vaccination the majority of

participants achieved protective levels (86.2% for Group A and 87% for Group B). Results are shown on Table Td502-17.4a.

Comparison of Seroprotective Rates – Primary Hypothesis
Non-inferiority of Group A seroprotection rates compared to those of Group B was to be concluded if the upper limit of the 2-sided 95% CI for the difference between Groups A and B (B-A) rates was < 10%. Group A was found to be non-inferior to Group B.

Table TD502 - 17.4.a. Comparison of Seroprotective Rates (> 0.1 IU/ml) for Diphtheria and Tetanus

Antigen	Time	Seroprotection Rate				
		Group A %	Group B %	Diff %	LCL	UCL
Diphtheria	**Pre**	36.4	32.5	-3.9	-11.1	3.2
	Post	86.2	87.0	0.9	-4.3	6.0
Tetanus	**Pre**	89.5	86.1	-3.5	-8.4	1.5
	Post	99.7	98.1	-1.6	-1.6	0

Adapted from Aventis Pasteur eBLA, Tables 5.7 – 5.9 in Td502 pages 75-77.
Group A (Tdap + Flu, N=354) and Group B (Flu, Tdap, N=324)
Diff % - difference between Group B and Group A
LCL, UCL – lower and upper limit of the 2-sided 95% CIs for the difference in proportions

17.4.2.2. Booster Response Rates
The booster response rates for diphtheria were similar between Group A and Group B, but for tetanus the rate in Group A was 5.5% lower than the rate in Group B. For diphtheria, the non-inferiority criterion was met, but for tetanus, the upper limit of the 95% CI was 10.42%, slightly exceeding 10%.

Table TD502 - 17.4.a Comparison of Booster Response Rates for Diphtheria and Tetanus

Antigen	Time	Booster Response Rates				
		Group A %	Group B %	Diff %	LCL	UCL
Diphtheria	**Post**	87.01	87.0	-0.01	-5.08	5.06
Tetanus	**Post**	78.8	83.3	4.53	-1.37	**10.42**

Adapted from Aventis Pasteur eBLA, Tables 5.7 – 5.9 in Td502 pages 75-77.
Group A (Tdap + Flu, N=354) and Group B (Flu, Tdap, N=324)
Diff % - difference between Group B and Group A
LCL, UCL – lower and upper limit of the 2-sided 95% CIs for the difference in proportions

17.4.2.3. GMCs
Pre- to post-vaccination GMCs for diphtheria increased from 0.05 to 0.66 IU/ml for Group A and from 0.04 to 0.74 IU/ml for Group B, and for tetanus increased from 0.79 to 6.90 IU/ml for Group A and from 0.65 to 7.31 IU/ml for Group B. Non-inferiority of GMCs for dip and tet was demonstrated, *data not shown*.

17.4.3. Pertussis
The pre-vaccination GMCs for the antibodies to the pertussis antigens were similar between the 2 groups; however, the post-vaccination GMCs were consistently higher in Group B.

17.4.3.1. Comparison of GMCs
Non-inferiority of the pertussis responses was to be established if the lower limits of the 90% CI for the ratio of post-vaccination GMCs for the pertussis antigens between Groups A and B (GMCA/GMCB) are > 0.67. The non-inferiority criteria were met for PT, FHA and FIM, but

not PRN (LCL = 0.61). Table Td502 – 17.4c shows the GMCs and a comparison of the ratios. The same findings were seen when comparisons were performed using the 95% CIs.

Table Td502 – 17.4b. Pertussis Antibodies: Comparison of GMCs between Groups A and B

		Group A (Tdap + Flu)		Group B (Flu, Tdap)		GMCA/GMCB	90% CI	
Antigen (EU/ml)	**Sample**	**M1**	**GMCA**	**M2**	**GMCB**	**GMC Ratio**	**LCL**	**UCL**
PT	Pre	354	12.8	321	12.6	1.02	0.88	1.18
	Post	352	186.4	322	234.5	0.79	0.70	0.90
FHA	Pre	354	16.7	322	15.7	1.06	0.92	1.23
	Post	354	200.6	323	242.2	0.83	0.75	0.91
FIM	Pre	354	30.9	322	29.6	1.04	0.90	1.22
	Post	354	925.8	323	1136.3	0.81	0.68	0.98
PRN	Pre	354	6.9	322	6.7	1.03	0.88	1.21
	Post	354	191.7	323	260.3	0.74	**0.61**	0.88

Adapted from Aventis Pasteur eBLA, Tables 5.13 in Td502, page 82
GMCs Ratio - Ratio of GMCs for Tdap+Flu over Flu, Tdap
M1, M2 - Sample sizes (missing observations not included) for Tdap + Flu and Flu, Tdap, respectively
LCL, UCL - Lower and upper limits of the two-sided 90% CI for the ratio of GMCs for Tdap+Flu over Flu, Tdap

17.4.3.2. Four-fold Response Rates – Additional Analysis

Non-inferiority comparisons of the rates of $\geq$ 4-fold rises in antibodies to each of the pertussis antigens between Group A and Group B were provided for descriptive purposes only. For FHA, FIM and PRN, the percent of subjects in Group A and Group B with $\geq$ 4-fold rises met the non-inferiority criterion (UCL of the 95% CI on the difference in rates < 10%). For PT the UCL of the 95% CI = 10.07 for rate difference of 4.94 (rates = 84.09% in Group A and 89.03% in Group B).

17.4.4. Influenza

17.4.4.1. Seroprotection and Seroconversion Rates

Although not universally accepted as a marker of protection, the sponsor has evaluated strain-specific HAI titers $\geq$ 1:40 IU/ml as a seroprotective level for influenza antibodies. The results for seroprotective HAI titers for each of the three strains were comparable between Groups A and B (Table Td502-17.4c).

Seroconversion was defined as 4-fold rise in antibody titers post-vaccination. The results for proportion of subjects with seroconversion were similar between Groups A and B.

Geometric Mean Titers (GMTs)

Strain-specific HAI GMTs were provided for descriptive purposes only. For each of the 3 strains in both the pre and post-vaccination samples GMTs were similar between Group A and Group B.

17.4.5. Comparison of Influenza Seroprotection and Seroconversion Rates - Primary Hypothesis

Non-inferiority was to be concluded if the UCL of the 2-sided 95% CI for the differences between Groups A and B (B minus A) post-vaccination seroprotection and seroconversion rates were < 10%. For all 3 influenza strains for seroprotective levels and seroconversion rates, non-inferiority of Group A compared to Group B was demonstrated.

Table Td502-17.4c. Influenza Antibodies: Comparison of Rates of Strain-Specific Seroconversion and Seroprotection (HAI ≥ 1:40)

		Group A Tdap + Flu		Group B (Flu, Tdap)		P2-P1	95% CI of Diff	
SEROPROTECTIVE RATES	**Sample**	**M1**	**P1 (%)**	**M2**	**P2 (%)**	**Diff %**	**LCL**	**UCL**
A/H3N2 (A/Panama/2007/99)	Pre	341	26.4	294	20.7	-5.6	-12.2	0.9
	Post	341	86.5	294	88.8	2.3	-2.9	7.4
A/H1N1 (A/New Caledonia/20/99)	Pre	341	3.5	294	3.4	-0.1	-3.0	2.7
	Post	341	54.0	294	46.9	-7.0	-14.8	0.8
B/Yamanashi/166/98	Pre	341	20.8	297	19.5	-1.3	-7.5	4.9
	Post	341	80.6	295	80.3	-0.3	-6.5	5.9
SEROCONVERSION RATES								
A/H3N2 (A/Panama/2007/99)	Post/pre	341	69.5	294	69.4	-0.1	-7.3	7.1
A/H1N1 (A/New Caledonia/20/99)	Post/pre	341	68.3	294	67.7	-0.6	-7.9	6.6
B/Yamanashi/166/98	Post/pre	341	62.8	295	65.1	2.3	-5.1	9.8

Adapted from Aventis Pasteur eBLA, Tables 5.14 – 5.18 in TD502 pages 86 - 89.
M1, M2 = Sample sizes (missing observations not included) for Tdap + Flu and Flu, Tdap, respectively.
P1, P2 - Proportions of subjects with 4-fold response rates in Group A and Group B.
Diff % - Difference between Tdap + Flu and Flu, Tdap in the proportion of subjects with 4-fold rises
LCL, UCL = Lower and upper limits of the two-sided 95% CI for the difference in proportions.
Group A = Tdap + Flu (N=354)
Group B = Flu, Tdap (N=324).

17.5. Safety

Monitoring for safety events was performed similar to Td506 and Td505. The clinical safety data were analyzed using the ITT population. Solicited reactions were collected only after the Tdap vaccine (i.e., not after flu vaccine only at Visit 1 for Group B).

A summary of the safety results are provided on Table Td502-17.5a Non-inferiority was demonstrated for safety for erythema, swelling and fever. For pain, the upper limit of the 2-sided 95% CI exceeded 10% for both "any" and "moderate and severe" intensity. The safety profile of the Tdap vaccine in this trial was similar to that observed in other trials in adults (e.g., Td506 and TC9704).

Table Td502 - 17.5a Summary of Safety Results for the ITT Population

	Group A Tdap + Flu		Group B Flu, Tdap		Total N=696	
Type of Adverse Event	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Immediate AE (within 30 min)	3/356	0.8	1/340	0.3	4/696	0.6
Any Solicited Local Reaction (Days 0-14)	246/356	69.1	218/340	64.1	464/696	66.7
Any Solicited Systemic Reaction(Days 0-14)	219/356	61.5	191/340	56.2	410/696	58.9
Solicited Reactions Day 0-14						
Erythema	38/352	10.8	42/339	12.4	80/691	11.6
Swelling	54/352	15.3	35/339	10.3	89/691	12.9
Pain	235/353	66.6	206/339	60.8	441/692	63.7
Fever (≥ 38°C/100.4°F)	15/352	4.3	8/336	2.4	23/688	3.3
Solicited Reactions Day 0-3						
Fever	6/352	1.7	3/336	0.9	9/688	1.3
Unsolicited AEs	123/356	34.6	108/340	31.8	231/691	33.2
Serious AEs	1/356	0.3	1/340	0.3	2/696	0.3

Adapted from Aventis Pasteur eBLA, Table 5.18 in Td502, page 90.
n = number of participants reporting the specified reaction of any intensity.
N = total number of participants evaluated for indicated adverse event.
Any Solicited Local Reactions include Erythema, Pain, Swelling, and Underarm Lymph Node Swelling.
Any Solicited Systemic Reactions include Fever, Headache, Sore/Swollen Joints, Chills, Bodyache, Tiredness, Nausea, Vomiting, Diarrhea, and Rash.

17.5.1. Immediate Reactions

Four immediate AEs were observed, 3 in Group A and 1 after Tdap in Group B; none were considered as SAEs. The four events included dizziness, hypoasthesia, vasovagal attack and hematoma. All participants recovered without sequelae. No anaphylaxis events were reported.

17.5.2. Solicited Reactions

Solicited events were monitored after the Tdap vaccine, as described for Td505 and 506.

17.5.2.1. Solicited Local Reactions

Comparable proportions of subjects in both study groups experienced at least one local reaction during Days 0-14 monitoring period (69% of Group A and 64.1% of Group B). For both study groups, the highest rate of reactions occurred during Days 0-3.

Other than erythema, most of solicited local AEs occurred at a higher rate in Group A than Group B during all of the time periods evaluated. Pain was the most frequently reported AE from Day 0-14 period (as well as the other time periods), with "any" pain being reported by 66.6% of Group A and 60.8% of Group B from Day 0-14. Swelling was the AE most frequently rated as "severe" in both groups, occurring in 6.5% of Group A and 4.1% in Group B from Day 0-14.

17.5.2.2. Comparison of Solicited Local Reactions – Secondary Hypothesis

As shown on Table Td502-17.5b, for erythema and swelling, non-inferiority was demonstrated. For pain, the upper limit of the 2-sided 95% CI exceeded 10% at Day 0-14 for both "any" pain (UCL = 12.96%) and for "moderate & severe" intensity (UCL = 10.71%). The UCL for the difference in rate of "any" swelling was 9.98, though it did not exceed 10%. No difference in the rate of axillary node swelling was noted (descriptive only).

Table Td502 -17.5b Comparison of Rates of Erythema, Swelling, and Pain from Day 0-14 for Group A and Group B in the ITT Population

	Participants		Rates of Events		2-Sided 95% CI		
Adverse Event by Intensity	**N1**	**N2**	**P1**	**P2**	**Diff%**	**LCL**	**UCL**
Any							
Erythema	352	339	10.8	12.4	-1.6	-6.37	3.18
Swelling	352	339	15.3	10.3	5.0	0.05	9.98
Pain	353	339	66.6	60.8	5.8	-1.35	**12.96**
Moderate & Severe							
Erythema	352	339	5.7	6.5	-0.8	-4.38	2.76
Swelling	352	339	11.1	7.4	3.7	-0.60	8.01
Pain	353	339	13.3	7.1	6.2	1.76	**10.71**

Adapted from Aventis Pasteur eBLA, Table 5.26 in Td502 page 102.
N1, N2 = Number of evaluated participants receiving Tdap+Flu (Group A) and Flu, Tdap (Group B) respectively. Participants with missing observations not included in the comparison.
P1, P2 = Incidence rate of evaluated participants of Groups A (Tdap+Flu) and B (Flu, Tdap) respectively. Participants with missing observations not included.
Diff% = Difference in reaction rates between groups: Tdap+Flu vs. Flu, Tdap.
LCL, UCL = Lower and upper limits of the 2-sided 95% confidence interval for the difference.
Days 0–14: Maximum intensity of reactions reported during the time period.

17.5.2.3. Solicited Systemic Reactions

Generally, participants in Group A (Tdap + Flu) reported slightly higher rates of systemic AEs than Group B. An overview of the results is shown in Table Td502-17.5c. Headache was the most common systemic AE reported, with "mild" headache occurring from Day 0-14 in 39.8% of Group A and 37.8% of Group B.

Rates of "any" sore and/or swollen joints for Day 0-14 were higher for Group A participants (12.2%) compared to Group B (9.4%).

17.5.2.4. Comparison of Fever Rates – Secondary Hypothesis

Non-inferiority of fever rates in Group A as compared to Group B was demonstrated.

Table Td502-17.5c Overview of the Number and Percentage of Group A and Group B with "Any" Solicited Systemic Event from Days 0-14

	Group A (Tdap + Flu)		Group B (Flu, Tdap)	
Type of Adverse Event	**n/N**	**%**	**n/N**	**%**
Any Solicited Systemic Events (Days 0-14)	**246/356**	**69.1**	**218/340**	**64.1**
Solicited Reactions (Days 0-14)				
Fever (≥ 38°C/100.4°F)	15/356	4.26	8/340	2.38
Headache	140/356	39.77	128/340	37.76
Generalized Body Aches	103/356	29.26	74/340	21.83
Tiredness/Decreased Energy	115/356	32.67	107/340	31.56
Chills	51/356	14.49	46/340	13.57
Nausea	47/356	13.35	47/340	13.86
Vomiting	12/356	3.41	13/340	3.83
Diarrhea	53/356	15.06	39/340	11.5
Sore and/or Swollen Joints	44/356	12.5	32/340	9.44
Presence of Rash	1/356	0.28	5/340	1.47
Solicited Reactions (Days 0-3) Fever (≥ 38°C/100.4°F)	6/356	1.70	3/340	0.89

Adapted from Aventis Pasteur eBLA, Tables 5.27 – 5.36, in Td502 pages 104 - 113.
n/N, % = Number and percentage of participants. The percent value is based on the number of evaluated participants excluding missing observations.

17.5.3. Unsolicited AEs

The proportion of subjects reporting at least one unsolicited AE post-Tdap was higher in Group A than Group B, 34.6% vs. 31.8% respectively. The most commonly reported unsolicited AEs were classified under Infections and Infestations, followed by Respiratory, Thoracic and Mediastinal Disorders. The events do not have an apparent relationship with receipt of the Tdap.

Whole arm swelling, new onset diabetes, autoimmune disorders, and seizures were specifically monitored during the trial, and none of these events were observed.

17.5.4. SAEs

Two SAEs, one from each study group, were reported in the trial. In Group A, 63.3 year old male had a myocardial infarction on Day 3 post-vaccination. In Group B, 12 days prior to receipt of Tdap (but after study enrollment and receipt of flu vaccine), a 49.6 year old female was hospitalized for a right inguinal hernia.

18. ASSESSMENT

Not all of the primary and secondary objectives for this trial were met. Non-inferiority was not clearly demonstrated for the immune responses to tetanus and the pertussis antigens. For tetanus, non-inferiority of Group A was not demonstrated for booster response rates (Group A = 78.8% and Group B = 83.3%, UCL = 10.42%, slightly exceeding the criterion of 10%), though non-inferiority was demonstrated for percent of subjects with seroprotective levels $\geq$ 0.1 IU/ml and for GMCs. For the tetanus booster response rates, though statistically significant, the difference in rates is not likely of clinical significance.

For pertussis responses, the non-inferiority following concomitant (Group A) as compared to separate (Group B) administration was demonstrated for antibodies to PT, FHA and FIM, but not PRN. Additionally, the pertussis antibodies to all of the antigens were consistently lower in Group A than those in Group B. However, both Group A and Group B had robust rises in pertussis antibodies to each of the antigens, with values similar to those in adults in Td506 for PT, FHA and FIM, though the PRN antibodies are lower. No formal statistical comparisons were planned or performed for comparing results from Td502 with those from TD506 or Sweden I.

For safety, non-inferiority criteria were met for erythema, swelling and fever but not for pain at the injection site (UCL for 95% CI exceed 10%, equaling 12.96% for "any" and 10.71% for "moderate and severe" intensities). The incidence of other solicited AEs, unsolicited AEs and SAEs were not different between the 2 study groups.

Overall, Group A appeared to have more frequent and possibly more severe, solicited reactions though the differences between the groups were not substantial. Additionally, Group A had lower antibody responses to some of the vaccine antigens, though again the clinical significance is not clear. The risks of increased reactogenicity, and possibly lower immunogenicity, should be considered in the context of possible benefits of concomitant immunization.

Td501: Safety and Immunogenicity of Tetanus and Diphtheria Toxoids Adsorbed, Combined with Component Pertussis (Tdap) Vaccine Given Concurrently with Hepatitis B Vaccine Compared to Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Given 4-6 Weeks Before Hepatitis B Vaccine in Adolescents 11- 14 Years of Age.

19. SUMMARY

Td501 was a multi-center, open-labeled, randomized, controlled non-pivotal study designed to assess the safety and immune responses generated by Tdap vaccine and hepatitis B vaccine given concurrently or separately in adolescents, 11-14 years of age.

In Td501, 410 adolescents age 11-14 years were divided into 2 vaccine groups. In Group A, 206 subjects received Tdap and hepatitis B vaccines concurrently and in Group B, 204 subjects received the Tdap vaccine at the first visit, then 4-6 weeks later received the Hep B vaccine (a 2nd dose of Hep B was given 4-6 weeks later at Visit 3 for this group). The primary objective was assessment of immunogenicity and the secondary objective was assessment of the safety profiles.

Non-inferiority of the immune responses to all of the vaccine antigens was demonstrated when the Tdap and Hep B vaccines were given concurrently (Group A) or separately (Group B). For safety parameters, non-inferiority of Group A compared to Group B was not demonstrated for erythema ("any" intensity) and swelling ("any" and "moderate and severe" intensities), though it was observed for pain and fever.

20. HYPOTHESES AND OBJECTIVES

20.1. Primary Objective

To determine whether the concurrent administration of Tdap and Hepatitis B (Hep B) vaccine in adolescents 11-14 years of age induces antibody responses that are similar to those observed when the vaccines are given 4-6 weeks apart.

20.2. Primary Hypothesis

20.2.1. The seroprotection rates for tetanus and diphtheria, as well as the post-vaccination GMCs for pertussis antigens PT, FHA, FIM and PRN, measured 4-6 weeks after a booster dose of Tdap given concurrently with Hep B vaccine in adolescents 11-14 years of age are non-inferior to those achieved by participants receiving Tdap Vaccine alone 4-6 weeks before Hep B vaccine.

20.2.2. The Hep B seroprotection rate measured 4-6 weeks after the 2nd dose of Hep B vaccine given to participants 11-14 years of age who received the 1st dose of Hep B concurrently with Tdap is non-inferior to the seroprotection rate of participants receiving the 1st dose of Hep B alone, 4-6 weeks after Tdap vaccine.

Comparisons of booster rates and GMCs for diphtheria and tetanus were added to the immunogenicity analysis during the conduct of the trial.

20.3. Secondary Objective

To determine whether the safety following a booster dose of Tdap vaccine given concurrently with Hep B is comparable to the safety of a booster dose of Tdap administered alone in adolescents.

20.4. Secondary Hypothesis

The safety, in terms of erythema, swelling, pain and fever rates, of a booster dose of Tdap given concurrently with Hep B is non-inferior to the same safety measures in participants given a booster dose of Tdap alone, 4-6 weeks prior to Hep B vaccine.

Safety in terms of other local and systemic solicited AEs, as well as unsolicited AEs and serious AEs is comparable between the groups. The non-inferiority analysis was performed on adverse events (AEs) that are rated as either "any" or "moderate and severe."

21. STUDY DESIGN

Td501 was a Phase 3, randomized, controlled, open-label multi-center trial designed to measure the safety and immunogenicity of Tdap vaccine and the immunogenicity of Hep B vaccine when given concurrently or separately in adolescents 11-14 years of age.

21.1. General Study Methods

General study procedures were similar to those described for Td502, 505 and 506.

21.2. Duration of Participation

All subjects received one dose of Tdap and two doses of Hep B (~ 4 months apart). Both study groups had a total of 4 visits.

Group A (Tdap + Hep B)
Visit 1 - One dose of Tdap plus the 1st dose of Hep B were administered concurrently,
Visit 2 – 4-6 weeks later for serum sampling (post-Tdap serology testing),
Visit 3 – 16-18 weeks later for 2nd dose of Hep B,
Visit 4 – 4-6 weeks later for serum sampling (post-Hep B serology testing)

Group B (Tdap, Hep B)
Visit 1 - One dose of Tdap was administered at enrollment,
Visit 2 – 4-6 weeks later, 1st dose of Hep B vaccine and Tdap serology testing,
Visit 3 – 16-18 weeks later, a 2nd dose of Hep B vaccine,
Visit 4 – 4-6 weeks later for serum sampling (post-Hep B serology testing).

21.3. Safety Monitoring

Safety monitoring was the same as described for the other trials, e.g. Td502, 505 and 506. Safety monitoring was not performed following receipt of Hep B vaccine alone. Subjects in each group had 150-180 day duration of safety follow-up. Because of the study design, Group B was followed about 4-6 weeks longer than Group A.

21.4. Immunogenicity Monitoring

Serum samples were obtained prior to and 4-6 weeks after Tdap, as well as 4-6 weeks after the 2nd dose of Hep B for all subjects.

21.5. Laboratory Methods

The dip, tet and pertussis assays were performed as described in Td506. The ----------®------- ---------- was used to measure antibodies to HbsAg with results in mIU/ml.

22. PRODUCT DESCRIPTION

22.1. Tdap

As described above.

22.2. Hepatitis B Vaccine (Recombivax®)

A two-dose regimen (1.0 ml/dose) for Hep B was used. Each 1.0 ml dose contained 10 μg pf Hep B surface antigen (HbsAg),--- ---------- and Al hydroxide as the adjuvant.

23. STUDY POPULATIONS

The analysis populations used in this study:

- Intent-to-treat (ITT) population – included all participants who were randomized and received Tdap vaccine. The ITT population was used for all safety analyses.
- Per-protocol population – included a subset of the ITT population who were vaccinated and bled with no study violations, which might have impacted upon the immune responses. All immunogenicity analyses were performed using the ITT and PP populations. The PP population was used for analyses fir the primary hypotheses.

24. RESULTS

24.1. Description of the Participants

A total of 410 subjects were randomized in the study; 206 into Group A (Tdap + Hep B) and 204 into Group B (Tdap, Hep B). A total of 95.6% of each group completed the trial.

Groups A and B had comparable distribution for age, gender and ethnic origin. There were more male participants (58.6% of all enrollees), and the majority of subjects were Caucasian (93.3%). The ethnicities of the remaining subjects were 2.0% Asian, 0.5% Black, and 4.0% "other."

24.1.1. Vaccination History

The proportion of participants who had at least 5 doses of a diphtheria-tetanus-pertussis-containing vaccine documented was comparable for Group A (88.1%) and B (90%).

24.2. Immungoenicity Results

The PP population was evaluated for the primary immunogenicity analyses, though the analyses were also performed for the ITT population. Except the pertussis GMC comparisons, the results for the PPI and ITT populations were similar. An overall summary of the immunogenicity results is shown in Table Td501-24.2a.

Table Td501-24.2a. Summary of Primary Immunogenicity Endpoints

	Group A (Tdap +Hep B)		Group B (Tdap, Hep B)	
Endpoint	**n/N**	**%**	**n/N**	**%**
Seroprotection ≥ 0.1 IU/ml				
Diphtheria	161/161	100	150/151	99.3
Tetanus	161/161	100	151/151	100
Seroprotection ≥ 10.0 mix/ml				
Hepatitis B	155/161	96.3	146/150	97.3
Booster Response Rates*				
Diphtheria	157/161	97.5	145/151	96.0
Tetanus	1579161	98.8	148/151	98.0
GMCs	**N**	**GMC**	**N**	**GMC**
Diphtheria(IU/ml)	161	6.7	151	6.2
Tetanus (IU/ml)	161	11.7	151	11.5
PT (EU/ml)	161	303.5	151	321.6
FHA (EU/ml)	161	301.5	151	305.4
FIM (EU/ml)	161	1906.4	151	1926.7
PRN (EU/ml)	161	292.9	151	284.6
Hep B	161	950.9	150	998.0

Adapted from Aventis Pasteur eBLA, Table 5.6 in Td501 page 74.
n, % = number and percent of participants who achieved seroprotective levels and booster response.
N = number of participants evaluated.
GMC = Geometric mean concentration post-vaccination, excluding missing observations.
*Booster rates were defined as for diphtheria: 4-fold rises if pre-vac titers were < 2.56 IU/ml or 2-fold rises if pre-vac titer were >2.56 IU/ml and for tetanus: 4-fold rises if pre-vac titers were ≤ 2.7 IU/ml or 2-fold rises if pre-vac titer were >2.7 IU/ml

24.2.1. Diphtheria and Tetanus

24.2.1.1. Seroprotection Rates

Pre-vaccination seroprotection rates at level ≥ 0.1 IU/ml were high for both groups for diphtheria (78.3% of Group A and 77.5% of Group B) and for tetanus (89.4% of Group A and 96% of Group B). At 4-6 weeks post-vaccination, seroprotective levels were achieved by 100% of Group A and 99.3% of Group B to diphtheria and 100% of both groups to tetanus. For both diphtheria and tetanus, non-inferiority of the seroprotection rates of Group A to Group B was observed, *data not shown*.

24.2.1.2. Booster Response Rates – Diphtheria and Tetanus

For diphtheria, 97.5 % of Group A and 96% of Group B, and for tetanus 98.8% of Group A and 98.0% of Group B achieved booster responses. For both dip and tet, the upper limits of the 95% CI of the difference between Groups B and A were < 10%, demonstrating non-inferiority.

24.2.1.3. GMCs – Diphtheria and Tetanus

Prior to vaccination, GMCs were similar for diphtheria GMCs 0.31 and 0.3 and for tetanus 0.39 and 0.39 respectively for Groups A and B. Robust rises from pre to post-vaccination for GMCs to both antigens were observed for both Group A and Group B. Post-vaccination GMCs are shown on Table Td501-24.2a. Non-inferiority of GMCs for both dip and tet was also demonstrated with comparisons of GMC ratio using 90% CI, as well as 95% CI.

24.2.2. Pertussis

24.2.2.1. Pertussis GMCs

The pre- and post-GMCs were similar for Groups A and B for the PP population. The post-vaccination GMCs are shown on Table Td501-24.2a. In comparison of the ITT with the PP population, the pertussis GMCs were similar for PT, FHA and PRN, though they were lower for FIM (1744.6 EUs/ml for ITT and 1906.4 EUs/ml for PP).

24.2.2.2. Comparison of Pertussis GMCs – Primary Hypothesis

Non-inferiority criteria, comparing GMC ratios using 90% CI, were met for each of the pertussis antigens (Table Td501 - 24.2b). Additionally, non-inferiority was demonstrated for the GMC ratio comparisons using 95% CIs.

Table Td501 - 24.2b. Pertussis Antibodies – Comparison of GMCs

		Group A (Tdap + Hep B)		Group B (Tdap, Hep B)		GMCA/GMCB	90% CI	
Antigen (EU/ml)	**Sample**	**M1**	**GMCA**	**M2**	**GMCB**	**GMC Ratio**	**LCL**	**UCL**
PT	**Pre**	161	12.5	151	11.9	1.05	0.8	1.4
	Post	161	303.5	151	321.6	0.94	0.8	1.3
FHA	**Pre**	161	16.5	151	17.8	0.93	0.7	1.2
	Post	161	301.5	151	305.4	0.99	0.8	1.2
FIM	**Pre**	161	43.1	151	40.4	1.07	0.9	1.3
	Post	161	1906.4	151	1926.7	0.99	0.8	1.2
PRN	**Pre**	161	7.9	151	8.3	0.95	0.7	1.2
	Post	161	292.9	151	284.6	1.03	0.8	1.3

Adapted from Aventis Pasteur eBLA, Tables 5.14 and 9.32 in Td501 pages 82 and 178.
GMCs Ratio = Ratio of GMCs for Tdap+Hep B over Tdap, Hep B.
M1, M2 = Number of participants, not including missing observations, used for comparison.
LCL, UCL = Lower and upper limits of the 2-sided 90% confidence interval for the ratio of GMCs for Tdap+Hep B (Group A) over Tdap, Hep B (Group B).

24.2.3. Hepatitis B

24.2.3.1. Seroprotection Rates

The protective level of antibody to Hep B is considered to be $\geq$ 10 mIU/ml. Prior to vaccination, both study groups had low rates of seroprotective levels: 0.6% in Group A and 0.7% in Group B. At 4-6 weeks after the 2nd dose of Hep B, the majority of participants in both groups achieved protective levels (96.3% of Group A and 97.3% of Group B) as shown on Table Td501-24.2a.

24.2.3.2. Comparison of Seroprotection Rates – Primary Hypothesis

Non-inferiority of the Hep B seroprotection rates was to be concluded if the UL of the 2-sided 95% CI for the difference in rates between Group A and Group B (B-A) is < 10%. Non-inferiority criteria were met (Table Td501-24.2c).

Table Td501-24.2c. Hepatitis B: Comparison of Seroprotection Rates (> 10.0 mIU/ml) for the PP Population.

	Group A Tdap + Hep B		Group B Tdap, Hep B		P2-P1	95% CI of Diff	
Sample	**M1**	**P1**	**M2**	**P2**	**Diff %**	**LCL**	**UCL**
Pre	161	0.62	151	0.66	0.04	-1.73	1.81
Post	161	96.27	150	97.33	1.06	-2.84	4.96

Adapted from Aventis Pasteur Table 5.15, in Td501 page 82
M1, M2 – Sample size, not including missing observations;
P1, P2 – Proportion of Group A and Group B with Hep B seroprotective levels
Diff % = Difference between Group A and Group B

GMCs – Hepatitis B

Pre-vaccination GMCs were similar and low for both Group A [0.32 (95% CI: 0.3, 0.35)] and B [0.33 (95% CI: 0.3, 0.35)]. Post-vaccination GMCs were high for both groups (950.95 for Group A and 998.03 for Group B), as shown on Table 24.2a.

24.3. Safety

The safety analyses were performed using the ITT population. Solicited reactions were collected only after Tdap. A summary of the safety results is shown in Table Td501-24.3a.

Table Td501-24.3a Summary of Safety Results

	Group A Tdap + Hep B		Group B Tdap, Flu		Total N=403	
Type of Adverse Event	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Immediate AE (within 30 min)	1/202	0.5	4/201	2.0	5/403	1.2
Any Solicited Local Reaction (Days 0-14)	178/202	88.1	174/201	86.6	352/403	87.3
Any Solicited Systemic Reaction (Days 0-14)	160/202	79.2	150/202	74.6	310/403	76.9
Solicited Reactions Day 0-14						
Erythema	47/201	23.4	43/201	21.4	90/402	22.4
Swelling	49/201	23.9	36/201	17.9	84/402	20.9
Pain	172/201	85.6	171/201	85.1	343/302	85.3
Fever (≥ 38°C/100.4°F)	11/201	5.5	12/200	6.0	23/401	5.7
Solicited Reactions Day 0-3						
Erythema	40/201	19.9	32/201	19.9	80/402	19.9
Swelling	44/200	22.0	32/201	15.9	76/401	19.0
Pain	168/201	83.6	165/201	82.1	333/402	82.8
Fever (≥ 38°C/100.4°F)	7/201	3.5	7/200	3.5	14/401	3.5
Unsolicited AEs (Day 0 – Day 150 or 180)	74/202	36.6	95/201	47.3	169/403	41.9
Serious AEs (Day 0 – Day 150 or 180)	1/202	0.5	1/201	0.5	2/403	0.5

Adapted from Aventis Pasteur eBLA Table 5.17, in Td501 pages 85-86.
n, % = number and percentage of subjects reporting the event
Any Solicited Local Reactions include Erythema, Pain, Swelling, and Underarm Lymph Node Swelling.
Any Solicited Systemic Reactions include Fever, Headache, Sore/Swollen Joints, Chills, Bodyache, Tiredness, Nausea, Vomiting, Diarrhea, and Rash.

24.3.1. Immediate Reactions

Five immediate reactions following Tdap were reported (1 in Group A and 4 in Group B). One event of severe erythema at the injection site occurred in an 11 year old Group B participant. All participants recovered by 24 hours without sequelae. No anaphylaxis events were reported.

24.3.2. Solicited Reactions

Monitoring solicited reactions was performed similarly to Td502, 505 and Td506.

24.3.2.1. Solicited Local Reactions

Comparable proportions of subjects in both groups experienced at least one local adverse event (AE) during Days 0-14 after Tdap vaccination (88.1% in Group A and 86.6% in Group B). The majority of local AEs occurred from Day 0-3.

The occurrence of "any" swelling was more frequent in Group A (23.9%) than Group B (17.9%) from Days 0-14 and "moderate" swelling also occurred more frequently in Group A (7.5%) than Group B (2.0%). Swelling was also the event most frequently scored as "severe", reported by ~8.5% of both groups.

Erythema, pain and fever occurred at similar rates in Group A and Group B. Pain was the most frequently reported local AE at all time periods. "Any" pain was reported by 85.6% of Group A and 85.1%% of Group B from Days 0-14.

For Limb Swelling, changes of 1-1.99 cm occurred more in Group A (30.41%) than Group B (19.5%), though increases $\geq$ 3cm were more common in Group B (10.5%) than Group A (3.1%). Axillary lymph node swelling occurred in 8 – 9% of both groups. Recurrences of erythema, swelling, pain and fever during Days 0-14 occurred from 0 to 14.9% for each event, and at similar rates in each study group. Late onset reactions for each of the 3 solicited local events occurred in <3.5% of both groups. Late onset reactions for each of the 3 solicited local events occurred in <3.5% of both groups.

24.3.2.2. Comparison of Erythema, Swelling, and Pain Rates

Results for comparisons are shown on Table Td501-24.3b. Non-inferiority criteria were met for pain of "any" intensity from Day 0-14, but not for "any" erythema or for "any" and "moderate & severe" swelling. Pain of "moderate & severe" intensity occurred more frequently in Group B (23.4%) than Group A (19.9%).

Table Td501-24.3b Comparison of Rates for Erythema, Swelling, Pain and Fever at Days 0-14 between Group A (Tdap + Hep B) and Group B (Tdap, Hep B)

	Any					Moderate & Severe				
Adverse Event	**P1 N=201**	**P2 N=201**	**Diff %**	**LCL**	**UCL**	**P1 N=201**	**P2 N=201**	**Diff %**	**LCL**	**UCL**
Erythema	23.4	21.4	1.99	-6.2	10.1	13.4	11.4	2.0	-4.5	8.4
Swelling	23.9	17.9	5.97	-1.9	13.9	15.9	11.9	4.0	-2.8	10.7
Pain	85.6	85.1	0.50	-6.4	7.4	19.9	23.4	-3.9	-11.	4.6
Fever	5.5	6.0	-0.53	-5.1\	4.0	1.5	1.5	-0.0	-2.4	2.4

Adapted from Aventis Pasteur eBLA, Table 5.25 in Td501 page 97.
P1, P2 = Incidence rate of evaluated participants in Group A (Tdap + Hep B) and Group B (Tdap, Hep B) respectively. Each group had 201 participants.
Diff % = Difference in event rates between groups: Group A vs. Group B.
LCL, UCL = Lower and upper limits of the 2-sided 95% CI for the difference.
Fever was defined on Table Td506.3a.

24.3.2.3. Solicited Systemic Reactions

Group A participants had higher rates of solicited systemic AEs than Group B participants during Days 0-14 post-Tdap 79.2% vs. 74.6% respectively. Headache was the most common systemic AE during Days 0-14, occurring in 54% of Group A and 47.3% of Group B.

Sore and/or swollen joints were reported from Days 0-14 by 22.5% of Group A and 17.91% of Group B. These rates are slightly higher than those observed in Td505 and Td506 following Tdap alone (14% and 11.32%, respectively) and than observed in Td502 following concomitant Tdap and influenza vaccines (12.5%). Most of the joint related events were scored as mild or moderate, with 0.5% of Group A and 0.0% of Group B reporting the joints symptoms as "severe" intensity.

Table Td501 - 24.3c. Overview of the Number and Percentage of Group A and Group B with "Any" Solicited Systemic Event from Days 0-14

	Group A (Tdap + Hep B)		Group B (Tdap, Hep B)	
Type of Adverse Event	**n/N**	**%**	**n/N**	**%**
Any Solicited Systemic Events (Days 0-14)	178/202	88.1	174/201	86.6
Solicited Reactions (Days 0-14)				
Fever (≥ 38°C/100.4°F)	11/201	5.5	12/200	6.0
Headache	108/202	54.0	95/201	47.3
Generalized Body Aches	103/202	51.5	82/201	40.8
Tiredness/Decreased Energy	102/202	50.0	90/201	44.8
Chills	34/202	17.0	27/201	13.4
Nausea	31/202	15.5	30/201	14.9
Vomiting	13/202	6.5	5/201	2.5
Diarrhea	24/202	12.0	19/201	9.5
Sore and/or Swollen Joints	45/202	22.5	36/201	17.9
Presence of Rash	9/202	4.5	9/201	4.5
Solicited Reactions (Days 0-3)				
Fever (≥ 38°C/100.4°F)	7/201	3.5	7/200	3.5

Adapted from Aventis Pasteur eBLA, Tables 5.26 – 5.35 in Td501, pages 100 – 109
n/N, % = Number and percentage of participants. The percent value is based on the number of evaluated participants excluding missing observations.
Days 0–3 and Days 0–14: Maximum intensity of event was reported during that period.
Presence of rash = number of participants reporting a rash.

Comparison of Fever Rates – Secondary Hypothesis

For comparison of fever rates, the upper limit of the 95% CI for the difference in "any" and "moderate & severe" were < 10% for all time points.

24.3.3. Unsolicited Adverse Events

Assessments of unsolicited AEs were performed as described for TD506.

The proportion of subjects reporting at least one unsolicited AE post-Tdap vaccination was higher in Group B (47.3%) than Group A (36.6%). The most commonly reported unsolicited AEs were classified under Infections and Infestations (58 participants reported 71 events).

Whole arm swelling, new-onset diabetes, seizures and new-onset autoimmune disorders were also collected. There were no cases of whole arm swelling in either group. One case of new onset-diabetes occurred on Day 23 post-vaccination with Tdap in an 11 year old in Group B. He started insulin therapy and successfully completed the study. This subject's younger sibling had a history of IDDM. There was one possible seizure reported in a 13 year old in Group B, 23 days after Tdap vaccination. The child was seen the following day by the PMD, who performed an

evaluation including an EEG, and the physician did not think the episode was a seizure. The child did not receive any medications and did not have any additional episodes during the study. No other new-onset medical conditions were reported.

24.3.4. Serious Adverse Events

Two SAEs, one from each study group, were reported during the trial. In Group A, a 13.9 year old female was hospitalized for pyelonephritis on Day 87 after Tdap immunization. In Group B, an 11.1 year old male was hospitalized for appendicitis on Day 35 after Tdap vaccination. Neither event was considered to be related to study vaccine.

25. ASSESSMENT

The immune responses to all of the vaccine antigens after concomitant vaccination were non-inferior to the responses after separate administration. For safety parameters, non-inferiority of Group A to the profile of Group B was not demonstrated for solicited local reactions of "any" erythema and "any" and "moderate & severe" swelling. Non-inferiority was observed for pain and fever, the other two parameters assessed as part of the safety hypothesis.

The incidence of other solicited AEs, unsolicited AEs and SAEs were not different between the 2 study groups. Of note, reports of swollen and/or sore joints were frequent (~22% for concomitant vaccination and ~12% for separate administration) and appeared more frequent in this trial compared to the others in the BLA.

In summary, non-inferiority of the immune responses to concomitant administration was demonstrated and the overall safety profiles were similar for concomitant and separate administration of Tdap and Hep B, though there was an increase in local reactions for participants who received concomitant administration. The increase rate of local reactions for concomitant use of Tdap and Hep should be considered in context with the possible benefits of concurrent administration.

SUPPORTIVE TRIALS

TITLE: Serology Bridging Plan for the Pertussis Responses in the Tdap Vaccine Clinical Trial Td505 in the United States and the Sweden I and II Efficacy Trials (ADACEL Serology Bridging Study).

1. SUMMARY

This Serology Bridging Study was designed for comparing pertussis antibodies in serum samples following ADACEL™ (Td505) with antibodies in serum samples obtained in the Swedish Efficacy trials. Data from this laboratory-based study were used to demonstrate that the immune responses to the pertussis antigens in ADACEL™ are similar to the responses observed after three doses of DAPTACEL in the Swedish efficacy trials. The sponsor states that this comparison will provide additional assurance that efficacy of the component pertussis vaccine can be extrapolated to US subjects.

For the primary analysis of the ADACEL Serology Bridging Study, available sera form Sweden I were tested simultaneously with sera obtained from Td505 (lot consistency study). The pertussis antibody results for the samples from Sweden I tested in this Serology Bridging Study were used for comparison of the pertussis antibody responses achieved by adolescents and adults in Td506. Additionally, Aventis elected to evaluate available sera from Sweden II Efficacy Trial as an observational objective.

Serum testing for anti-pertussis antibodies was conducted in the CIP- CA over approximately 8 to 9 weeks in 2002. The protocol for the Serology Bridging Study was submitted to CBER in August 2003, after the assays had been completed.

2. BACKGROUND

2.1. Sweden I Efficacy Trial

The Sweden I Trial was initiated in March 1992 as a randomized, blinded, controlled multicenter trial designed to assess the efficacy of a 2-component acellular pertussis vaccine ($DTaP_2$ containing PT and FHA, GlaxoSmith Kline, Belgium) and 5-component DTAP from AP (APL, Canada) as compared to whole cell pertussis vaccine (DTwP, AP United States) and a diphtheria and tetanus vaccine (DT, Swedish Bacteriological Laboratories). Infants were vaccinated at 2, 4 and 6 months of age and were followed through February 1995. Of 9829 infants enrolled, 2551 received DTAP and efficacy against the primary case definition of pertussis [i.e. laboratory-confirmed cased with $\geq$ 21 days of paroxysmal cough (WHO criteria)] was 85% (95% CI: 79.5%, 89%). Furthermore, the efficacy conferred by DTaP against mild and atypical pertussis (defined as laboratory-confirmed pertussis with at least one day of cough) was 77.9% (95% CI: 72.6%, 82.5%). Additionally, the efficacy of DTaP remained at 80% or higher during the two years of follow-up. The results for DTaP and the other vaccines in Sweden I are shown in Table 1.2.1.

Table 2.1.Sweden I Acellular Pertussis Vaccine Efficacy Trial

Vaccine	N[1]	Efficacy, %[2]	95% CI
DTAP (APL - Canada)	2069	85	79.5, 89
$DTaP_2$, (GSK)	2082	57.2	47.3, 65.3
DTwP, (API – U.S.)	2001	48.3	37, 57.6
DT (SBL)	2068	Negative control	-

[1]Number of subjects completed 3 doses at 2, 4, and 6 months.
[2]Efficacy estimates are based on the 4-armed part of the study.

2.2. Sweden II Efficacy Trial

The Sweden II Efficacy Trial was designed to assess the efficacy of 3 acellular pertussis vaccines combined with diphtheria and tetanus toxoids: 1) hybrid (higher content of PT and FHA) DTAP [HDTAP, APL Canada], 2) $DTaP_2$ (described above, GSK), and 3) $DTaP_3$ (containing PT, FHA and PRN from Chiron, Italy). The trial enrolled 82, 892 children. Most infants were immunized at 3, 5, and 12 months, except a subset (n=10,194) received vaccines on a 2, 4, and 6 month schedule. Because no placebo was included in this trial, absolute efficacy could not be calculated. Relative efficacy was estimated from hazard ratios obtained by Cox's proportional hazards ratio regression model, comparing HDTAP (as well as the other ACVs) to DTwP.

Results in this trial showed that the HDCPT and $DTaP_3$ did not differ significantly from the DTwP against culture-confirmed pertussis with paroxysmal cough for $\geq$ 21 days in the primary analysis.

3. DESIGN

3.1. Serum Availability

From Sweden I, 181 paired sera (pre-immunization and one month post-dose 3) were collected from the subset of subjects enrolled in a 2, 4, and 6 mo schedule, and 80 pairs were available for testing in this Bridging Study. These samples were not randomized. They were chosen because they had sufficient volume available for testing. The sponsor provided a summary of the GMCs for the anti-pertussis antibodies for the 81 sera (including the 80 pairs available for current testing), as compared to the GMCs for the total 181 sera from Sweden I (testing done by the Swedish Institute of Infectious Diseases Control Laboratory as part of Sweden I). For comparisons of the GMCs in samples from Sweden I, the GMC ratios ranged form 0.98 to 1.17 for the pertussis antigens, with the high of 1.17 for PRN. The ratios for the GMCs (GMC of 80 available paired sera/GMC of all 181 paired sera) suggest that the 80 available pairs are representative of 181 paired sera from Sweden I.

From the Sweden II trial, 17 paired sera were available from the 58 post-3rd dose sera (collected at 13 months from subjects on a 3, 5, and 12 mo schedule).

For Td505, a subset of 1051 of the 1811 subjects were in the per protocol (PP) population for serology. Immunogenicity results from the different lots of Tdap in Td505 were combined, which was acceptable since consistency of the immunogenicity of the lots was demonstrated.

3.2. Laboratory Methods

3.2.1. Pertussis ELISA

Serum samples were stored at $\leq$ -20°C. The indirect ELISA assays for antibodies to each pertussis antigen were performed by the CIP-CA. Results were calculated in ELISA units per milliliter (EU/ml) by comparison to a pool of in-house reference antibody standards of assigned units. The in-house standards were calibrated to the US Human Reference Lots 3 or 4.

For values of antibodies recorded as less than the lower limit of quantitation (LOQ), the following approach was used:

- LOQ was used for the calculation of 4-fold response rates, and
- LOQ/2 was used for the calculation of GMCs.

4. PRIMARY AND OBSERVATIONAL CRITERIA

4.1. Primary Evaluation Criteria

4.1.1. Hypothesis #1

The evaluation criterion for Primary Hypothesis #1 was the percentage of subjects in Td505 and Sweden I Efficacy Trial who achieved seroconversion to each pertussis antigen. Seroconversion was defined as $\geq$ 4-fold rise in antibody level from the pre-booster (in Td505) or from the pre-1st dose (in Sweden I) antibody level.

4.1.2. Hypothesis #2

The evaluation criterion for Primary Hypothesis #2 was the GMC to each pertussis antigen in sera from Tdap recipients in Td505 and DTaP recipients in Sweden I. GMCs were calculated for pre- and post-booster (Tdap) and for pre-1st and post-3rd dose (DTaP) sera samples.

4.1.3. Observational Evaluation Criteria

The evaluation criterion for the observational objective was the percentage of samples from subjects in Td505 and Sweden II that achieved seroconversion to each pertussis antigen.

GMCs were also calculated for each pertussis antigen for the pre- and post-booster for samples from Td505 and for pre-1st and post-3rd dose for samples from Sweden II.

5. RESULTS

5.1. Immunogencity for Td505

The pertussis immunogenicity results for Td505 are provided above in the Summary for Td505.

5.2. Seroconversion Rates – Hypothesis #1

Non-inferiority of responses to Tdap compared to DTaP was demonstrated for all of the pertussis antigens with the upper limits of the 2-sided 95% CI of the differences in the seroconversion rates were less than 10% (Table 5.2a). Seroconversion rates following Tdap were greater than after DTaP for PT, FHA and FIM, but not PRN (results were similar).

5.2.1. RCDs

For each pertussis antigen, there was very little overlap between the pre- and post-immunization RCD curves between infants and adolescents in Td505. The RCD curves were similar to those observed for Td506. *Td505 RCD curves not shown.*

Table 5.2a Comparison of Four-Fold Rises in Pertussis Antibodies Following Tdap in Study Td505 or DTaP in Sweden I Efficacy Trial

	DTaP - Sweden I Trial 4-fold Rises				Tdap – Td505 Trial 4-fold Rises				DTaP vs. Tdap	
Pertussis Antigens	**N**	**n**	**%**	**95% CI**	**N**	**n**	**%**	**95% CI**	**Diff %**	**95% CI**
PT	80	69	86.3	(76.7, 92.9)	1051	937	89.2	(87.1, 91.0)	-2.9	(-10.7, 4.9)
FHA	80	55	68.8	(57.4, 78.7)	1050	867	82.6	(80.1, 84.8)	-13.8	(-24.2, -3.4)
FIM	80	69	86.3	(76.7, 92.9)	1050	979	93.2	(91.5, 94.7)	-7.0	(-14.7, 0.7)
PRN	80	79	98.8	(93.2, 100)	1051	989	94.1	(92.5, 95.4)	4.6	(1.8, 7.5)

Adapted from Aventis Pasteur eBLA, Table 5.2, page 36
N=sample size evaluated from each study
n,% = Number and percent of subjects with post/pre titer $\geq$ 4
Diff % = difference between DTaP and Tdap groups in $\geq$ 4-fold rises
95% CI = 2-sided 95% confidence interval

5.3. GMCs – Hypothesis #2

5.3.1. GMCs– Paired Data

GMCs to each of the pertussis antigens were 3.3 to 6.5 fold higher after Tdap in adolescents compared to after 3 doses of DTaP in infants. Non-inferiority of the Tdap vaccine was demonstrated, with the upper limit of the 2-sided 90% CI of the GMC ratio (DTaP/Tdap) less than 1.5 for each of the antigens (See Table 5.3).

Table 5.3. Comparison of GMCs of Pertussis Antibodies Following Tdap in Study Td505 or DTaP in Sweden I Efficacy Trial

		DTaP – Sweden I		Tdap – Td505		DTAP vs. Tdap	
Pertussis Antigens*	**Time**	**N**	**GMC**	**N**	**GMC**	**GMC Ratio**	**90% CI**
PT	**Pre**	80	5.2	1051	15.7	0.33	(0.27, 0.42)
	Post	80	86.6	1051	337.9	0.26	(0.21, 0.31)
FHA	**Pre**	80	5.2	1050	21.6	0.24	(0.19, 0.30)
	Post	80	39.9	1050	265.4	0.15	(0.13, 0.17)
FIM	**Pre**	80	13.3	1050	32.3	0.41	(0.33, 0.51)
	Post	80	341.1	1050	1803.5	0.19	(0.15, 0.24)
PRN	**Pre**	80	2.2	1051	10.1	0.21	(0.17, 0.27)
	Post	80	108.1	1051	367.7	0.29	(0.24, 0.36)

*****Antibody results to the pertussis antigens in EUs/ml.
Adapted from Aventis Pasteur eBLA Table 5.2, page 36.
N=sample size tested in each study
n,% = Number and percent of subjects with post/pre titer $\geq$ 4
Diff % = difference between DTaP and Tdap groups in $\geq$ 4-fold rises
95% CI = 2-sided 95% confidence interval

5.4. Sweden II Results (Observational Objective)

Only 17 pairs of serum samples were available from Sweden II for this evaluation, and no statistical analysis was performed. For the Tdap PP population, the Tdap group had higher seroconversion rates for PT, FHA, and FIM, and the rate for PRN was the same in the 2 groups. Additionally, the GMCs were generally higher after Tdap than after HCPDT.

6. CONCLUSIONS

The sponsor stated that the purpose of this trial was to bridge the pertussis immunogenicity following Tdap with that following DTaP from the Sweden I Efficacy Trial. Aventis chose to use samples form Td505 (rather than Td506) for this Serology Bridging Study for a few reasons including, the adolescent population in Td505 was more uniform with respect to age and immunization history, earlier availability

for testing of the Td505 samples and minimal risk of unblinding because everyone in Td505 had received a Tdap vaccine.

This Serology Bridging Study successfully demonstrated that the pertussis antibodies (based upon seroconversion rates and GMCs) achieved following Tdap in adolescents in Td505 were non-inferior to those achieved following DTaP in infants in the Efficacy Trial.

CBER considered the purpose of this study differently from the sponsor's purpose. In CBER's view, this study established the values for the pertussis antibodies for the serum samples from the Sweden I Efficacy trial, when assayed contemporaneously with samples following Tdap using current laboratory methods. CBER discussed with the sponsor that comparison of Sweden I with Td505 would be viewed as supportive, but comparison of antibodies with the samples from adolescents and adults in Study Td506 would be considered as the primary analysis for the serologic bridge to efficacy. The results of the comparison of immunogenicity in Td506 and Sweden I are discussed in the Summary of Td506.

SUPPORTIVE TRIALS - ABBREVIATED CLINICAL STUDY REPORTS

TC9704: Safety and Immunogenicity of One Lot of Tetanus and Diphtheria Toxoids Adsorbed Combined with Three Lots of Component Pertussis (Tdap) Vaccine Compared to Tetanus and Diphtheria Toxoids Adsorbed (Td) and Component Pertussis (ap) Vaccine Given Separately in Adults and Adolescents.

SUMMARY of TC9704
This was a randomized, double-blind, controlled clinical trial with five groups (planned 152 subjects/group, total = 760). The five groups included three groups that received one of 3 lots of Tdap (Lots 1, 2 and 3), one group that received Td then ap vaccine one month later, and one group that received ap followed by Td vaccine one month later. Only the three lots of Tdap evaluated for lot consistency are considered relevant for the ADACEL BLA. The recipients of the 3 lots of Tdap contributed 749 subjects to the BLA safety database, including 92 (12.3%) adolescents aged 12-17 years and 657 (87.7%) adults aged 18-54 years.

The safety profiles (solicited events from Days 0-8 were collected) and the immune responses were similar to those observed in the pivotal and non-pivotal studies in the BLA. The results from this trial were used to support further clinical development of the reduced antigen formulation Tdap for use in adolescents and adults.

TD9707: Safety and Immunogenicity of Tetanus and Diphtheria Toxoids Adsorbed Combined with Three Lots of Component Pertussis Vaccine and Inactivated Poliomyelitis Vaccine Grown on ------ Cells (TdcP-vIPV Vaccine) in Adolescents and Adults *Compared to* One Lot of Tetanus and Diphtheria Toxoids Adsorbed in Combination with Inactivated Poliomyelitis Vaccine Grown on --------- Cells (Td-mIPV Vaccine) Given Separately from One Lot of Component Pertussis Vaccine (cP Vaccine) in Adolescents *and* One Lot of Tetanus and Diphtheria Toxoids Adsorbed (Td Vaccine) and One Lot of Component Pertussis Vaccine (cP Vaccine) Given Separately in Adults *and* One Lot of Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis Vaccine (Tdap Vaccine) Given Separately from Inactivated Poliomyelitis Vaccine Grown on Vero Cells (vIPV Vaccine) in Adults.

SUMMARY of TD9707
This was a randomized, blinded, controlled clinical trial with ten groups (planned 125 subjects per group, total = 1250). The ten groups included three groups that were considered relevant to this BLA: one group that received Td then ap vaccine one month later, and one group that received Tdap followed by vIPV vaccine one month later), and one group received Tdap followed by ap one month later (Study Groups 5,

6 and 7 respectively), for a contribution of 374 adult subjects (age 18-60 years) to the ADACEL BLA safety database. Safety monitoring was performed similarly to the pivotal studies.

The safety profiles, including in Group 7 who received two doses of the ap vaccine, were similar to those observed in the pivotal and non-pivotal studies in the BLA. Interestingly, the rates for solicited local AEs tended to be lower following the second dose of ap vaccine during the >24 to 72 hour period.

TD9805: Safety And Immunogenicity of Tetanus And Diphtheria Toxoids Adsorbed Combined With Component Pertussis (Tdap) Vaccine, Compared To Tetanus And Diphtheria Toxoids Adsorbed Combined With Component Pertussis (Tdap) Vaccine And Hepatitis B Vaccine Given Concurrently In Adolescents 11-14 Years of Age

SUMMARY OF TD9805
This was a randomized, controlled clinical trial with two groups: Group 1 received Tdap vaccine followed 4-6 weeks later by Hep B vaccine and Group 2 received Tdap + Hep B vaccine concurrently (n = 136 subjects per group were enrolled). Participants were adolescents 11-14 years of age. A three-dose regimen for Hep B vaccine was used, and the 2nd and 3rd doses of Hep B were given 1 and 6 months after the 1st dose. Safety monitoring was performed similarly to the pivotal and non-pivotal trials.

The safety profiles of both study groups were similar to each other, as well as to the profiles observed in the pivotal and non-pivotal studies in the BLA.

For immunogenicity, over 99% of participants in both groups achieved seroprotective levels (≥ 10 mIU/mL) for Hepatitis B antibodies, suggesting that concurrent administration with Tdap vaccine does not interfere with Hepatitis B immunization. Additionally, comparability was observed for the immunogenicity profiles for dip and tet (seroprotective levels ≥ 0.1 IU/ml and ≥ 1.0 IU/ml) and pertussis antibodies (percent with 4-fold rises) for Groups 1 and 2, suggesting that concurrent administration with Hepatitis B Vaccine does not interfere with Tdap vaccination. This trial was used to support licensure of Tdap in Canada. This study contributed 269 adolescents to the ADACEL safety database.

Additionally, the immuogenicity results from TC9704 and TD9707 were used for the historical controls, including antibody cut-off values, though the data are not discussed in this document.

CONCLUSIONS
The clinical trials with ADACEL™ demonstrated the safety and immunogenicity of the vaccine as compared to a U.S. licensed Td. Non-inferiority of the immune responses elicited by ADACEL™ compared to those of infants following DTaP in the Sweden I Efficacy Trial was also demonstrated. The ADACEL™ vaccine elicited booster responses to the vaccine antigens in most recipients. Additionally, data have been provided that support concomitant administration of ADACEL™ with influenza vaccine in adults and hepatitis B vaccine in adolescents.

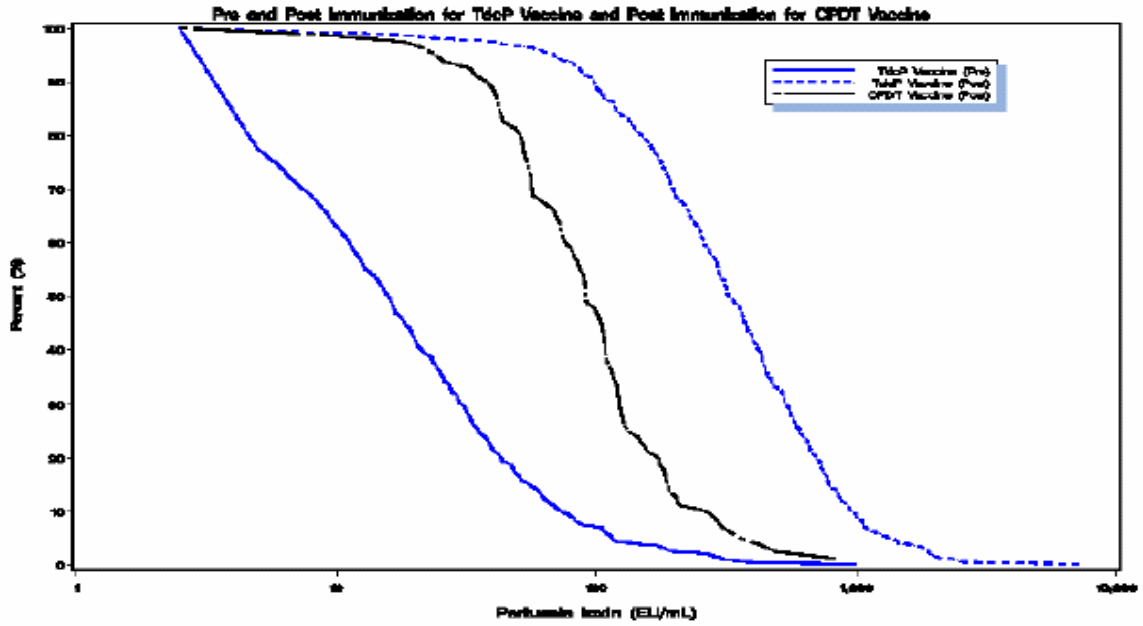

Figure 5.2: PT RCD Curves CPDT (DAPTACEL) Vaccine in Sweden I Trial and TdcP Vaccine in Adolescents 11-17 Years in Td506 Trial, PP population

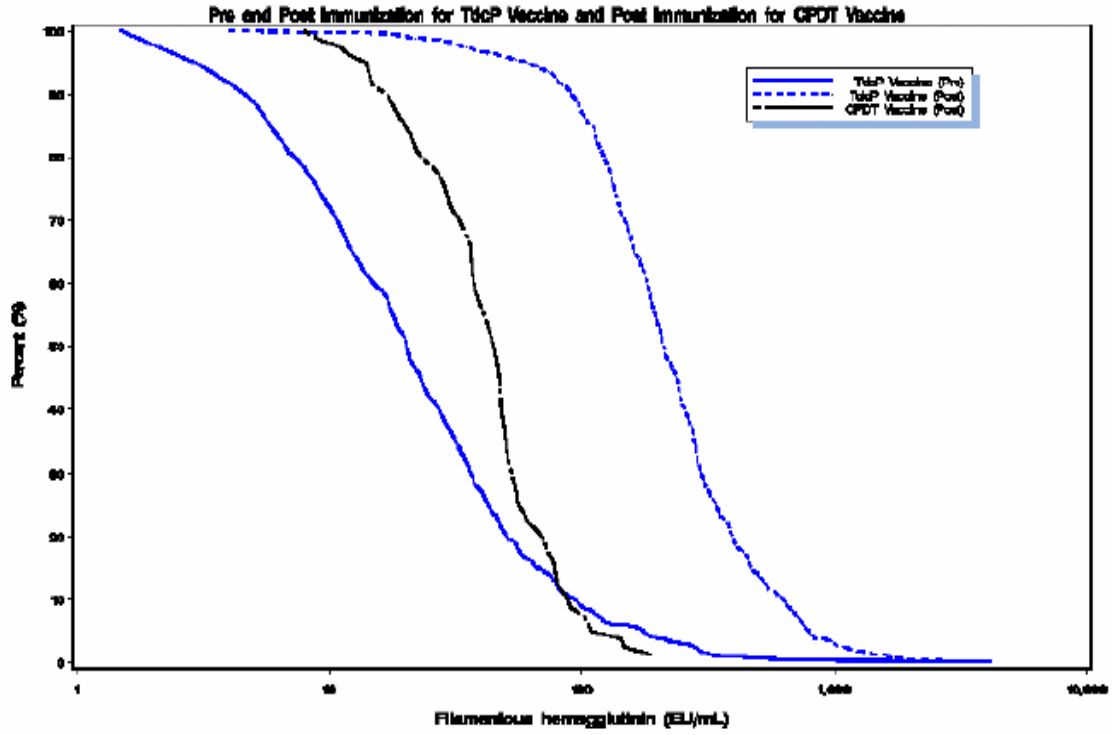

Figure 5.4: FHA RCD Curves CPDT (DAPTACEL) Vaccine in Sweden I Trial and TdcP Vaccine in Adolescents 11-17 Years in Td506 Trial, PP population

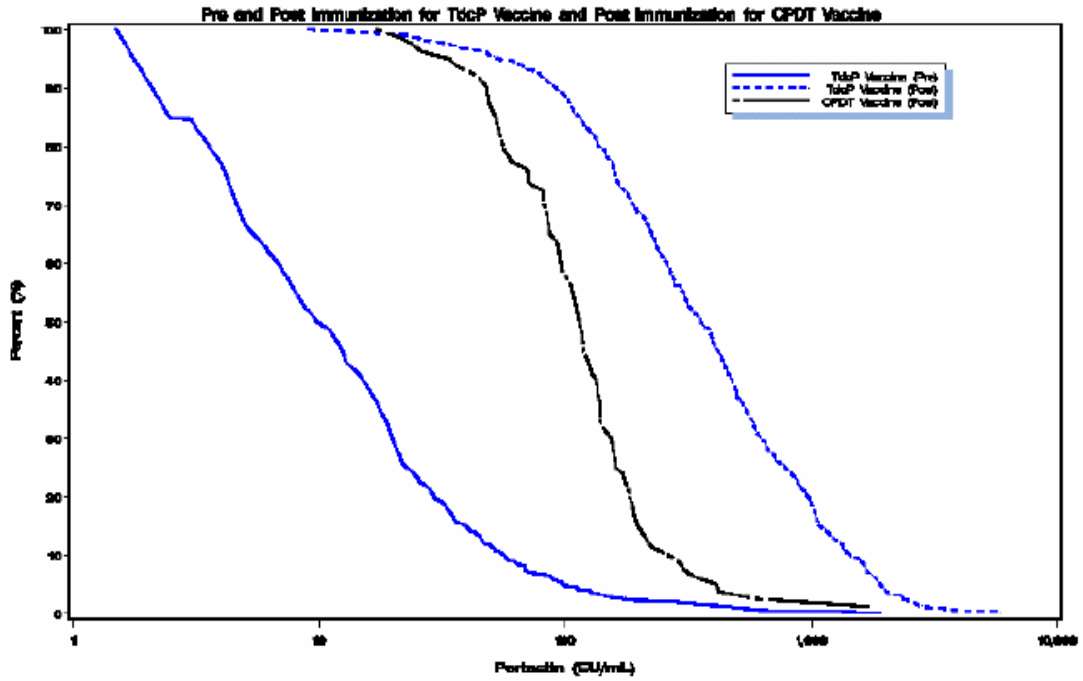

Figure 5.8: PRN RCD Curves CPDT (DAPTACEL) Vaccine in Sweden I Trial and TdcP Vaccine in Adolescents 11-17 Years in Td506 Trial, PP population

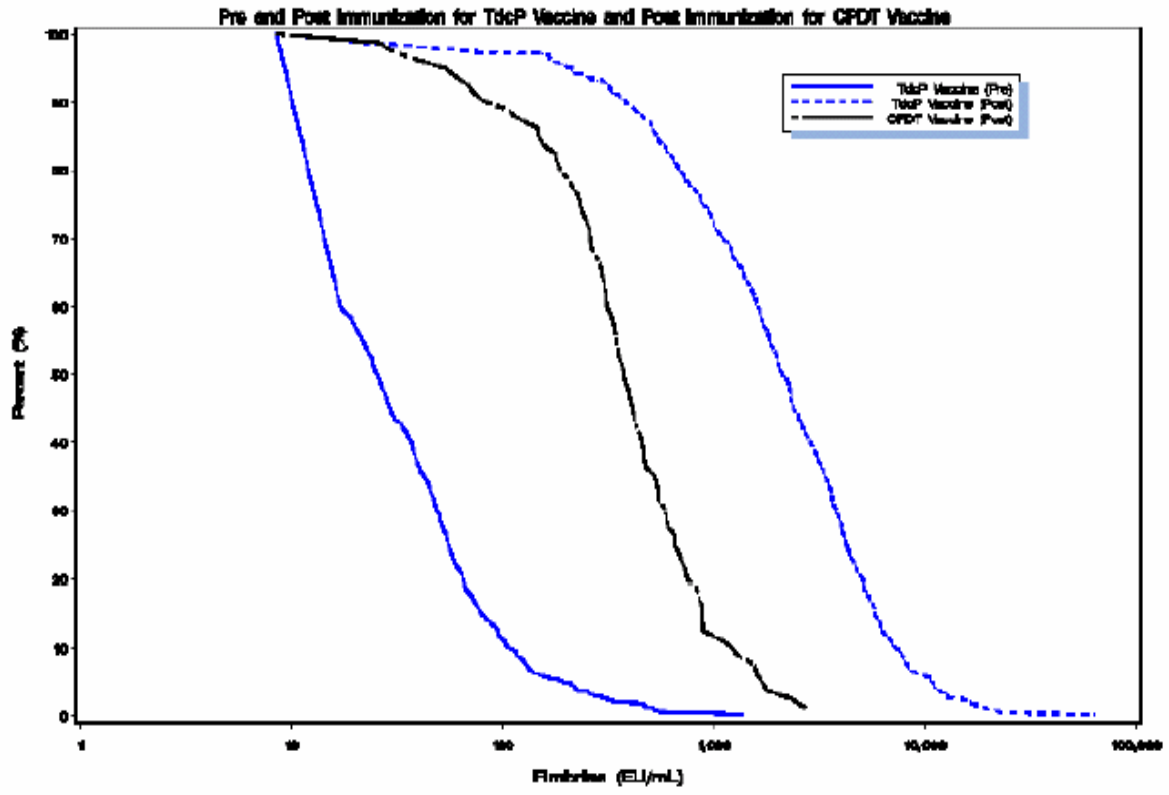

Figure 5.6: FIM RCD Curves CPDT (DAPTACEL) Vaccine in Sweden I Trial and TdcP Vaccine in Adolescents 11-17 Years in Td506 Trial, PP population

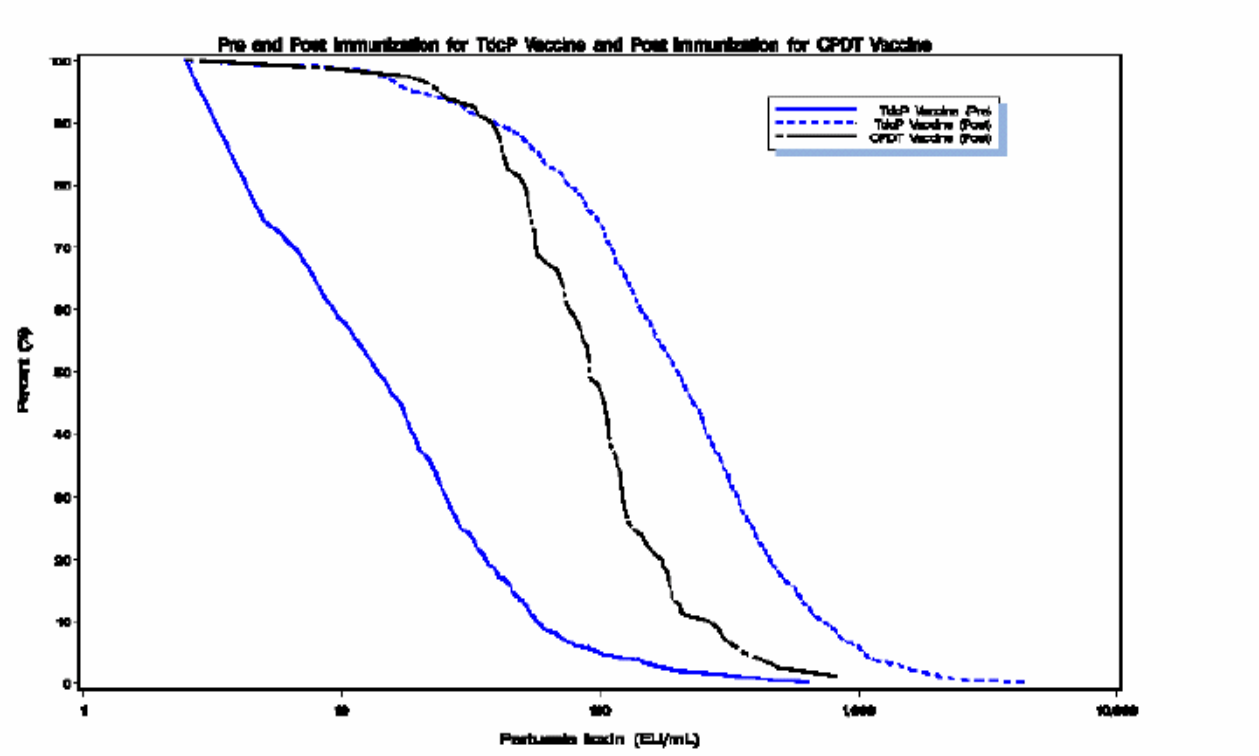

Figure 5.3: PT RCD Curves CPDT (DAPTACEL) Vaccine in Sweden I Trial and TdcP Vaccine in Adults 18-64 Years in Td506 Trial, PP population

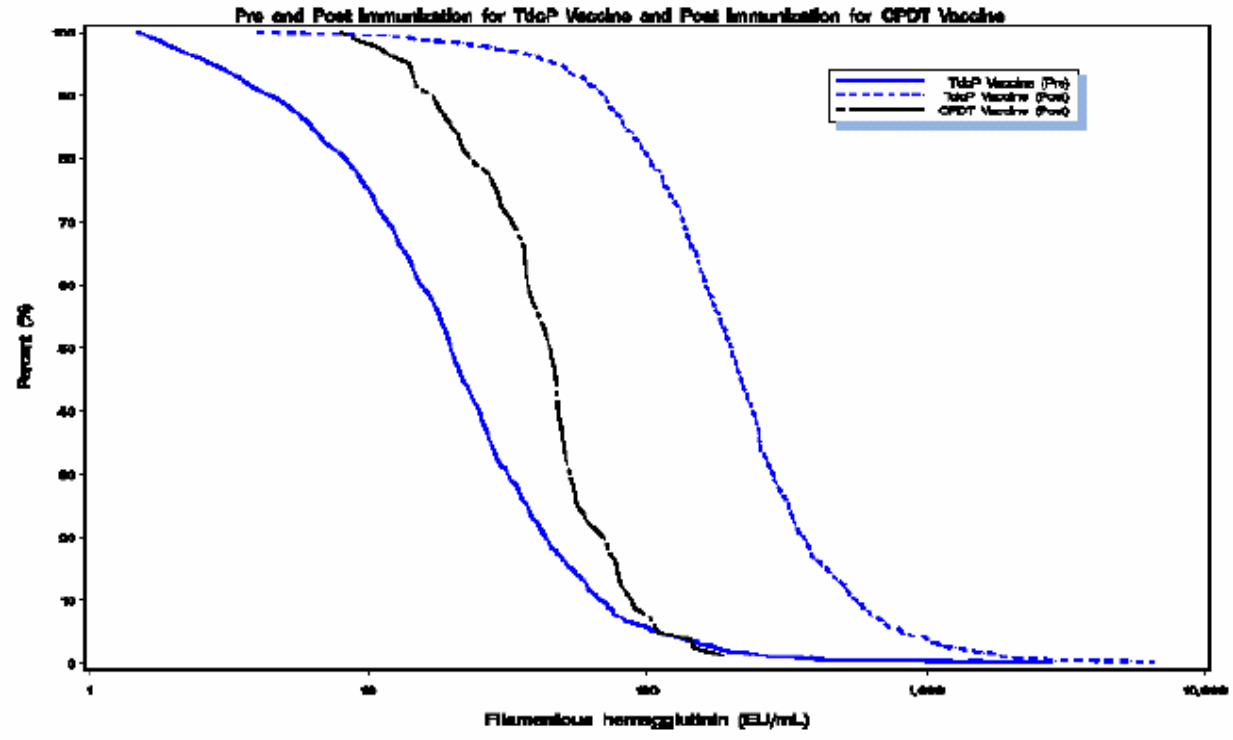

Figure 5.5: FHA RCD Curves CPDT (DAPTACEL) Vaccine in Sweden I Trial and TdcP Vaccine in Adults 18-64 Years in Td506 Trial, PP population

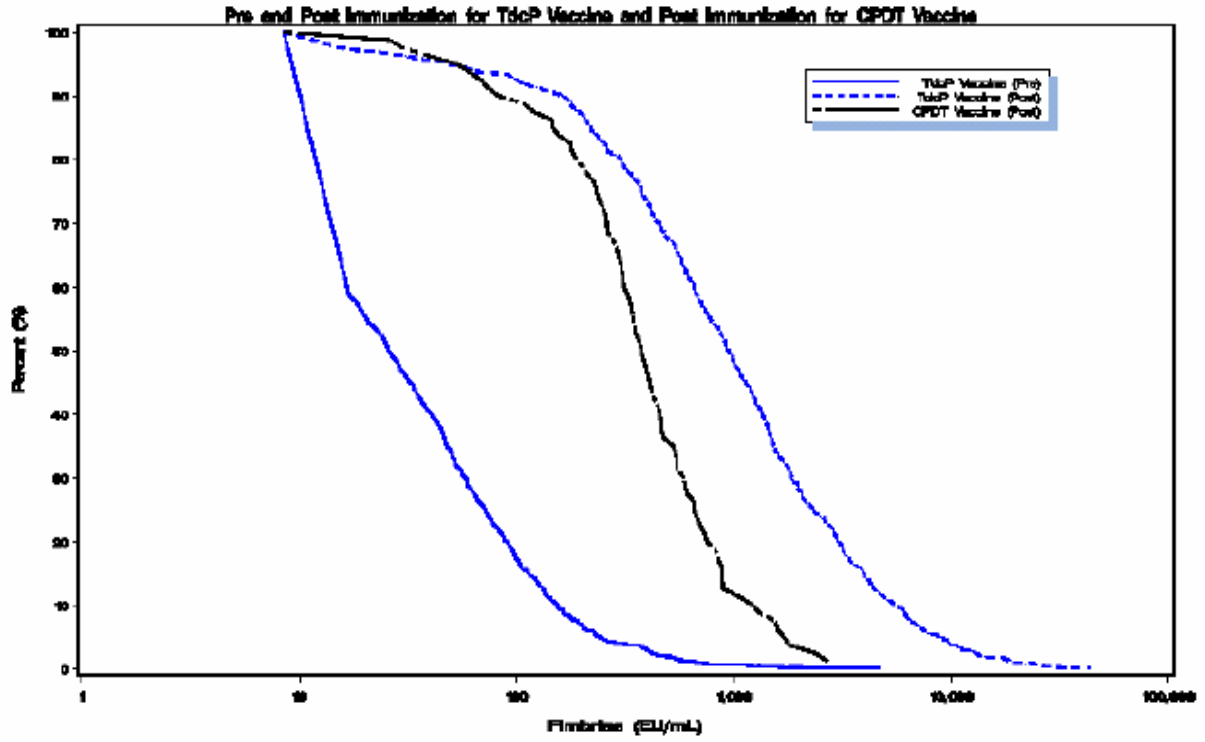

Figure 5.7: FIM RCD Curves CPDT (DAPTACEL) Vaccine in Sweden I Trial and TdcP Vaccine in Adults 18-64 Years in Td506 Trial, PP population

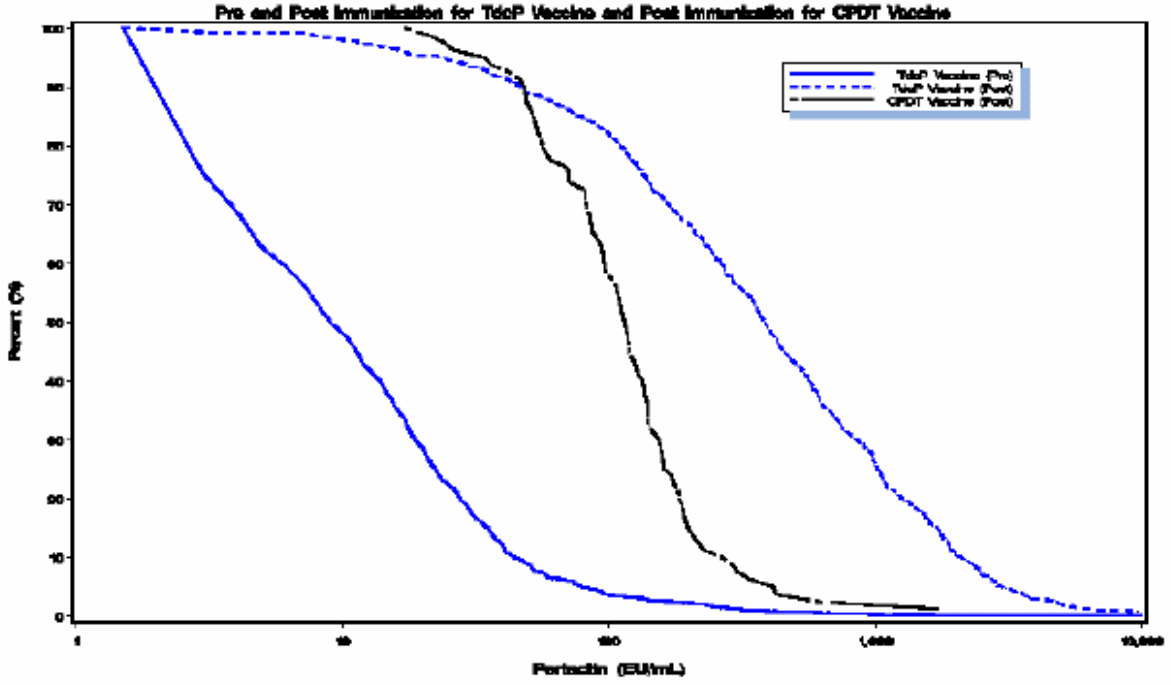

Figure 5.9: PRN RCD Curves CPDT (DAPTACEL) Vaccine in Sweden I Trial and TdcP Vaccine in Adults 18-64 Years in Td506 Trial, PP population