ADACEL™

Tdap Vaccine: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

VRBPAC Briefing Document

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List of Abbreviations

ADACEL™	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed
AE	Adverse event
B. pertussis	*Bordetella pertussis*
C. diphtheriae	*Corynebacterium diphtheriae*
CBER	Centers for Biologics Evaluation and Research
CI	Confidence Interval
COVAXiS™	European trade name of Tetanus and Diphtheria Toxoids Adsorbed, Combined with Component Pertussis Vaccine (Tdap Vaccine)
CRF	Case Report Form
DAPTACEL®	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (formerly TRIPACEL™)
eBLA	Electronic Biologic License Application
ELISA	Enzyme immunoassay or enzyme-linked immunosorbent assay
EU	ELISA units
FDA	Food and Drug Administration
FHA	Filamentous haemagglutinin / filamentous Hemagglutinin
FIM	Fimbriae Types 2 and 3
Flu	Influenza Vaccine
GMT	Geometric Mean Titer
HepB	Hepatitis B Vaccine
IM	Intramuscular
IND	Investigational New Drug
ITTI	Intent-to-treat Immunogenicity Population
ITTS	Intent-to-treat Safety Population
IU	International units
LCL	Lower Confidence Limit

Lf	Limits of flocculation
mg	Milligram
mL	Milliliter
NSAIDS	Non-steroidal anti-inflammatory drugs
PPI	Per Protocol Immunogenicity Population
PRN	Pertactin
PT	Pertussis toxin/toxoid
RCD Curves	Reverse Cumulative Distribution Curves
RR	Relative Risk
SAE	Serious Adverse Event
Td Vaccine	Tetanus and Diphtheria Toxoids Adsorbed
Tdap Vaccine	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (ADACEL™)
UCL	Upper Confidence Limit
US	United States of America
WHO	World Health Organization
µg	Micrograms

1 Executive Summary

1.1 Background Information

At the 15 March 2005 meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC), the Biologic License Application (BLA) for Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed, ADACEL™ (Tdap Vaccine), submitted by Sanofi Pasteur will be presented. ADACEL™, is an adolescent and adult formulation combination vaccine designed to provide protection for adolescents and adults against pertussis, diphtheria and tetanus with an acceptable tolerability profile. The proposed indication for ADACEL™ is for active immunization for the prevention of diphtheria, tetanus and pertussis in adolescents and adults aged 11-64 years.

Despite widespread use of pertussis vaccines in childhood, pertussis incidence is clearly increasing (1). In 2003, the numbers of reported cases of pertussis were higher than in the preceding 30 years, with 64% occurring in adolescents and adults (2). Pertussis has been found to produce significant morbidity in both adolescents and adults (3). Parents, older siblings, grandparents and great grandparents have all been shown to be a significant source of pertussis disease transmission to young infants (4) (5). By eliminating this reservoir of pertussis, disease in infancy, the age range in which pertussis has its highest morbidity and mortality, should also be reduced (6) (7). The epidemiological data (See Section 2) strongly supports the need for an adolescent and adult vaccine to reverse the increase in disease incidence.

ADACEL™ is part of the Sanofi Pasteur 5- component acellular pertussis vaccine program. This vaccine consists of five purified pertussis antigens (Pertussis Toxoid (PT), Filamentous Haemagglutinin (FHA), Pertactin (PRN), Fimbriae Types 2 and 3 (FIM)) combined with tetanus and diphtheria toxoids. The Sanofi Pasteur 5-component acellular pertussis vaccines are unique among currently available vaccines in containing the FIM components. FIM has been shown to play a significant role in protection against pertussis and contributes importantly to the multiple protective antigens in the 5-component vaccine (8) (9) (10). ADACEL™ is a sterile, cloudy, white to off-white uniform suspension of Tetanus Toxoid and Diphtheria Toxoid adsorbed onto aluminum phosphate, combined with acellular pertussis components that are each adsorbed onto aluminum phosphate. ADACEL™ is presented in 0.5 mL doses of sterile suspension for intramuscular injection. Each dose of ADACEL™ vaccine (0.5 mL) is formulated to contain the following active ingredients:

Tetanus toxoid (T)	5 Lf
Diphtheria toxoid (d)	2 Lf
Pertussis toxoid (PT)	2.5 µg
Filamentous haemagglutinin (FHA)	5 µg
Fimbriae Types 2 and 3 (FIM)	5 µg
Pertactin (PRN)	3 µg

Other ingredients include 3.3 mg (0.6% v/v) 2-phenoxyethanol and 1.5 mg aluminum phosphate (0.33 mg aluminum) per dose.

ADACEL™ contains the same antigens that are present in the pediatric formulation acellular pertussis combination vaccine DAPTACEL® and the adolescent and adult formulation vaccine, Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td Adsorbed), which are licensed in the US. All aspects of the manufacturing and testing methods for the components in ADACEL™ are identical to those used for DAPTACEL® and Td Adsorbed. ADACEL™ contains lower amounts of Diphtheria Toxoid and PT than does the pediatric combination vaccine DAPTACEL®, as reduced amounts of these antigens have been shown to be associated with a lower reactogenicity profile in children and adults (11) (12). The two vaccines are identical in all other aspects.

Tdap Vaccine has been licensed in Canada as ADACEL™ since May 1999 and in Germany as COVAXiS™ since July 2001. As of 01 January 2005, over 800,000 doses of ADACEL™ have been distributed since its licensure in Canada and Germany. During this period, there have been 20 spontaneous reports of adverse events (16 non-serious and 4 serious cases).

The following information on post-marketing and Canadian experience of ADACEL™ (also See Sections 3.1 and 3.2) has not been included in the eBLA submission and as such has not been reviewed by CBER:

Following the licensure of ADACEL™ in Canada in 1999, one province and two territories launched adolescent (Grade 9) programs. Newfoundland and the Northwest Territories have reported a reduction in pertussis rates since this introduction (See Section 3.2.1). The remaining provinces in Canada initiated an ADACEL™ immunization program in 2004.

Antibody persistence, to five years post-immunization, was evaluated in follow-up studies for the three studies (TC9704, TD9707 and TC9805) that were the basis of licensure in Canada. A decline in antibody levels at 1-year, was observed followed by proportionally smaller increments of decline at 3 and 5 years post-immunization**.** At 5 years post-immunization, antibody levels for all antigens were higher than the pre-immunization levels.

1.2 Overview of Clinical Program

The investigational new drug application (IND) for ADACEL™ was submitted to CBER in July 2000. The clinical development program executed under this IND (BB-IND No. 9226) studied ADACEL™ as a booster vaccine against tetanus, diphtheria, and pertussis in adolescents and adults. This program was designed to characterize the safety and immunogenicity profile of the vaccine when administered alone or concurrently with either Hepatitis B or Influenza Vaccines in adolescents and adults, respectively. The Biologic License Application (BLA) for ADACEL™ was submitted to CBER in August 2004.

Four clinical trials were conducted under this IND. A large-scale safety and immunogenicity study in adolescents and adults demonstrated the non-inferiority of ADACEL™ to Tetanus Toxoid and Diphtheria Toxoid Adsorbed for Adult Use (Td Vaccine), the current US standard of care (Td506). The consistency of manufacture was demonstrated in healthy adolescents using 3 consecutively manufactured lots of ADACEL™ (Td505). Co-administration of ADACEL™ with Hepatitis B Vaccine (Td501) in adolescents or with Influenza Vaccine (Td502) in adults was also

assessed (See Section 4). Three Canadian trials (TC9704, TD9707 and TD9805) that were the basis of licensure of Tdap Vaccine as ADACEL™ in Canada and COVAXiS™ in Germany (13) (14) were included in the BLA as supportive studies for safety (See Appendix 5).

A total of 7,206 individuals were analyzed for safety in 4 principal clinical trials. Of the 4,185 adolescents (11-17 years) in these studies, 3,393 received ADACEL™ and 792 received Td Vaccine. Of the 3,021 adults (18-64 years) in these studies, 2,448 received ADACEL™ and 573 received Td Vaccine. The immunogenicity profile of ADACEL™ was documented in a randomized subset of participants enrolled in the studies. Across 4 principal trials, a total of 3316 ADACEL™ and 1026 Td Vaccine recipients were included for immunogenicity assessment (See Table 6). The post-immunization responses to all antigens across all studies are presented in Table 1 and Table 2.

The large-scale safety and immunogenicity study, Td506, established the non-inferiority of ADACEL™ to Td Vaccine for diphtheria and tetanus responses. Efficacy for diphtheria and tetanus, where serological correlates of protection exist, was established based on non-inferiority to Td Vaccine for attainment of seroprotective levels of ≥0.1 IU/mL (See Section 4.3.3.1). Seroprotection rates (≥0.1 IU/mL) post-vaccination were high and were similar between the two groups for diphtheria and tetanus. In adolescents, the seroprotection rates were 99.8% for diphtheria and 100% for tetanus in both treatment groups (See Table 1). In adults, the rates were slightly lower but similar between the treatment groups (See Table 2).

There are no universally accepted correlates of protection for pertussis. As a result, in this clinical program ADACEL™ immunogenicity data were comparatively bridged to immunogenicity data from a well-controlled efficacy study, the Sweden I Efficacy Trial, in infants. The Sweden I Efficacy trial reported that 3 doses of DAPTACEL® given to infants at 2, 4, and 6 months of age provided efficacies of 84.9% against WHO-defined pertussis and 77.9% (95% CI 72.6 to 82.2) against laboratory-confirmed pertussis of any severity (i.e., cough of 1 day or more) (15). ADACEL™ vaccine is identical to DAPTACEL® vaccine with the exception of a lower quantity of one of the pertussis antigens, PT and the diphtheria toxoid content. This comparative bridging of immunogenicity data after administration of ADACEL™ in adolescents and adults to efficacy data in infants obtained from a controlled study with a vaccine that contains the same licensed components, DAPTACEL®, is consistent with the FDA Guidelines for the Evaluation of Combination Vaccines for Preventable Diseases, April 1997 (16) and the recommendations made at the 5 June 1997 VRBPAC meeting (17) (See Section 4.2.4).

Thus, in concurrence with CBER, the efficacy of ADACEL™ for the prevention of pertussis was established through a comparison of pertussis antibody levels achieved in the study Td506 with those of a representative subset of sera obtained in the Sweden I Efficacy Trial. Td506 established the non-inferiority of ADACEL™ to Sweden I for pertussis antigens (See Section 4.3.3.2). Pertussis GMTs post-immunization in both adolescents and adults were consistently higher than those achieved in the Sweden I Efficacy trial (See Table 1 and Table 2).

To assess the persistence of antibody levels following ADACEL™ administration, immunogenicity follow-up studies at 1, 3 and 5 years are being conducted on the large-scale safety and immunogenicity study Td506.

Lot consistency was assessed in study Td505 and immune responses were equivalent across all groups for all antigens except FIM where one comparison was just outside the pre-defined equivalency criteria of 1.5 (90% CI of 1.55; See Section 4.3.1.2); Table 1 presents the pooled results across three lots in study Td505. In study Td501, immunogenicity was assessed for the simultaneous and sequential administration of Hepatitis B with ADACEL™. Immune responses were similar for both groups for all antigens (See Section 4.3.4.1). In study Td502, immunogenicity was assessed for the simultaneous and sequential administration of Influenza vaccine with ADACEL™. Pertussis responses in the simultaneous group were lower than those in the sequential group and this difference reached statistical significance for PRN (90% LCL = 0.61 vs. 0.67, the pre-defined criteria; See Section 4.3.4.2). The GMT values for all antigens including PRN, however, exceeded those achieved after DAPTACEL® in the Sweden I trial (Table 2).

Table 1: Overall Immunogenicity Profile Across Studies, Adolescents 11-17 yrs (PPI Population)

Primary Immunogenicity Criteria	**Td506**		**Td505**[1]	**Td501**	
Seroprotection at a level ≥0.1 IU/ml	**ADACEL™ n/N (%)**	**Td n/N (%)**	**ADACEL™ n/N (%)**	**Simultaneous**[2] **n/N (%)**	**Sequential**[3] **n/N (%)**
Diphtheria	526/527 (99.8)	515/516 (99.8)	1050/1053 (99.7)	161/161 (100.0)	150/151 (99.3)
Tetanus	527/527 (100.0)	516/516 (100.0)	1054/1054 (100.0)	161/161 (100.0)	151/151 (100.0)
Post Vaccination GMTs (EU/mL)	**ADACEL™**	**Sweden I**[4]	**ADACEL™**	**Simultaneous**[2]	**Sequential**[3]
PT	309.26	86.55	338.09	303.50	321.56
FHA	214.83	39.95	265.47	301.51	305.41
FIM	1792.40	341.10	1804.77	1906.42	1926.71
PRN	344.52	108.12	367.31	292.92	284.63

PPI Population: Per-protocol immunogenicity population
n, %: Number and percent of participants who achieved the specified levels of Seroprotection
N: Number of participants evaluated
[1] Results presented are pooled for the three lots
[2]Simultaneous: ADACEL™+HepB (N=161) = Participants received ADACEL™ and HepB Vaccine Concomitantly at Visit 1.
[3]Sequential: ADACEL™, HepB (N=151) = Participants received ADACEL™ at Visit 1 and HepB Vaccine one month later at Visit 2
[4]Sweden I represents GMTs of a subset of representative sera from infants immunized with DAPTACEL® in the Sweden I Efficacy Trial.

Table 2: Overall Immunogenicity Profile Across Studies, Adults 18-64 yrs (PPI Population)

Primary Immunogenicity Criteria	Td506		Td502	
Seroprotection at a level ≥0.1 IU/ml	**ADACEL™ n/N (%)**	**Td n/N (%)**	**Simultaneous[1] n/N (%)**	**Sequential[2] n/N (%)**
Diphtheria	697/741 (94.1)	482/507 (95.1)	305/354 (86.2)	282/324 (87.0)
Tetanus	742/742 (100.0)	508/509 (99.8)	353/354 (99.7)	318/324 (98.1)
Post Vaccination GMTs (EU/mL)	**ADACEL™**	**Sweden I[3]**	**Simultaneous[1]**	**Sequential[2]**
PT	178.84	86.55	186.42	234.51
FHA	192.91	39.95	200.57	242.24
FIM	852.72	341.10	925.80	1136.32
PRN	341.89	108.12	191.66	260.27

PPI Population: Per-protocol immunogenicity population
n, %: Number and percent of participants who achieved the specified levels of Seroprotection
N: Number of participants evaluated
[1]Simultaneous: Flu+ADACEL™ (N=354) = Participants received Flu Vaccine and ADACEL™ concomitantly at Visit 1.
[2]Sequential: Flu, ADACEL™ (N=324) = Participants received Flu Vaccine at Visit 1 and ADACEL™ one month later at Visit 2.
[3]Sweden I represents GMTs of a subset of representative sera from infants immunized with DAPTACEL® in the Sweden I Efficacy Trial

Safety was assessed in a total of 6803 participants receiving ADACEL™. Of these, 5841 were ADACEL™ recipients from 4 principal clinical trials (See Section 4.7) and an additional 962 were adolescents and adults that received ADACEL™ in three supportive studies (See Appendix 5). Overall, ADACEL™ Vaccine was well-tolerated although slightly more reactogenic than Td Vaccine, the licensed standard of care in the US (See Table 3 and Table 4).

In Td506, ADACEL™ was compared to Td Vaccine with respect to four pre-defined safety endpoints (i.e., the solicited adverse events of Erythema, Swelling, Pain, and Fever) during Days 0 to 14. ADACEL™ was non-inferior to Td Vaccine with respect to rates of Erythema, Swelling and Fever, for both the adult and adolescent populations, and with respect to Pain in the adult population. For the adolescents, a slight difference in the rates of Any Pain was observed between the two treatment groups; the upper limit of 95% CI for the difference between the two treatment groups was 10.72% instead of the pre-defined difference of 10%. Pain was the most frequently reported local adverse event in both groups, was mostly mild in intensity and the mean duration of Pain was 2.1 days for both groups (See Section 4.7.1.1). There was an almost two-fold difference in reporting of Any Fever in adolescents receiving ADACEL™ as compared to Td Vaccine (4.96% vs. 2.68%), however, the majority of these were Mild in intensity and the mean duration was 1.2 days for both groups. The rates of all other local and systemic reactions were similar in both treatment groups for adolescents and adults as shown in Table 3, Table 4 and Appendix 4.

Table 3: Overall Safety Profile Across Studies, Adolescents 11-17 Years (ITTS Population)

Type of Adverse Event	Td506				Td505		Td501			
	ADACEL™		Td		ADACEL™		Simultaneous[1]		Sequential[2]	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Immediate Reactions (within 30 minutes)	6/1184	0.51	5/792	0.63	13/1806	0.72	1/202	0.50	4/201	2.0
Any Solicited Local Reaction (Days 0–14)	952/1184	80.41	586/792	73.99	1500/1806	83.06	178/202	88.12	174/201	86.57
Any Solicited Systemic Reaction (Days 0–14)	776/1184	65.54	483/792	60.98	1187/1806	65.73	160/202	79.21	150/201	74.63
Solicited Reactions (Days 0–14)										
Erythema	244/1175	20.77	155/787	19.70	436/1793	24.32	47/201	23.38	43/201	21.39
Swelling	246/1175	20.94	144/787	18.30	404/1793	22.53	48/201	23.88	36/201	17.91
Pain	914/1175	77.79	559/787	71.03	1433/1793	79.92	172/201	85.57	171/201	85.07
Fever	58/1170	4.96	21/783	2.68	93/1790	5.20	11/201	5.47	12/200	6.00
Unsolicited AEs[3]	301/1184	25.42	202/792	25.51	424/1806	23.48	74/202	36.63	95/201	47.26
Serious AEs[4]	11/1184	0.93	8/792	1.01	4/1806	0.22	1/202	0.50	1/201	0.50

ITTS Population: Intent-to-treat Safety Population
n/N: n-The number of participants reporting the event; N- The total number of participants evaluated
%: Percent of participants reporting the event
[1]Simultaneous: ADACEL™+HepB (N=202) = Participants received ADACEL™ and HepB Vaccine Concomitantly at Visit 1.
[2]Sequential: ADACEL™, HepB (N=201 = Participants received ADACEL™ at Visit 1 and HepB Vaccine one month later at Visit 2
[3]Collected in Td506 Days 0-28, in Td505 Days 0-28 and Td501 Days 0-180
[4]Collected in Td506 Days 0-180, in Td505 Days 0-28 and Td501 Days 0-180

In Td505, the reactogenicity profile was similar across all lots (See Section 4.7.1.2). Table 3 presents the pooled results across three lots in study Td505. In the concomitant administration studies Td501 and Td502, somewhat higher reactogenicity was observed for the simultaneous administration groups over the sequential groups, some of which reached statistical significance (See Sections 4.7.3.1 and 4.7.3.2). This finding is not unexpected and these differences in tolerability should be considered in light of the benefits of co-administration.

Across all four principal studies, 40 immediate events were reported in 32/5841 (0.55%) ADACEL™ recipients and 8 events were reported in 6/1365 (0.44%) Td Vaccine recipients. In adolescents, there were 31 immediate events reported in 24 (0.71%) ADACEL™ recipients and 6 events in 5(0.63%) Td Vaccine recipients. In adults, there were 9 immediate events reported in 8 (0.33%) ADACEL™ recipients and 2 in 1 (0.17%) Td Vaccine recipient. The most frequently reported immediate reactions in adolescents were dizziness, syncope, hypoesthesia/paresthesia, and vasovagal attack. In adults the most frequently reported immediate events were vaccination site reactions and hypoesthesia/paresthesia. In Td506, immediate events were comparable between ADACEL™ and Td recipients and were observed by less than 0.65% of participants.

Table 4: Overall Safety Profile Across Studies, Adults 18-64 Years (ITTS Population)

Type of Adverse Event	Td506				Td502			
	ADACEL™		Td		Simultaneous[1]		Sequential[2]	
	n/N	%	n/N	%	n/N	%	n/N	%
Immediate Reactions (within 30 minutes)	4/1752	0.23	1/573	0.17	3/356	0.84	1/340	0.29
Any Solicited Local Reaction (Days 0–14)	1199/1752	68.44	384/573	67.02	246/356	69.10	218/340	64.11
Any Solicited Systemic Reaction (Days 0–14)	881/1752	50.29	273/573	47.64	219/356	61.51	191/340	56.17
Solicited Reactions (Days 0–14)								
Erythema	420/1698	24.73	121/561	21.57	38/352	10.80	42/339	12.39
Swelling	356/1698	20.97	97/561	17.29	54/352	15.34	35/339	10.32
Pain	1115/1698	65.67	353/561	62.92	235/353	66.57	206/339	60.77
Fever	24/1688	1.42	6/551	1.09	15/352	4.26	8/336	2.38
Unsolicited AEs[3]	375/1752	21.40	120/573	20.94	123/356	34.55	108/340	31.76
Serious AEs[4]	33/1752[5]	1.88	11/573[5]	1.92	1/356	0.28	1/340	0.29

ITTS Population: Intent-to-treat Safety Population
n/N: n-The number of participants reporting the event; N- The total number of participants evaluated
%: Percent of participants reporting the event
[1]Simultaneous: Flu+ADACEL™ (N=356) = Participants received Flu Vaccine and ADACEL™ concomitantly at Visit 1.
[2]Sequential: Flu, ADACEL™ (N=340) = Participants received Flu Vaccine at Visit 1 and ADACEL™ one month later at Visit 2.
[3]Collected in Td506 Days 0-28, in Td502 Days 0-56
[4]Collected in Td506 Days 0-180, in Td502 Days 0-56
[5]Two ADACEL™ Participants with 3 SAEs from one site excluded from the analysis are not included. An additional participant receiving Td Vaccine with a hospitalization for pre-existing condition was not included as a SAE

As can be seen in Table 3 and Table 4, the frequency of unsolicited adverse events in Td506 was similar among ADACEL™ and Td Vaccine recipients over 0-28 days. Rates of unsolicited adverse events across studies were consistent taking into consideration variable duration of follow-up (See Section 4.7.4).

Across the four trials, a total of 87 SAEs were reported by 71 study participants. Of these, 30 SAEs were reported in 25 adolescents and 57 SAEs in 46 adults (See Section 4.7.5). Seventy-nine of the 87 SAEs were reported by 63 participants in the analysis population in Td506.For adolescents in Td506, the SAE rates were 0.93% and 1.01% for ADACEL™ and Td recipients, respectively (See Table 3). For adults in Td506, these rates were 1.88% and 1.92% for ADACEL™ and Td recipients, respectively (See Table 4). Two SAEs in the ADACEL™ group were considered possibly related to the vaccine by the investigator (See Section 4.7.5): one case of a severe migraine equivalent with unilateral facial paralysis and the other of radicular pain in the left upper arm.

No cases of extensive limb swelling were reported in the four principal studies. However, in one of the supportive clinical trials, two ADACEL™ recipients and one Td Vaccine recipient reported whole arm swelling (See 4.7.4.3).

The data from studies in this clinical program demonstrate that ADACEL™ Vaccine is safe and immunogenic and induces protective immune responses against tetanus, diphtheria, and pertussis in adolescents and adults aged 11-64 years. These data support the conclusion that ADACEL™ provides protection against tetanus and diphtheria equivalent to that of Td, as well as providing pertussis antibody levels that exceed those proven to be 85% protective in infants, while maintaining an acceptable tolerability profile that is similar to Td Vaccine with slightly increased reactogenicity in adolescents. Thus, the combination ADACEL™ vaccine would be an alternative to Td Vaccine, the current standard of care in the US.

1.3 Conclusions

Epidemiological and clinical data summarized in this document support the following conclusions for ADACEL™:

- Pertussis produces significant morbidity in both adolescents and adults.
- Transmission of pertussis from adolescents and adults to susceptible infants is documented.
- A rise in pertussis reports particularly in adolescents and adults suggests that a vaccine is necessary in this population.
- ADACEL™ provides protection against pertussis in addition to providing protection against diphtheria and tetanus that is comparable to Td Vaccine, the licensed standard of care.
- ADACEL™ has a safety profile comparable to that of Td Vaccine, the current standard of care in US. Slightly increased reactogenicity was observed with respect to Any Pain and Any Fever in adolescents, however, these were mainly mild in intensity and of short duration. This is not unexpected due to the addition of pertussis antigens in the vaccine.
- ADACEL™ may be safely and effectively administered concomitantly with Hepatitis B Vaccine or Influenza vaccine. The slight increase in reactogenicity seen with concomitant administration of ADACEL™ with either of these vaccines is acceptable given the benefits of co-administration such as compliance and cost-savings. For concomitant administration of ADACEL™ with Influenza Vaccine, somewhat lower pertussis responses were observed.
- Data from a province and territory in Canada suggests a reduction in the incidence of pertussis since the introduction of ADACEL™.

2 Epidemiology

2.1 Tetanus and Diphtheria

Tetanus is an acute and often fatal disease caused by an extremely potent neurotoxin produced by *Clostridium tetani*. *Corynebacterium diphtheriae* may cause both localized and generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein of toxigenic strains of *C. diphtheriae.* The need for immunization and the epidemiology of tetanus and diphtheria are well documented (18) (19) and summarized in Appendix 1.

2.2 Pertussis

Pertussis, also called whooping cough, is a highly communicable respiratory disease caused by the gram-negative bacterium *Bordetella pertussis*. It is characterized by paroxysmal coughing which is associated with a whoop or even vomiting. The most severe disease occurs in infants, accounting for 90% of the mortality. In older individuals, clinical manifestations may be limited to a mild cough (20) (21) (22), but a severe, persistent cough (23) or the classic symptoms of paroxysmal cough, whoop, and post-tussive vomiting may also occur (5). Pertussis is a common and frequently unrecognized cause of cough illness in adolescents and adults (24) (25) (26) (27) (28) (29) causing 15-25% of acute respiratory illness with cough of ≥7 days duration in young adults. Complications of pertussis, thought to be uncommon in older individuals, actually occur with relatively high frequency. Paroxysms have been reported in as many as 83% of adolescents and 33% to 100% of adults, and hospitalizations in as many as 7.5% of adolescents and 5.7% of adults (5) (20) (26) (30) (31) (32) (33).

Disease caused by *B. pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States (1) with a peak incidence of 265,269 case reports and 7518 deaths in 1934. Respiratory droplets or direct contact transmits pertussis from the respiratory tract of an infected person, with secondary attack rates among non-immune household contacts as high as 90% (6). Antimicrobial therapy, although effective in eradicating the organism from the respiratory tract, does not alter the progression of disease, unless given in the early stages of the infection (catarrhal phase) when pertussis is rarely suspected (6). Therefore, control of the disease has been based on prevention through vaccination.

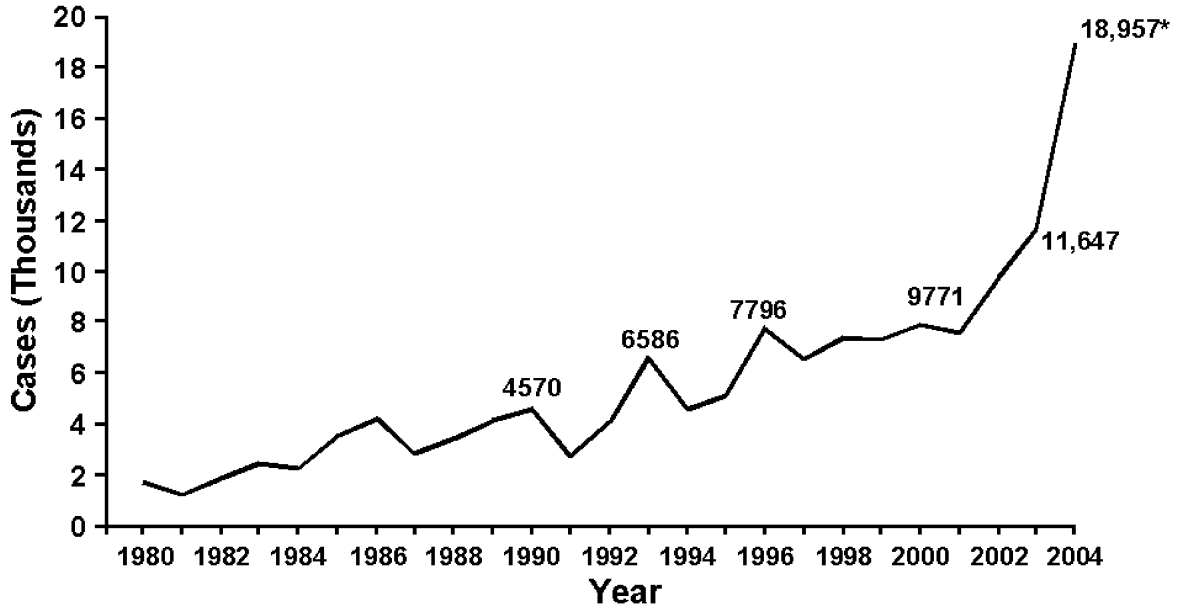
The introduction and widespread use of standardized whole-cell pertussis vaccines combined with Diphtheria and Tetanus Toxoids (DTP) in the mid-1940s in the US resulted in a substantial decline in reports of pertussis disease. In countries where pertussis vaccine coverage rates declined, pertussis epidemics reappeared (34) (35) (36). Epidemiologic analyses clearly indicate that the benefits of pertussis vaccination outweigh the risks (37) (38) (39) (40) (41) (42) (43). Due to poor tolerability of the whole cell pertussis vaccines with increasing age, these vaccines have been recommended only until 4 to 6 years of age. These recommendations have not changed since the advent of pediatric acellular pertussis vaccines.

Epidemics of pertussis continue to occur every 3 to 5 years, an interval unchanged from the pre–vaccination era (4) (36) (44) (45). The lack of interruption of the inter-epidemic interval is a significant public health concern and indicates that routine childhood vaccination has not

eliminated disease transmission. The large number of adolescents and young adults who are susceptible because of waning immunity induced by vaccine or infection can acquire pertussis and become the reservoir for infecting young infants (6) (24) (25) (45) (46). Infections in older populations may explain the recent increase in pertussis frequency.

From 1980-2003, the number of reported cases in the US has increased more than 6 fold (See Figure 1) (1) (2). Although some of this may reflect better diagnosis and reporting, such a large increase is unlikely to be explained by this alone. During 2003, 11,647 cases of pertussis were reported, the highest number of cases in several decades. Of these cases, 17% occurred among infants aged <6 months, who were too young to have received the primary diphtheria-tetanus-acellular pertussis (DTaP) vaccine series; 2% occurred among children aged 6-11 months; 10% among children aged 1-4 years; 7% among children aged 5-9 years; 39% among persons aged 10-19 years and 25% among persons aged ≥20 years (2). The proportion of reported cases in persons ≥10 years of age has increased steadily from 15% in 1977 to 64% in 2003 (2) (47).

Figure 1: Reports of Pertussis in United States, 1980-2004 (1) (2) (48) (49)



* The 2004 figure of 18,957 should be considered preliminary, as case reports from that year are still being tabulated.

Importance of Pertussis in Adults An outbreak of pertussis in oil refinery workers whose median age was 40 years, illustrated that adults are susceptible to the disease (50). In Massachusetts, where a specific serologic test is used and more active surveillance occurs, the rate in adults has been estimated to be 5 per 100,000 rather than 0.8 per 100,000 reported nationally (33). Eighty-seven percent (87%) of adults were observed to have severe disease, suggesting that this study was detecting only those with more severe disease**.**

Based on the overall frequency of medically attended cough illness that is due to pertussis, investigators at the Kaiser Health Maintenance Organization have estimated the incidence of adult pertussis to be 176 cases/100,000 (51). Similar adult incidence rates of 133/100,000 (26) have been observed using serodiagnosis in the USA and Germany, although these rates in Germany were observed during pertussis epidemics (52). The highest estimates of infection rates combined culture, PCR or serology to make a diagnosis in adolescent and adult members in a managed care organization (28). The highest incidence was in adolescents (997/100,000), but the rates were also high in 20-29 year olds (229/100,000), 30-39 year olds (375/100,000) and 40-49 year olds (409/100,000), the adult age groups that were studied.

Morbidity due to pertussis has been described for a large case series of 664 adolescents and adults diagnosed by culture or who met surveillance criteria of a cough of greater than 2 weeks and at least one pertussis related symptom without another cause (3). The mean duration of cough was 10 weeks in adolescents and 12 weeks in adults and the frequency of classic pertussis symptoms was similar. Complication rates were significantly higher in adults than adolescents (28% vs. 16%). These included pneumonia, rib fractures, and urinary incontinence. Even when not severe, pertussis causes a significant health burden. Up to 62% of older children, adolescents, and adults eventually diagnosed with pertussis had at least one medical visit (32). Thirty-five percent of those diagnosed with symptomatic pertussis have reported missing more than 5 days of work (31), and 16% were unable to work for more than 1 month (5).

A recent publication reported on the source of pertussis for a large series of infant cases in four states (53). Three quarters of the sources were family members, 25% out of home care-givers and other contacts. The sources were of all ages, but most were adolescents (20%) and adults (56%).

In summary, estimates of pertussis incidence vary greatly according to method of diagnosis. The relative incidence of disease is higher among adolescents, but there is still significant disease in adults. The morbidity seen in adults with pertussis is also greater than that seen in adolescents. Importantly, because pertussis is rarely considered in the differential of chronic cough in adults, disease transmission by this group may be even more frequent.

The recent rise in pertussis reports strongly supports the need for a vaccine in adolescents and adults. Adolescents and adults serve as the reservoir for infections in infants, who are too young to have completed the primary series of immunization and in whom pertussis may be severe and life-threatening (4) (54) (5) (7) (55) (56) (57) (58). The vaccination of the older individuals would not only reduce the morbidity associated with pertussis in vaccinees, but should also reduce disease in young infants.

3 Vaccine Development and Post-Marketing Experience with ADACEL™

3.1 Acellular Pertussis Vaccine Development

The widespread use of whole-cell pertussis vaccines since 1940 has reduced disease incidence and severity of pertussis dramatically. Despite the efficacy of whole cell vaccine, their reactogenicity prevents their use in adolescents and adults. The Sanofi Pasteur 5- component vaccine consists of five purified antigens (PT, FHA, PRN, FIM types 2 and 3), and has been shown to be highly protective against whooping cough in infants (8) (15) (59). PT, FHA and PRN have been demonstrated to protect against pertussis (6) (60) (61) (10). Fimbrial agglutinogens are important contributors to the synergy of multiple protective antigens (54) (62) (63) (64) (65). The World Health Organization recommended that whole-cell pertussis vaccines contain fimbrial agglutinogens types 1, 2 and 3 (66). The inclusion of both Fimbriae Types 2 and 3 (FIM) is unique to Sanofi Pasteur's acellular pertussis vaccine and in the Sweden I Efficacy trial, the 5-component vaccine (DAPTACEL®) had 84.9% protective efficacy against severe disease and 77.9% efficacy against mild pertussis (≥1 day of cough with laboratory confirmation) (59). The roles of PRN and FIM in the protection against typical and mild pertussis disease were established in several clinical studies (8) (67) (10). In the household contact study nested within the Sweden I Efficacy trial using DAPTACEL®, vaccinated children found to have low or unmeasurable antibody levels to all three antigens (PT, PRN and FIM) had the same risk of developing pertussis as unvaccinated children in the study (8). When levels of anti-PRN or anti-FIM were high, efficacy against severe pertussis was at least 70%, increasing to 84.9% when both were high in exposed individuals. This contrasts with efficacy against typical pertussis of only 46.1% when anti-PT only was high (8). These findings are consistent with results from two other household contact studies (67) (10).

The development of DAPTACEL® and other pediatric acellular pertussis vaccines, which are less reactogenic but as effective as whole cell pertussis vaccines, has increased the interest in the possibility of booster immunization of adolescents and adults against pertussis (6) (12) (59). Reactogenicity of acellular pertussis combination vaccines (pediatric formulation) in older populations has been associated with the content of Pertussis Toxoid (68) and especially Diphtheria Toxoid (69). Combination vaccines containing lower Diphtheria and Pertussis Toxoid (PT) concentrations have been shown to elicit lower reactogenicity rates (11) (12). ADACEL™, an adolescent and adult formulation combination vaccine, contains lower amounts of Diphtheria Toxoid and PT than the US licensed pediatric combination vaccine DAPTACEL®.

This adolescent and adult formulation combination vaccine, Tdap Vaccine, was initially studied in three Phase 3 clinical trials (TC9704, TD9707, and TD9805) that were the basis of licensure in other countries. Antibody persistence data to five years post-immunization, is available from follow-up studies of the three studies (TC9704, TD9707 and TC9805) that were the primary licensure trials in Canada. A decline in antibody levels at 1-year, was observed followed by proportionally smaller increments of decline at 3 and 5 years post-immunization. At 5 years post-immunization, antibody levels for all antigens were higher than the pre-immunization levels. This

information has not been included in the eBLA submission and as such has not been reviewed by CBER.

3.2 Post Marketing Experience with ADACEL™

The information presented in this section has not been included in the eBLA submission and as such has not been reviewed by CBER.

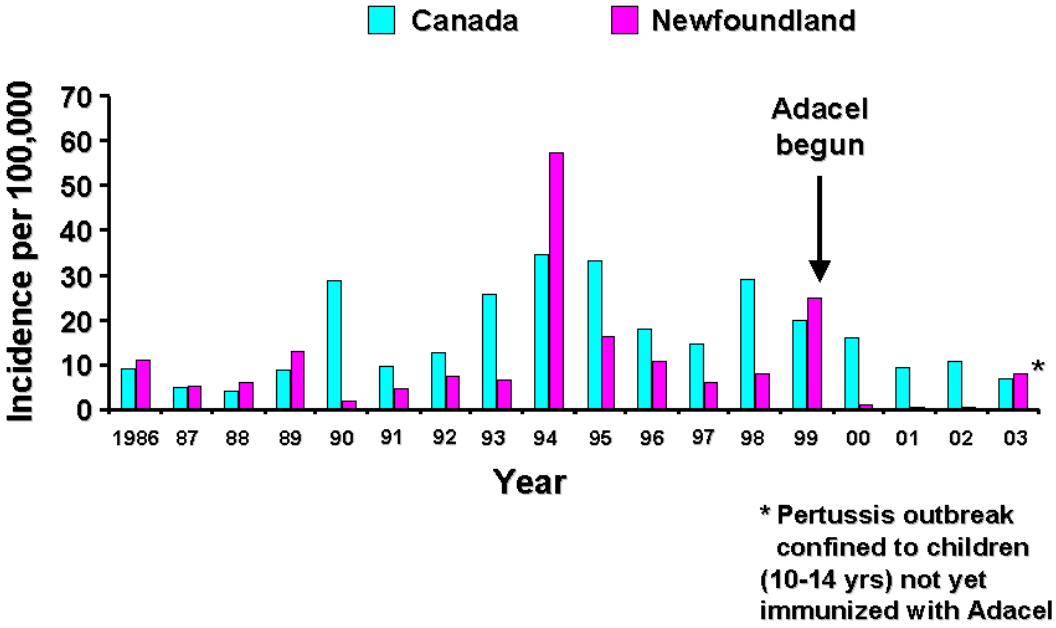
Tdap Vaccine was licensed as ADACEL™ in Canada in May 1999 for use in persons 11 to 54 years of age and in Germany in July 2001 as COVAXiS™ for use in persons 10 years and older. As of 01 January 2005, over 800,000 doses of ADACEL™ have been distributed since its licensure in Canada and Germany. During this period, there have been 20 spontaneous reports of adverse events (16 non-serious and 4 serious cases).

3.2.1 Canadian Experience with ADACEL™

Following the licensure of ADACEL™ in Canada in 1999, one province and two territories launched ADACEL™ vaccination programs. In the year 2000, the Canadian National Advisory Committee on Immunization (NACI) issued a statement on ADACEL™, noting that it could be used to replace the adolescent or adult Td booster, but at that time did not give a recommendation for universal routine use (70). Direct impact of the targeted immunization with ADACEL™ is now available from one province, as presented below.

In Newfoundland following the replacement of Td Vaccine with ADACEL™ for 14 year olds in the 1999 school year, the number of confirmed cases of pertussis decreased from 1999-2003 except for an outbreak in school age children 10-14 yrs in 2003. No cases of pertussis were reported in those who had received ADACEL™. Figure 2 shows the overall incidence of pertussis reported in Newfoundland and Canada since 1986.

Figure 2: Incidence of Pertussis, Canada vs. Newfoundland, 1986 to 2003



Source: Canadian Data derived from CCDR Notifiable Disease Annual Summaries

Pertussis rates in the Northwest Territories also showed a dramatic decline after the introduction of ADACEL™ in 2001. In 1997-2000, prior to vaccine introduction, the pertussis rate was 7.9 cases/10,000 and decreased to 1.1 cases/10,000 population during 2001-2004 (71) (72).

In September 2003, NACI issued an advisory statement recommending that all preadolescents and adolescents who have not received a dose of acellular pertussis vaccine should receive a single dose of the adolescent/adult formulation of acellular pertussis vaccine. For adults who have not previously received a dose of acellular pertussis vaccine, it is recommended that a single Td booster dose be replaced by the combined diphtheria-tetanus-acellular pertussis (dTap vaccine) (7). As of September 2004, all provinces and territories in Canada have included this vaccine in the routine adolescent vaccination schedule. The Quebec provincial government launched an adolescent, adult and "cocoon" program (immunization of those in close contact with infants) and recommended ADACEL™ for pertussis catch-up vaccination regardless of the interval since the vaccinees' last prior injection of tetanus toxoid-containing vaccine.

4 ADACEL™ Clinical Development Program

4.1 Summary of the Clinical Program

The objectives of the clinical development program for ADACEL™ licensure in the United States were to demonstrate that ADACEL™ is safe and immunogenic when given as a booster for the prevention of diphtheria, tetanus and pertussis in adolescents and adults aged 11-64 years.

The clinical program was initiated in July 2000 and included four clinical trials (See Table 5):

- Td506- a large-scale safety and immunogenicity comparative trial of ADACEL™ versus Td Vaccine in adolescents and adults
- Td505- a lot consistency trial of ADACEL™ in adolescents
- Two comparative trials of ADACEL™ given concomitantly with other licensed vaccines
  - Td501- ADACEL™ given concomitantly with, or separately from, Hepatitis B Vaccine in adolescents
  - Td502- ADACEL™ given concomitantly with, or separately from, Influenza Vaccine in adults

Study Td506 was designed to demonstrate non-inferiority compared to Td Vaccine with respect to safety and immunogenicity for diphtheria and tetanus and non-inferiority with respect to pertussis immunogenicity compared with antibody levels obtained in infants in the Sweden I Efficacy trial following 3 doses of DAPTACEL®. In addition, consistency of manufacturing processes (Td505) and the safety and immunogenicity profile of ADACEL™ when administered alone or concurrently with either Hepatitis B (Td501) or Influenza (Td502) Vaccines was also assessed.

Three Canadian trials (TC9704, TD9707 and TD9805) that were the basis of licensure of Tdap Vaccine as ADACEL™ in Canada and COVAXiS™ in Germany were included in the eBLA as supportive safety data (Table 5). These supportive trials included a comparative trial of ADACEL™ versus Td Adsorbed Vaccine in adolescents and adults aged 12-54 years (TC9704), and in adults aged 19 to 60 years (TD9707), as well as a comparative trial of ADACEL™ either given concomitantly with or separately from Hepatitis B Vaccine in adolescents aged 11-12 years (TD9805). Safety data from these studies are summarized in Appendix 5.

Table 5: Summary of Clinical Trials Included in the eBLA

Study Number.	ADACEL™ Lot # Used	Vaccine Groups	Age-Range (Years)	Number of Participants	Study Design/Objectives
Td506	C0614AA	ADACEL™ Td	11-64	Total Enrolled-4480 3032- ADACEL™ 1418- Td 30 - Vaccine Receipt Unknown	A randomized, controlled, double-blind, multicenter study to assess the safety and immunogenicity of ADACEL™ as compared to Td Vaccine in adolescents and adults. This study assessed the non-inferiority of ADACEL™ to Td Vaccine for diphtheria and tetanus antigens, and the non-inferiority of ADACEL™ to Sweden I (for level achieved after 3 doses of DAPTACEL® in infants) and historical Canadian trials for pertussis antigens.
Td505	C0192AC C0614AA C0632AA	ADACEL™ Lot 1 Lot 2 Lot 3	11-17	Total Enrolled- 1811	A randomized, controlled, double-blind, multicenter lot consistency study designed to assess the safety and immunogenicity responses generated by 3 consecutively manufactured lots of ADACEL™.
Concomitant use Trials					
Td501	C0614AA	Simultaneous: ADACEL™ + HepB Sequential: ADACEL™, HepB	11-14	Total Enrolled –410	A randomized, controlled, multicenter, open-labeled study designed to assess safety and immunogenicity of ADACEL™ and the immunogenicity of Hepatitis B Vaccine when given either concurrently or separately to adolescents 11 to 14 years of age.
Td502	C0614AA	Simultaneous: ADACEL™ + Flu Sequential: Flu, ADACEL™	19-64	Total Enrolled - 720	A randomized, controlled, multicenter, open-labeled study designed to assess safety and immunogenicity of ADACEL™ and the immunogenicity of Influenza Vaccine when administered either concurrently or separately in adults 19 to 64 years of age.

Study Number.	ADACEL™ Lot # Used	Vaccine Groups	Age-Range (Years)	Number of Participants	Study Design/Objectives
Supportive Canadian Trials					
TC9704	21-11 22-11 23-11	ADACEL™Lot 1 Lot 2 Lot 3 Td* , cP	12-54	Total Enrolled - 605 453-ADACEL™ 152- Td	A randomized, double-blind, multicenter study designed to assess safety and immunogenicity of 3 lots of ADACEL™ compared to Td and cP given separately in adults and adolescents.
TD9707	21-11	ADACEL™ ADACEL™, cP Td*, cP	12-60	Total Enrolled –374 248-ADACEL™- 126- Td	A randomized, double blind study with ten groups; only 3 groups were relevant to assess the safety and immunogenicity of ADACEL™ as compared to Td Vaccine in adults.
TD9805	23-11	ADACEL™ + HepB ADACEL™, HepB	11-14	Total Enrolled –272 272- ADACEL™	A randomized, open label study designed to assess the safety and immunogenicity of ADACEL™ when given Concomitantly with Hepatitis B Vaccine in adolescents.

* The Td Vaccine used in the Supportive studies was manufactured by Sanofi Pasteur Ltd., Canada; Td Vaccine used in the study Td506 was manufactured by Sanofi Pasteur Inc., US

Table 6 summarizes the participant enrollment and vaccine received in the four clinical trials. The four clinical trials (Td501, Td502, Td505, Td506) included in this program provide a total immunogenicity database (per-protocol immunogenicity population, PPI) of 3316 in the ADACEL™ group and 1026 in the Td group. The four clinical trials provide a total safety database of 7206 individuals (4185 adolescents 11 through 17 years of age and 3021 adults 18 through 64 years of age). Of these, 3393 adolescents and 2448 adults received ADACEL™ and 792 adolescents and 573 adults received Td Vaccine.

In studies Td505 and Td506, participants were enrolled and randomized across two age strata within the adolescent group (11-13 and 14-17 yrs). In addition, the adults in Td506 were enrolled and randomized across three age strata (18-28, 29-48 and 49-64 yrs).

Table 6: Summary of Participant Enrollment and Vaccine Received in the Clinical Trials

	Td506		**Td505**	**Td501**	**Td502**	**Total**
	11-17 yrs	**18-64 yrs**	**11-17 yrs**	**11-14 yrs**	**19-64 yrs**	**11-64 yrs**
Enrolled and Randomized	2053	2427	1811	410	720	**7421**
Discontinued	48	112	20	18	24	**222**
Completed	2005	2315	1791	392	696	**7199**
ITTS[1]	**1976***	**2325****				
ADACEL™	1184	1752	1806	403	696	**5841**
Td	792	573				**1365**
PPI[2]	**1043**	**1253**				
ADACEL™	527	743	1056	312	678	**3316**
Td	516	510				**1026**

[1]ITTS- Intent-to-treat Safety Population- all enrolled participants who were included in the safety analyses
* 77 participants in study Td506 were excluded from ITTS population, these included 10 participants whose vaccine receipt could not be confirmed, 15 participants who did not receive a vaccine and 52 participants from a site not included in the analysis.
** 102 participants in study Td506 were excluded from ITTS population, these included 20 participants whose vaccine receipt could not be confirmed, 4 participants who did not receive a vaccine and 78 participants from a site not included in the analysis.[2] PPI- Per-protocol Immunogenicity Population- all enrolled participants who were randomized, vaccinated, provided blood samples, and who did not have any major protocol violation

4.2 Immunogenicity Assessment

The goals of the clinical development program were to demonstrate the immunogenicity profile of ADACEL™ against diphtheria, tetanus, and pertussis in adolescents and adults aged 11-64 years. The establishment of non-inferiority of antibody responses to diphtheria and tetanus in comparison to the licensed Td Vaccine, the current standard of care, will support the acceptance of ADACEL™ as being protective against these diseases. Since the immunologic correlates of protection for pertussis have not been universally accepted, the antibody levels achieved after ADACEL™ in adolescents and adults were compared with those achieved after 3 doses of DAPTACEL® given to infants in the Sweden I Efficacy trial (See Section 4.2.4).

4.2.1 Study Cohorts for Immunogenicity

Per-Protocol Immunogenicity Population

The primary analysis population was specified as the per-protocol immunogenicity (PPI) population and included all enrolled participants who were randomized, vaccinated, provided blood samples, and who did not have any major protocol violation as listed below:

- Participants not vaccinated or vaccinated with a vaccine not assigned by the randomization code
- Study vaccine administered outside of the time window specified by the protocol
- Blood samples were missing or taken outside of the time windows specified by the study protocol
- Participants discontinued study prior to completing all blood draws
- Other study violation, as defined by the medical monitor in the Protocol Violation Log

Intent-to-Treat Immunogenicity Population

Analysis of immunogenicity endpoints were also conducted on a modified Intent-to-Treat Immunogenicity (ITTI) population which included all participants who were randomized, received a study vaccine and who were bled. Participants who were randomized to one study group, but received vaccines specified for another study group were included in the study group for the vaccine(s) that they actually received. Immunogenicity data were obtained from the subgroup that submitted blood samples.

4.2.2 Criteria for Immunogenicity Endpoints

The criteria for the primary immunogenicity endpoints that were used in assessing the four clinical studies submitted in the eBLA are summarized below in Table 7. For diphtheria and tetanus, the most clinically relevant immunogenicity endpoints are the achievement of seroprotective levels ≥0.1 IU/mL (11) (73) (74) and the booster response rates based on pre-vaccination titers. For pertussis antigens, the most clinically relevant endpoints are GMTs. The assessments were made for the age strata 11 to 17 and 18 to 64 years, respectively.

Since ADACEL™ is intended for adolescents and adults, a population that is expected to have pre-existing antibodies to the antigens due to prior immunization or exposure, baseline antibody

levels were considered in assessing booster response rates. The booster response rate for all antigens was defined as a 4-fold rise in participants with pre-vaccination titers below a pre-defined cut-off level and a two-fold rise in participants with pre-vaccination titers above a pre-defined cut-off value. These cut-off values for calculating booster response rates were determined based on the 95th percentile of the pre-vaccination levels from the available clinical data in the studies conducted to support licensure in Canada. A cut-off value of 2.56 IU/mL for diphtheria and 2.7 IU/mL for tetanus was used for determining the booster response in the clinical program for ADACEL™. The cut-off levels used for determining the booster response for pertussis antigens are: for PT 85 EU/mL, for FHA 170 EU/mL, for FIM 285 EU/mL, for PRN 115 EU/mL, respectively.

Table 7: Criteria for Immunogenicity Endpoints

Endpoint	Antigen	Study	Analysis	Comparison	Criteria
Seroprotection level at ≥0.1 IU/mL	Diphtheria, Tetanus	Td506	Primary	Non-inferiority testing (one-sided) of ADACEL™ compared to Td, using the two-sided 95% CI for the difference in rates	10% Margin
		Td505	Primary	Equivalency testing (two-sided) for 3 lots of ADACEL™, using the two-sided 95% CI for the difference in rates between any 2 lots.	(-10%, 10%)
		Td501 Td502	Primary	Non-inferiority testing (one-sided) of ADACEL™+ HepB (or Influenza) compared to ADACEL™ given separately from HepB (or Influenza), using the two-sided 95% CI for the difference in rates.	10% Margin
GMTs	Pertussis	Td506	Primary	Non-inferiority testing (one-sided) of ADACEL™ sera compared to Sweden I sera using the two-sided 95% CI of the GMT ratios.	Lower limit of 95% CI >0.67
		Td505	Primary	Equivalency testing (two-sided) for 3 lots of ADACEL™, using the two-sided 90% CI of the GMT ratios between any two lots.	(0.67, 1.5)
		Td501 Td502	Primary	Non-inferiority testing (one-sided) of ADACEL™+ HepB (or Influenza) compared to ADACEL™ given separately from HepB (or Influenza), , using the two-sided 90% CI of the GMT ratios.	Lower limit of 90% CI >0.67
	Diphtheria, Tetanus	Td506	Additional	Non-inferiority testing (one-sided) of ADACEL™ compared to Td, using the two-sided 90% CI and 95% CI of the GMT ratios	Lower limit of 90% CI >0.67

		Td505	Additional	Equivalency testing (two-sided) for 3 lots of ADACEL™, using the two-sided 90%CI of the GMT ratios between any two lots.	(0.67, 1.5)
		Td501 Td502	Additional	Non-inferiority testing (one-sided) of ADACEL™ ™+ HepB (or Influenza) compared to ADACEL™ given separately from HepB (or Influenza), using the two-sided 90% CI of the GMT ratios.	Lower limit of 90% CI >0.67
Booster Response	Diphtheria, Tetanus	Td506	Primary	Non-inferiority testing (one-sided) of ADACEL™ compared to Td, using the two-sided 95% CI for the difference in rates.	10% Margin
		Td505	Additional	Equivalency testing (two-sided) for 3 lots of ADACEL™, using the two-sided 95% CI for the difference in rates between any 2 lots.	(-10%, 10%)
		Td501 Td502	Additional	Non-inferiority testing (one-sided) of ADACEL™+ HepB (or Influenza) compared to ADACEL™ given separately from HepB (or influenza), using the two-sided 95%CI for the difference in rates.	10% Margin
	Pertussis	Td506	Primary	ADACEL™ compared to the booster response observed in the historical trials using the two-sided 95% CI on the booster response.	Lower limit of the 95% CI > acceptable booster response defined from the Supportive studies
Seroprotection level at ≥ 10 mIU/mL	Hepatitis B	Td501	Primary	Non-inferiority testing (one-sided) of ADACEL™+ HepB compared to ADACEL™ given separately from HepB, using the two-sided 95%CI for the difference in rates.	10% Margin
Seroprotection level HAI titer at ≥ 40	Influenza	Td502	Primary	Non-inferiority testing (one-sided) of ADACEL™+ Influenza compared to ADACEL™ given separately from Influenza, using the two-sided 95%CI for the difference in rates.	10% Margin

4.2.3 Assay Descriptions

Antibody assays were performed in a blinded manner at the clinical immunology laboratories of Sanofi Pasteur using validated methods. Anti-PT, anti-FHA, anti-FIM, anti-PRN immunoglobulin G (IgG), and anti-tetanus antibody titers were determined by an indirect ELISA method. Results for pertussis antibodies were calculated in ELISA units per milliliter (EU/mL) by comparison to in-house standard antisera of assigned unitage, calibrated to the US Human Reference Lots 3 or 4. Anti-tetanus titers were calculated as IU/mL by comparison to an international standard, Lot TE-3, available from the World Health Organization (WHO). Anti-diphtheria antibody responses were measured by the ability of test sera to protect Vero cells from a diphtheria toxin challenge. Results were reported as IU/mL by comparison to a calibrated WHO reference serum and were determined by the highest serum dilution that allowed cell metabolism in the presence of the challenge dose of diphtheria toxin.

4.2.4 Efficacy Assessment

Defined correlates of protection exist for diphtheria and tetanus, therefore evidence of efficacy is provided by demonstrating that the immune responses to these antigens attain levels previously established as protective (≥0.1 IU/mL) (73) (74). Efficacy of ADACEL™ against diphtheria and tetanus was assessed in study Td506 by evaluating seroprotection rates and by demonstrating that the diphtheria and tetanus seroresponses for ADACEL™ were non-inferior to the current standard of care Td Vaccine.

There are no universally accepted correlates of protection for pertussis. In concurrence with CBER, the efficacy for ADACEL™ in adolescents and adults was established based on comparison of pertussis antibody levels achieved in the study Td506, with those obtained after 3 doses of DAPTACEL® in the Sweden I Efficacy trial (See below). ADACEL™ vaccine is identical to DAPTACEL® vaccine with the exception of a lower quantity of one of the pertussis antigens (PT) and the diphtheria toxoid content. Although the subjects in the Sweden I Efficacy Trial were infants, similar pathogenesis and similar mechanisms of immunologic protection in adolescents and adults is suggested by (i) the fact that pertussis is a respiratory disease characterized by prolonged spasmodic coughing that is similar in adults and children (46) (75) and (ii) in a Household Contact Study nested within the Sweden I Efficacy Trial, household contacts who developed clinical pertussis had PT or PRN and agglutinin titers below the same cut-off level regardless of age (8) (67). It is therefore reasonable to extrapolate immunogenicity data from ADACEL™ in adolescents and adults to efficacy data from DAPTACEL® in infants. At the June 1997 meeting of VRBPAC, at which adult pertussis was discussed, the committee agreed that 1) demonstration of efficacy of a given acellular pertussis vaccine administered as a primary series to infants can serve as the basis of efficacy of that vaccine when administered as a booster dose to adolescents and adults; and 2) the demonstration of comparable antibody responses in adolescents/ adults and infants is an appropriate indicator that the different age groups respond to the vaccine in equivalent manners (17). The comparative bridging of immunogenicity data after administration of ADACEL™ to efficacy data obtained from a controlled study with a vaccine that contains the same licensed components, DAPTACEL®, is also consistent with the FDA Guidelines for the Evaluation of Combination Vaccines for Preventable Diseases, April 1997 (16).

In the Sweden I Efficacy trial a total of 9,829 infants received 1 of 4 vaccines: DAPTACEL®, Sanofi Pasteur, Canada; $DTaP_2$, Glaxo-SmithKline, Belgium; DTwP; Sanofi Pasteur, United States; or DT vaccine as placebo. In this study it was demonstrated that the protective efficacy of DAPTACEL® after 3 doses of vaccine using the World Health Organization (WHO) case definition of pertussis (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was high at 84.9% (95% confidence interval [CI] 80.1 to 88.6). The protective efficacy of DAPTACEL® against mild pertussis (≥1 day of cough with laboratory confirmation) was also high at 77.9% (95% CI 72.6 to 82.2). DAPTACEL® was the only vaccine whose efficacy exceeded the pre-set standard of at least 70%. While the efficacy of the DTwP vaccine tended to decline over time, the efficacy of DAPTACEL® remained at 80% or higher during the 2 years of follow-up (15).

In order to compare immunogenicity to trials with ADACEL™, a subset of representative sera from the infants immunized with DAPTACEL® in the Sweden I Efficacy trial was tested in the same Sanofi Pasteur laboratory contemporaneously to sera from ADACEL™ recipients, in a validated assay and using identical methodology. Non-inferiority of antibody levels was assessed using the two-sided 95% CI around the ratios of GMTs of ADACEL™ for both adolescents and adults in the Td506 trial vs. GMTs after three doses of DAPTACEL® in infants from the Sweden I Efficacy Trial. This approach provided a direct link between ADACEL™ clinical performance and efficacy in the Sweden I study.

4.3 Immunogenicity Results

Immunogenicity results from the clinical trials are presented in the following order:

- **Adolescents**- Immunogenicity results from adolescents in the study Td506 and the lot consistency study Td505.
- **Adults** - Immunogenicity results from adults in the study Td506.
- **Concomitant Administration** - Immunogenicity results from the two clinical trials of ADACEL™ with concomitant administration with Hepatitis B Vaccine (Study Td501) and Influenza Vaccine (Study Td502).

For all categories the evaluation of immunogenicity is presented for the primary immunogenicity endpoints (Table 7) for the PPI population.

4.3.1 Immunogenicity Results in Adolescents (Studies Td506 and Td505)

Table 8 summarizes the information on adolescents that were enrolled, randomized and included in the PPI population.

Table 8: Summary of Participant Disposition and Immunogenicity Analysis Population for Adolescents in Studies, Td506 and Td505

Age (Years)		Td506			Td505
		ADACEL™	**Td**	**Total**	**ADACEL™**
Adolescents	Enrolled and Randomized	1225	818	2043	1811
	Participants Who Provided Blood Samples	603	605	1208	1175
	Excluded from PPI Population*	76	89	165	119
	PPI Population	**527**	**516**	**1043**	**1056**

*Most of the exclusions were due to visit schedule/interval related protocol violations

4.3.1.1 Td506 –Immunogenicity of ADACEL™ vs. Td Vaccine (11-17 yrs)

Of a total of 2043 adolescents enrolled in this study that received a study vaccine, 1225 were randomized to receive ADACEL™ and 818 were randomized to receive Td Vaccine (Table 8). Participants were similarly distributed by age, sex and race between the two study groups. For the immunogenicity assessment, a subset of participants provided blood samples. Bleeds were randomly assigned based on treatment groups and age-strata (11-13 yrs and 14-17 yrs). A total of 527 (87.4%) adolescents in the ADACEL™ group and 516 (85.3%) adolescents in the Td group were included in the PPI population.

Seroprotection rates (≥0.1 IU/mL) post-vaccination were high and were similar between the ADACEL™ and Td Vaccine groups, for both diphtheria and tetanus. Diphtheria rates were 99.8% for both groups (526/527 for ADACEL™ and 515/516 for Td Vaccine). Tetanus seroprotection rates were 100% for all adolescents. Booster response rates were adequate and similar between Td Vaccine and ADACEL™ recipients for both diphtheria and tetanus (See Figure 3). The rates for diphtheria were 95.1% for ADACEL™ and 95.0% for Td Vaccine and rates for tetanus were 91.7% and 91.3% for ADACEL™ and Td Vaccine recipients, respectively. Non-inferiority was demonstrated in both seroprotection and booster response rates (See Table 9). The ADACEL™ group was also comparable to the Td group with respect to the seroprotection rate at the ≥1.0 IU/mL level both for tetanus and diphtheria (See Table 17). Diphtheria and tetanus GMTs at 1-month post-vaccination were similar among groups (See Table 17).

Figure 3: Diphtheria and Tetanus- Seroprotection Rates at a Level of ≥ 0.1 IU/mL and Booster Response Rates, Td506 Adolescents

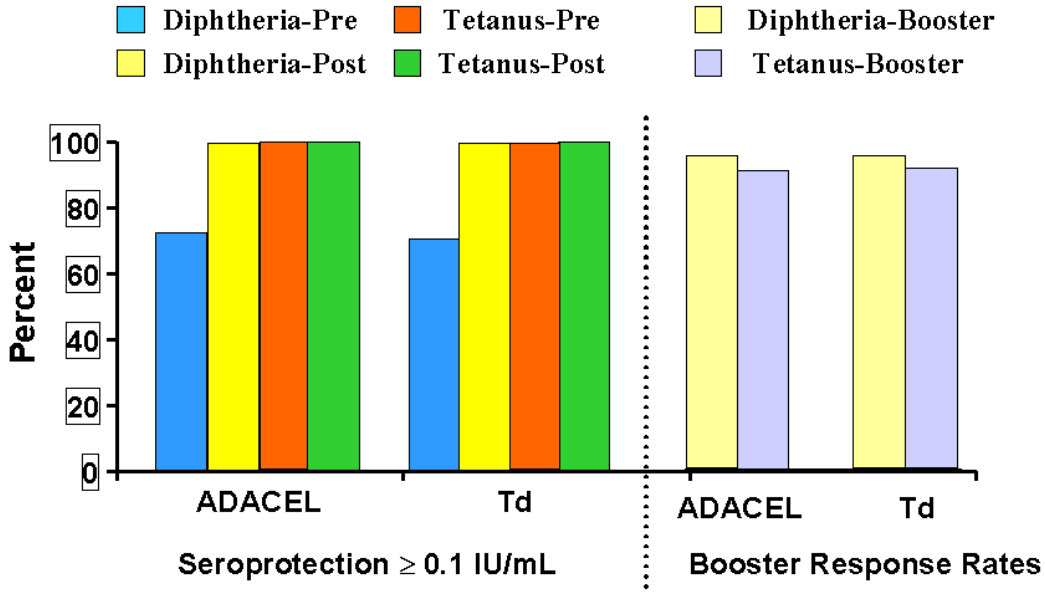


Table 9: Diphtheria and Tetanus - Comparison of Seroprotection Rates at a Level of ≥0.1 IU/mL and Booster Response Rates (95% CI of the Difference in Rates), Td506 Adolescents

Antigen	Seroprotection at ≥0.1 IU/mL					Booster Response Rate				
	ADACEL™	Td	Diff%	LCL	UCL	ADACEL™	Td	Diff%	LCL	UCL
Diphtheria	99.8%	99.8%	0.00	-0.53	0.54	95.1%	95.0%	0.11	-2.53	2.76
Tetanus	100.0%	100.0%	0.00	0.00	0.00	91.7%	91.3%	0.37	-3.02	3.76

Geometric Mean Titers (GMTs) for ADACEL™ were consistently higher than Sweden I Efficacy trial levels for all pertussis antigens (See Table 10). As per the primary hypothesis, the lower limits of the 95% CIs for the ratio (ADACEL™/Sweden I) of GMTs for all pertussis antigens are above 0.67; it can thus be concluded that the responses to ADACEL™ are non-inferior to the responses observed after DAPTACEL®. Based on the 95% CI of the ratio, in each case, the responses to ADACEL™ far exceeded the DAPTACEL® responses in Sweden I. Post-vaccination GMTs for the pertussis antigens PT, FHA, FIM, and PRN for Td Vaccine recipients were similar to the pre-vaccination levels for ADACEL™ recipients (data not shown).

Table 10: Pertussis Antigens - Comparison of Geometric Mean Titers (GMTs) Between ADACEL™ in Td506 (Adolescents, 11-17 Years, PPI Population) and DAPTACEL® (Three doses in Infants) in the Sweden I Efficacy Trial

Antigens (EU/mL)	Time	ADACEL™ Td506			DAPTACEL® Sweden I Efficacy Trial			Td506 ADACEL™/ DAPTACEL®	
		N*	GMT	95% CI†	N	GMT	95% CI†	GMT Ratio‡	95% CI
PT	**Pre**	527	14.46	(12.95, 16.14)	80	5.24	(4.23, 6.48)	2.76	(2.06, 3.70)
	Post	524	309.26	(283.59, 337.25)	80	86.55	(71.31, 105.04)	3.57	(2.83, 4.52)
FHA	**Pre**	527	19.49	(17.51, 21.69)	80	5.21	(4.18, 6.49)	3.74	(2.81, 4.99)
	Post	526	214.83	(200.34, 230.37)	80	39.95	(34.62, 46.10)	5.38	(4.46, 6.49)
FIM	**Pre**	527	25.80	(23.49, 28.33)	80	13.26	(11.23, 15.67)	1.94	(1.52, 2.50)
	Post	526	1792.40	(1603.74, 2003.24)	80	341.10	(270.23, 430.56)	5.25	(3.90, 7.09)
PRN	**Pre**	526	10.01	(8.93, 11.24)	80	2.15	(1.85, 2.49)	4.67	(3.46, 6.30)
	Post	526	344.52	(313.28, 378.87)	80	108.12	(91.41, 127.88)	3.19	(2.48, 4.10)

* N = Number of participants evaluated, not including missing observations, used for calculating GMTs.

† 95% CI=Two-sided 95% confidence interval

‡ GMT Ratio = Ratio of Td506 ADACEL™ and DAPTACEL® GMTs.

The booster response for each pertussis antigen was considered comparable to the booster response observed in the supportive trials. For each pertussis antigen, the lower limit of the 95% CI for the booster rate is above the pre-defined reference booster rate (as defined from the supportive trials: 81.2% for PT, 77.6% for FHA, 82.4% for FIM, and 86.4% for PRN). The observed booster response rates with their 95% CI were: 92.0% (89.3, 94.2) for PT, 85.6% (82.3, 88.4) for FHA, 94.9% (92.6, 96.6) for FIM and 94.5% (92.2, 96.3) for PRN.

An on-going long-term immunogenicity follow-up study for Td506 will provide data on the anti-pertussis, anti-diphtheria toxin and anti-tetanus toxin immune responses of participants in the US at one, three and five years after immunization.

4.3.1.2 Td505 – Lot Consistency Study

A total of 1811 participants, 11-17 yrs of age, were enrolled and randomized in the study to receive one of 3 consecutively manufactured lots of ADACEL™, 603 participants received lot 1, 605 received lot 2 and 603 received lot 3. Of the 1811 enrolled participants, 1791 (98.9%) completed the study and a subset of these was bled for immunogenicity assessment (see Table 8). Participants from whom blood samples were obtained for the immunogenicity assessment, were randomly selected for the 3 lots and age-strata (11-13 yrs and 14-17 yrs). One case of suicide was classified as discontinuation due to an adverse event. The overall mean age of participants in the study was 13.9 years and was similar for the 3 groups. Gender and ethnic origin distributions were comparable among the 3 lots.

Immune responses were compared between groups receiving the 3 lots of ADACEL™ in the subset of randomized participants who were bled (PPI population [N=1056]). Seroprotective rates (≥0.1 IU/mL) and booster response rates post-vaccination were high and were consistent between the 3 study groups. For both diphtheria and tetanus: seroprotection rates were 100% for tetanus and 99.7% (100% in lot 1, 99.4% in lot 2, and 99.7% in lot 3) for diphtheria. All of the statistical tests for equivalency between lots (Table 11) were met for both diphtheria and tetanus.

Table 11: Diphtheria and Tetanus- Comparison of Seroprotection Rates at Level of ≥0.1 IU/mL and Booster Response Rate (95% CI of the Difference in Rates), Td505

Antigen	Seroprotection at ≥0.1 IU/mL					Booster Response Rate				
	Rate1	Rate2	Diff %	LCL	UCL	Rate1	Rate2	Diff %	LCL	UCL
Diphtheria										
Lot 1 - Lot 2	100.0	99.4	0.57	-0.22	1.36	96.0	95.7	0.31	-2.75	3.37
Lot 1 - Lot 3	100.0	99.7	0.28	-0.50	1.07	96.0	94.9	1.11	-1.94	4.16
Lot 2- Lot 3	99.4	99.7	-0.29	-1.08	0.50	95.7	94.9	0.80	-2.25	3.86
Tetanus										
Lot 1 - Lot 2	100.0	100.0	0.00	0.00	0.00	92.6	93.7	-1.12	-4.99	2.74
Lot1 - Lot 3	100.0	100.0	0.00	0.00	0.00	92.6	91.8	0.79	-3.06	4.64
Lot 2 - Lot 3	100.0	100.0	0.00	0.00	0.00	93.7	91.8	1.91	-1.94	5.77

Geometric Mean Titers for the pertussis antigens PT, FHA, FIM, and PRN before vaccination and at 1-month post-vaccination are presented in Table 12. Post vaccination GMTs were similar for all three lots for PT, FHA and PRN. For FIM, the upper limit of 1.55 for the 90% CI GMT ratio between lots 2 and 3 was marginally above the pre-defined equivalency criteria of 1.5 (See Table 13). The lowest GMT for FIM (1528.75 EU/mL) however, is at least four fold higher than that achieved after DAPTACEL® in the Sweden I trial (341.10 EU/mL).

Table 12: Pertussis Antigens: Geometric Mean Titers (GMTs) at Pre- and One-Month Post-Vaccination, Td505

	PT		FHA		FIM		PRN	
ADACEL™	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
Lot 1	14.70	343.65	19.88	285.10	31.97	1901.60	9.11	366.14
Lot 2	16.87	347.36	24.56	264.98	33.08	2025.38	11.75	394.69
Lot 3	15.53	323.89	20.70	247.76	31.87	1528.75	9.66	343.21

Table 13: Pertussis Antigens - Comparison of Geometric Mean Titers (GMTs) of 3 lots of ADACEL™ (90% CI of the GMTs Ratio) at One Month Post-Vaccination, Td505

	PT			FHA			FIM			PRN		
	Ratio	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**
Lot 1/ Lot 2	0.99	0.87	1.13	1.08	0.98	1.19	0.94	0.80	1.10	0.93	0.81	1.07
Lot 1/ Lot 3	1.06	0.93	1.21	1.15	1.04	1.27	1.24	1.06	1.45	1.07	0.93	1.23
Lot 2/ Lot 3	1.07	0.94	1.22	1.07	0.97	1.18	1.32	1.13	1.55	1.15	1.00	1.32

4.3.2 Immunogenicity Results in Adults (Study Td506)

4.3.2.1 Td506 –Immunogenicity of ADACEL™ vs. Td Vaccine (18-64 yrs)

Of a total of 2407 adults enrolled in this study that received a known vaccine, 1807 received ADACEL™ and 600 received Td Vaccine (Table 14). Participants were similarly distributed by age, sex and race between the two study groups. For the immunogenicity assessment, a subset of participants provided blood samples. Bleeds were randomly assigned based on randomization into treatment groups and age-strata (18-28 yrs, 29-48 yrs and 49-64 yrs). In the ADACEL™ group, 743 (82.5%) participants as compared to 510 (86.0%) in the Td group were included in the PPI population.

Table 14: Summary of Participant Disposition and Immunogenicity Analysis Population for Adults in Study, Td506

		Td506	
		ADACEL™	**Td**
Adults (18-64)	Enrolled and Randomized	1807	600
	Participants Who Provided Blood Samples	901	593
	Excluded from PPI Population*	158	83
	PPI Population	**743**	**510**

*Most of the exclusions were due to visit schedule/interval related protocol violations

Seroprotection rates (≥0.1 IU/mL) at 28–42 days post-vaccination were high and were similar between the ADACEL™ and Td Vaccine groups, both for diphtheria and tetanus. Diphtheria rates were 94.1% and 95.1% for the ADACEL™ and Td Vaccine groups, respectively. For both groups, pre-vaccination diphtheria seroprotection rates decreased as age increased across the 3 adult age strata. Baseline seroprotection rates were 78.3%, 66.8%, and 43.2% in the ADACEL™ group and 70.4%, 67.1%, and 52.9% in the Td group for the 18 to 28, 29 to 48, and 49 to 64 year-old age groups, respectively. Post-vaccination, the rates were: 99.2%, 97.6%, and 85.5%, after ADACEL™ Vaccine and 100.0%, 97.0%, 88.5%. after Td Vaccine. Tetanus seroprotection rates were 100% for all adults in the ADACEL™ group and 99.8% for adults in the Td Vaccine group.

Booster response rates were adequate and similar between the Td Vaccine and ADACEL™ recipients for both diphtheria and tetanus (See Figure 4). Booster response rates for diphtheria were 87.4% and 83.4% for the ADACEL™ and Td Vaccine groups, respectively. For tetanus, the booster response rates were 63.1% and 66.8% for the ADACEL™ and Td Vaccine groups, respectively. Non-inferiority was demonstrated for both seroprotection as well as booster response rates (See Table 15). The ADACEL™ group was also comparable to the Td group with respect to the seroprotection rate at the ≥1.0 IU/mL level both for tetanus and diphtheria (See Table 17). Diphtheria and tetanus GMTs at 1-month post-vaccination were similar among groups (See Table 17).

Figure 4: Diphtheria and Tetanus- Seroprotection Rates at Level ≥0.1 IU/mL and Booster Response Rates, Td506 Adults

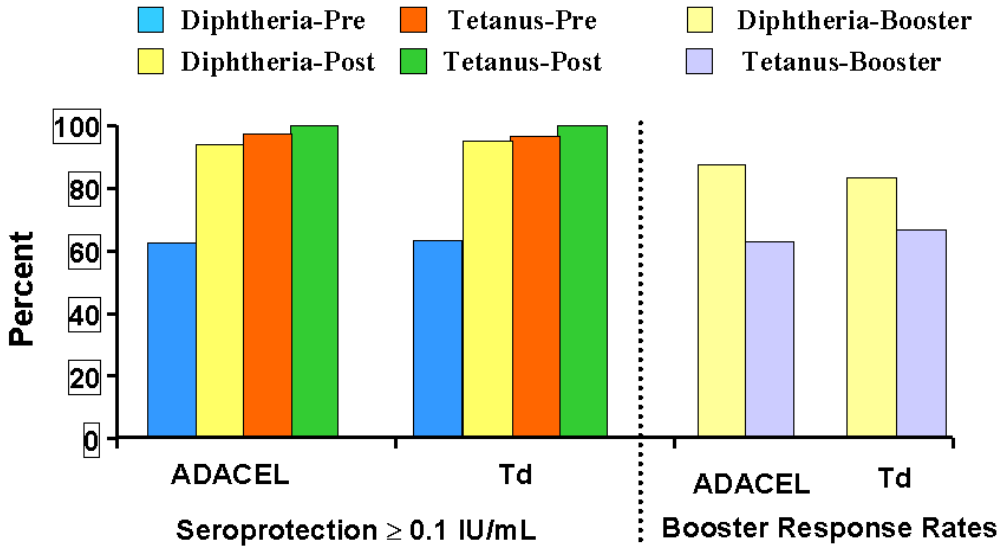


Table 15: Diphtheria and Tetanus - Comparison of Seroprotection Rates at Level of ≥0.1 IU/mL and Booster Response Rates (95% CI of the Difference in Rates), Td506 Adults

Antigen	Seroprotection rates at ≥0.1 IU/mL(%)					Booster Response Rate (%)				
	ADACEL™	Td	Diff%	LCL	UCL	ADACEL™	Td	Diff%	LCL	UCL
Diphtheria	94.1	95.1	-1.01	-3.55	1.53	87.4	83.4	4.02	-0.01	8.04
Tetanus	100.0	99.8	0.20	-0.19	0.58	63.1	66.8	-3.72	-9.09	1.64

GMTs for ADACEL™ recipients were consistently higher than the Sweden I Efficacy trial levels for all pertussis antigens (See Table 16). As per the primary hypothesis, the lower limits of the 95% CIs for the ratio of GMTs for all pertussis antigens are above 0.67; it can thus be concluded that the responses to ADACEL™ are non-inferior to the responses observed in the subset of DAPTACEL® recipients from the Sweden I Efficacy trial. Based on the 95% CI of the ratio, in each case, the responses to ADACEL™ far exceeded the DAPTACEL® responses in Sweden I.

Table 16: Pertussis Antigens-Comparison of Geometric Mean Titers (GMTs) Between ADACEL™ in Td506 (Adults 18-64 Years, PPI Population) and DAPTACEL® (Three doses in Infants) in the Sweden I Efficacy Trial

Antigens	Time	ADACEL™ Td506			DAPTACEL® Sweden I Efficacy Trial			Td506 ADACEL™ / DAPTACEL®	
		N*	GMT	95% CI†	N	GMT	95% CI†	GMT Ratio‡	95% CI†
PT (EU/mL)	Pre	741	12.54	(11.46, 13.73)	80	5.24	(4.23, 6.48)	2.39	(1.80, 3.18)
	Post	741	178.84	(164.24, 194.74)	80	86.55	(71.31, 105.04)	2.07	(1.58, 2.70)
FHA (EU/mL)	Pre	741	18.13	(16.69, 19.68)	80	5.21	(4.18, 6.49)	3.48	(2.68, 4.52)
	Post	741	192.91	(180.72, 205.93)	80	39.95	(34.62, 46.10)	4.83	(3.94, 5.92)
FIM (EU/mL)	Pre	741	28.56	(26.12, 31.23)	80	13.26	(11.23, 15.67)	2.15	(1.63, 2.84)
	Post	741	852.72	(762.82, 953.20)	80	341.10	(270.23, 430.56)	2.50	(1.77, 3.54)
PRN (EU/mL)	Pre	741	8.45	(7.65, 9.34)	80	2.15	(1.85, 2.49)	3.94	(2.89, 5.36)
	Post	741	341.89	(306.19, 381.75)	80	108.12	(91.41, 127.88)	3.16	(2.25, 4.44)

* N= Number of participants evaluated, not including missing observations, used for calculating GMTs.

† 95% CI= Two-sided 95% confidence interval

‡ GMT Ratio= Ratio of ADACEL™ and DAPTACEL® GMTs

The booster response for each pertussis antigen was comparable to the booster response observed in the supportive trials, as the lower limit of the 95% CI for the booster rate was above the pre-defined reference booster rate (as defined from the supportive trials: 81.2% for PT, 77.6% for FHA, 82.4% for FIM, and 86.4% for PRN) for each pertussis antigen. The observed booster response rates (with the 95% CI) were: 84.4% (81.6, 87.0) for PT, 82.7% (79.8, 85.3) for FHA, 85.9% (83.2, 88.4) for FIM and 93.8% (91.8, 95.4) for PRN.

An on-going long-term immunogenicity follow-up study for Td506 will provide data on the anti-pertussis, anti-diphtheria toxin and anti-tetanus toxin immune responses of participants in the US at one, three and five years after immunization.

4.3.3 Efficacy of ADACEL™ in Adolescents and Adults

4.3.3.1 Diphtheria and Tetanus

Efficacy of ADACEL™ against diphtheria and tetanus was demonstrated by attaining non-inferiority of the diphtheria and tetanus seroresponses to the current standard of care, Td Vaccine, in the Td506 study. As summarized in Table 17, ADACEL™ was found to be non-inferior to Td Vaccine for adolescents and adults for all immunogenicity endpoints including seroprotection rates at levels ≥0.1 IU/mL and ≥1.0 IU/mL, booster rates and GMTs (See Table 17). It should be noted that pre-vaccination diphtheria seroprotection rates decreased as age increased across the three adult age strata, with the most dramatic decline in the 49 to 64 year old age group for both ADACEL™ and Td Vaccine groups (See Section 4.3.2.1). Despite this, even for the oldest age group more than 85% of participants achieved seroprotective levels of ≥0.1 IU/mL.

Table 17: Summary of Immunogenicity Endpoints (PPI Population) for Diphtheria and Tetanus at One-Month Post Vaccination in Study Td506

	11–17 yrs				18–64 yrs			
	ADACEL™		Td		ADACEL™		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	100.0	516/516	100.0	742/742	100.0	508/509	99.8
Seroprotection ≥1.0 IU/mL								
Diphtheria	520/527	98.7	508/516	98.4	578/741	78.0	405/507	79.9
Tetanus	525/527	99.6	513/516	99.4	726/742	97.8	500/509	98.2
Booster Response Rates								
Diphtheria	501/527	95.1	489/515	95.0	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
GMTs (Post-vaccination)	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**	**N**	**GMT**
Diphtheria (IU/mL)	527	8.46	516	7.10	741	2.49	507	2.37
Tetanus (IU/mL)	527	12.87	516	14.35	742	7.65	509	8.18

n, % = number and percent of participants who achieved the specified levels for seroprotection and booster response.
N = number of participants evaluated.
GMT = Geometric Mean Titer, calculated excluding missing observations.
In 11-17 years ADACEL™ (PPI=527) and Td (PPI=516), in 18-64 years ADACEL™ (PPI=743) and Td (PPI=510)

4.3.3.2 Pertussis

As outlined in Section 4.2.4, immunogenicity in the study Td506 was comparatively bridged to Sweden I Efficacy Trial to establish efficacy of ADACEL™ against pertussis. Comparisons of GMT responses for adolescents and adults in Td506 with those of Sweden I Efficacy Trial showed that GMTs for all pertussis antigens were consistently 2 to 5-fold higher than those of DAPTACEL® in the Sweden I Efficacy trial (See Table 10 and Table 16). The pertussis antigen Reverse Cumulative Distribution (RCD) curves observed in the PPI population clearly demonstrate that prior to vaccination the pertussis antibody levels are below those obtained after three doses in Sweden I but undergo a robust rise after vaccination (See Appendix 2). The RCD Curves displaying the post-vaccination antibody levels of the different trials in adolescents and adults are consistently higher than those achieved after DAPTACEL® (See Appendix 2: Figure 7 and Figure 8). Demonstration of comparative bridging of immunogenicity data from trial Td506 to the immunogenicity data from the Sweden I Efficacy trial in infants supports the efficacy of ADACEL™ against pertussis in adolescents and adults.

4.3.4 Immunogenicity Results in Concomitant Vaccine Administration Studies (Td501 and Td502)

Table 18 summarizes the information on participants that were enrolled, randomized and included in the intent-to-treat immunogenicity (ITTI) population and PPI population in the concomitant administration studies, Td501 and Td502.

Table 18: Summary of Participant Disposition and Immunogenicity Analysis Population by Study for Concomitant Vaccine Administration Studies, Td501 and Td502

	Td501 (11–14 yrs)			Td502 (19–64 yrs)		
	Simultaneous	Sequential	Total	Simultaneous	Sequential	Total
	ADACEL™ + HepB	ADACEL™, HepB		Flu + ADACEL™	Flu, ADACEL™	
Enrolled and Randomized	**206**	**204**	**410**	**359**	**361**	**720**
Participants Who Provided Blood Samples	206	204	410	359	361	720
Excluded from PPI Population	45	53	98	5	37	42
PPI Population	**161**	**151**	**312**	**354**	**324**	**678**

4.3.4.1 Td501 – Concomitant Administration of ADACEL™ with Hepatitis B Vaccine (11-14 yrs)

A total of 410 participants were enrolled and randomized in the study, of which 206 received ADACEL™ and Hepatitis B Vaccine concomitantly (simultaneous group) and 204 received ADACEL™ followed by Hepatitis B Vaccine one month later (sequential group). The study was

completed by 392 participants and 18 participants discontinued. No participants discontinued due to an adverse event. For the immunogenicity analysis, 312 (76.10%) of the randomized participants were included in PPI population.

For diphtheria, 100% of participants in the simultaneous group and 99.3% of the sequential group achieved seroprotective levels ≥0.1 IU/mL. For tetanus, all participants in both groups achieved seroprotective levels. All of the pre-defined non-inferiority criteria as summarized in Table 7 were met for diphtheria and tetanus (See Table 19). The post-vaccination hepatitis B seroprotective rates at the level of ≥10 mIU/mL were similar between groups and the criterion for non-inferiority was met (See Table 19).

Table 19: Diphtheria, Tetanus and Hepatitis B- Comparison of Seroprotection Rates (95% CI of the Difference in Rates) at One-Month Post Vaccination at a Level of ≥0.1 IU/mL for Diphtheria and Tetanus and at a Level of ≥10 mIU/mL for Hepatitis B, Td501

	Diphtheria			Tetanus			Hepatitis B		
Simultaneous	100%			100%			96.27%		
Sequential	99.34%			100%			97.33%		
Comparison	**Diff%**	**LCL**	**UCL**	**Diff%**	**LCL**	**UCL**	**Diff%**	**LCL**	**UCL**
Sequential - Simultaneous	-0.66	-1.96	0.63	0.00	0.00	0.00	1.06	-2.84	4.96

Non-inferiority criteria were met for all pertussis antigens as the lower limits of the 90% CIs of the GMT ratio were above 0.67. Table 20 presents the statistical comparisons of the PPI population post-vaccination GMTs using the 90% CI for the GMT ratio between simultaneous and sequential groups for the pertussis antigens.

Table 20: Pertussis antigens - Comparison of Geometric Mean Titer (GMTs) at One Month Post-Vaccination (90% CI of the GMTs Ratio), Td501

	PT (EU/mL)			FHA (EU/mL)			FIM (EU/mL)			PRN (EU/mL)		
Simultaneous	303.50			301.51			1906.42			292.92		
Sequential	321.56			305.41			1926.71			284.63		
Comparison	**Ratio**	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**
Simultaneous / Sequential	0.94	0.79	1.13	0.99	0.84	1.16	0.99	0.81	1.22	1.03	0.83	1.28

4.3.4.2 Td502 - Concomitant Administration of ADACEL™ with Influenza Vaccine (19-64 yrs)

A total of 720 participants were enrolled and randomized in this study, of which 359 received ADACEL™ and Flu Vaccine concomitantly (simultaneous group) and 361 received Flu Vaccine followed by ADACEL™ one month later (sequential group). The study was completed by 696 participants and 24 participants discontinued. No participants discontinued due to an adverse event. For immunogenicity analysis, 678 of the randomized participants (94.2%) were included in PPI population.

For diphtheria, 86.2% of participants in the simultaneous group (Flu + ADACEL™) and 87.0% of sequential group (Flu, ADACEL™) achieved seroprotective levels ≥0.1 IU/mL. For tetanus, 99.7% of participants in the simultaneous group and 98.1% of the sequential group achieved seroprotective levels ≥0.1 IU/mL. For each of the influenza antigens, the post-vaccination influenza seroconversion rates at the level of HAI titer ≥40 were similar between groups. The primary immunogenicity criteria for non-inferiority were met for diphtheria, tetanus and influenza (See Table 21 and Table 22).

Table 21: Diphtheria and Tetanus – Comparison of Seroprotection Rates at a Level of ≥0.1 IU/mL One Month of Post-Vaccination (95% CI of the Difference in Rates), Td502

	Diphtheria			Tetanus		
Simultaneous	86.2%			99.7%		
Sequential	87.0%			98.1%		
Comparison	**Diff%**	**LCL**	**UCL**	**Diff%**	**LCL**	**UCL**
Sequential - Simultaneous	0.9	-4.3	6.0	-1.6	-3.1	-0.0

Table 22: Influenza antigens Comparison of Seroprotection Rates at ≥40 HAI titer Level at One Month of Post-Vaccination (95% CI of the Difference in Rates), Td502

	A/H3N2 Panama			A/H1N1 Caledonia			B/Yamanashi		
Simultaneous	86.5%			54.0%			80.6%		
Sequential	88.8%			46.9%			80.3%		
Comparison	**Diff%**	**LCL**	**UCL**	**Diff%**	**LCL**	**UCL**	**Diff%**	**LCL**	**UCL**
Sequential - Simultaneous	2.3	-2.9	7.4	-7.0	-14.8	0.8	-0.3	-6.5	5.9

The post-vaccination GMTs were consistently higher for all pertussis antigens in the sequential group. While the non-inferiority criterion was achieved for PT, FHA, and FIM, it was not achieved for PRN. The lower limit of the 90%CI of the GMT ratio was lower (LCL=0.61) as compared to the non-inferiority criterion of 0.67 (See Table 23). The GMT values for all pertussis antigens, including PRN (191.66 EU/mL), far exceeded those achieved after DAPTACEL® in the Sweden I trial (108.12 EU/mL; See Appendix 2). This evidence supports the adequacy of the pertussis response following concomitant administration with Flu Vaccine.

Table 23: Pertussis Antigens – Comparison of Geometric Mean titer (GMT) at One month Post-Vaccination (90% CI of the GMTs Ratio), Td502

	PT (EU/mL)			FHA (EU/mL)			FIM (EU/mL)			PRN (EU/mL)		
Simultaneous	186.42			200.57			925.80			191.66		
Sequential	234.51			242.24			1136.32			260.27		
Comparison	**Ratio**	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**	**Ratio**	**LCL**	**UCL**
Simultaneous/ Sequential	0.79	0.70	0.90	0.83	0.75	0.91	0.81	0.68	0.98	0.74	0.61	0.88

4.4 Immunogenicity Conclusions

In results from four clinical trials, the immunogenicity profile of ADACEL™ has been documented in 3316 vaccinees receiving ADACEL™ as compared to 1026 vaccinees receiving the Td Vaccine. In Td506, ADACEL™ was shown to be non-inferior to Td Vaccine with respect to rates of seroprotection and booster response rates for diphtheria and tetanus. The post-immunization GMTs for the ADACEL™ pertussis antigens were robust across all studies and the values were consistently above the GMTs obtained in the Sweden I Efficacy Trial.

This clinical program also documented that ADACEL™ can be administered concomitantly with Hepatitis B Vaccine and Influenza Vaccine, while retaining robust immune responses for the concomitantly administered vaccine and for ADACEL™. For concomitant administration of ADACEL™ with Influenza Vaccine, pertussis responses were somewhat lower than those in the sequential group and this difference reached statistical significance for PRN. The GMT values for all pertussis antigens, including PRN, exceeded those achieved after DAPTACEL® in the Sweden I trial.

In comparing the immune response for adolescents and adults in Td506, a clear effect of age on pre-vaccination titers was observed, in that adolescents have higher titers to both diphtheria and tetanus. In particular, pre-vaccination diphtheria seroprotective rates decreased with increase in age. This resulted in higher post-vaccination seroprotection rates at a level of ≥ 0.1 IU/mL in adolescents (>99%) vs. adults (>85% in the 49-64 year old adult age strata) for diphtheria. This trend was similar for both ADACEL™ and Td groups. Generally, antibody levels to pertussis antigens were also lower in adults, although the differences appear smaller than for diphtheria and

tetanus antigens. Importantly, despite these differences in pre-vaccination seroprotection rates, the post-vaccination rates demonstrated a substantial rise compared with the pre-vaccination levels. These observations emphasize that the benefit from the vaccine can be seen in subjects despite different pre-immunization titers. Thus, ADACEL™ can be considered an appropriate booster in both older as well as younger individuals**.**

In terms of the pertussis immune response, the RCD curves displaying the post-vaccination antibody levels of the different trials in adolescents and adults are consistently higher than those achieved after DAPTACEL®. Thus, it can be inferred that ADACEL™ will protect adolescents and adults from pertussis.

The immunogenicity data presented in this document supports the overall conclusion that ADACEL™ can be administered to adolescents and adults with the benefits of protection against pertussis in addition to protection against diphtheria and tetanus presently provided by Td Vaccine. Specific immunogenicity conclusions that can be made from the data are as follows:

- ADACEL™ was non-inferior to Td Vaccine in adolescents and adults for diphtheria and tetanus; ADACEL™ is protective against diphtheria and tetanus in 11-64 year olds.
- Non-inferiority to pertussis antibody levels achieved in Sweden I Efficacy trial was demonstrated; ADACEL™ is protective against pertussis in 11-64 year olds.
- Consistency of manufacture with respect to immunologic outcomes has been demonstrated.
- Excellent seroprotection rates and GMTs were observed despite variability in diphtheria and tetanus pre-vaccination titers.
- ADACEL™ can be administered concomitantly with Hepatitis B Vaccine or Influenza Vaccine. For concomitant administration of ADACEL™ with Influenza Vaccine, somewhat lower pertussis responses were observed.
- ADACEL™ was highly immunogenic across all studies.

4.5 Safety – Assessment

The clinical development program was designed to determine the safety and tolerability of ADACEL™ in adolescents and adults aged 11-64 years. The safety profile of ADACEL™ was compared with that of Td Vaccine. In addition this clinical program evaluated the safety of concomitant administration of ADACEL™ with Hepatitis B or Influenza vaccines.

The ADACEL™ safety database consists of a total of 6803 participants from four main (5841 participants) and three supportive clinical trials (962 participants) as summarized in Table 6 and Table 43 of Appendix 5, respectively. The safety profile has been established based on the hypothesis testing of four safety endpoints (i.e., the solicited adverse events of Erythema, Swelling, Pain, and Fever) during Days 0 to 14 after a single dose of ADACEL™. Additionally, other solicited and unsolicited events as well as SAEs and events of special interest were assessed to further characterize the safety profile. Additional safety data was provided by the three supportive trials that were analyzed separately and are presented separately in Appendix 5.

4.6 Safety Parameters

4.6.1 Study Cohorts for Safety

The primary population for the safety analysis was specified as the Intent-to-Treat Safety (ITTS) population, which includes all participants who were randomized and received either ADACEL™ or Td Vaccine. Participants were analyzed according to the vaccine they actually received.

4.6.2 Criteria for Safety Endpoints

The categories of safety information that were collected and the duration of follow-up for safety variables are summarized in Table 24. Definition and severity rating scales for each type of event are detailed in Appendix 3.

Table 24: Summary of Safety Variables and Follow-Up Duration for clinical Trials

Safety Parameter	Td506	Td505	Td501	Td502
Immediate Reactions	30 minutes post-vaccination			
Solicited Local and Systemic Reactions	Collected daily from Days 0 to 14 after ADACEL™ vaccination			
Unsolicited AEs	Collected from Days 0 to 14 after vaccination			
Unsolicited AEs requiring medical contact	Anytime during the study 0-6 months	Anytime during the study 0-1 month	Anytime during the study 0-5 or 6 months	Anytime during the study 0-1 or 2 months
SAEs	Anytime during the study 0-6 months	Anytime during the study 0-1 month	Anytime during the study 0-5 or 6 months	Anytime during the study 0-1or 2 months

For Td501, Td502, Td505 and Td506, the safety endpoints that were used for hypothesis testing were the solicited adverse events of Erythema, Swelling, Pain, and Fever (See Table 25). Solicited Local and Systemic adverse events were recorded as Mild, Moderate and Severe and were collected from Day 0 (i.e., the day of immunization) to 14 days post immunization. 'Any' or 'Moderate & Severe' intensity occurrences in the Day 0–14 time period were compared. Per the secondary (safety) hypotheses of the protocol, for Erythema, Swelling, Pain and Fever, the non-inferiority of ADACEL™ to Td Vaccine would be concluded if the upper limit of the 2-sided 95% CIs of the differences in rates between the 2 groups were below 10%.

All other Local and Systemic solicited events as well as unsolicited events, including immediate and serious adverse events, were evaluated by descriptive comparisons. In addition to Erythema, Swelling and Pain, Underarm Lymph Node Swelling and Limb Circumference were also observed as local solicited reactions. Other systemic adverse events for which data were collected included: Chills, Generalized Body Ache/Muscle Weakness, Tiredness and/or Decreased Energy, Nausea, Vomiting, Diarrhea, Sore/Swollen Joints and Rash. All of these except Rash were classified as None, Mild, Moderate, or Severe. Rash was recorded as present or not present (See Appendix 3).

Since the reaction rates for some of the hypothesis-driven safety endpoints, such as Fever, were lower than expected, a Relative Risk (RR) assessment was also performed for the differences in rates between the treatment groups for all solicited local and systemic events.

Table 25: Criteria for Safety Comparisons Across Trials

Endpoint	Severity	Study	Comparison	Criteria
Erythema **Swelling** **Pain** **Fever**	Any, Moderate & Severe	Td506	Non-inferiority of ADACEL™ compared to Td. 95% CI for difference between groups	10% Margin (ADACEL™-Td)
		Td505	Equivalence (two sided) for 3 lots of ADACEL™. 95% CI for difference between any two groups	(-10%, 10%)
		Td501 Td502	Non-inferiority of ADACEL™ +HepB (or Influenza) compared to ADACEL™ given separately from HepB (or influenza). 95%CI for difference between groups	10% Margin (Simultaneous – Sequential)

4.7 Safety Results

Safety results from the clinical trials are presented in the following order:

- **Adolescents-** Safety results from adolescents in the study Td506 and the lot consistency study Td505.
- **Adults -** Safety results from adults in the study Td506.
- **Concomitant Administration -** Safety results from the two clinical trials that studied concomitant administration with either Hepatitis B Vaccine (Study Td501) or Influenza Vaccine (Study Td502).

Within each category, data are presented for the overall safety profile, immediate reactions, solicited local and systemic reactions and the safety hypothesis endpoints of Erythema, Swelling, Pain and Fever by study. Data on serious adverse events (SAEs) and unsolicited adverse events are presented collectively by pooling data from ADACEL™ recipients in all four studies.

4.7.1 Safety Results in Adolescents (Studies Td506 and Td505)

4.7.1.1 Td506 – Safety of ADACEL™ vs. Td Vaccine (11-17 Years)

More than 96% of the 2053 enrolled participants were included in the safety analysis. There were no withdrawals due to adverse events.

Overall Safety Profile

The overall safety profile for the ITTS population of adolescents is presented in Table 26. In general the safety profile was acceptable and comparable between the two vaccine groups. There was a slightly higher rate of solicited local and systemic events observed following ADACEL™ administration as compared to Td Vaccine.

Statistical testing of the secondary hypothesis showed that all non-inferiority criteria were met for Erythema, Swelling and Fever but not for Any Pain (95% CI of 2.80, 10.72) as shown in Table 27. Although the Fever comparisons met the pre-specified non-inferiority criteria, the Relative Risk of Any fever in ADACEL™ as compared to Td was 1.85 with a 95% CI of (1.13, 3.02). For both Pain and Fever, most events were of mild intensity and of short duration.

Table 26: Td506, Summary of Overall Safety of Adolescents (11-17 Years), ITTS Population

Type of Adverse Event	ADACEL™		Td	
	n/N	%	n/N	%
Immediate Reactions (within 30 minutes)	6/1184	0.51	5/792	0.63
Any Solicited Local Reactions Event (Days 0–14)	952/1184	80.41	586/792	73.99
Any Solicited Systemic Reactions Events (Days 0–14)	776/1184	65.54	483/792	60.98
Solicited Reactions (Days 0–14)				
Erythema	244/1175	20.77	155/787	19.70
Swelling	246/1175	20.94	144/787	18.30
Pain	914/1175	77.79	559/787	71.03
Fever (≥38.0°C or 100.4°F)	58/1170	4.96	21/783	2.68
Unsolicited AEs (Day 0–28)	301/1184	25.42	202/792	25.51
Unsolicited AEs (Onset After Day 28)	474/1184	40.03	289/792	36.49
Serious AEs	11/1184	0.93	8/792	1.01

n= number of participants reporting the event.

Immediate Reactions

Eleven participants (6 ADACEL™ participants and 5 Td Vaccine participants) experienced 17 immediate adverse events (See Table 26). The majority of immediate reactions were systemic reactions reported by adolescents between 11 to 13 years of age. Most events were Mild in intensity and all participants recovered without sequelae. Eleven of the 17 events were classified under Nervous System Disorders [hypoesthesia/paresthesia (2 events), dizziness (4 events), syncope (3 events), and vasovagal attack (2 events)]. Other events were General Disorders and Administration Site Conditions (1 event; weakness), Musculoskeletal and Connective Tissue Disorders (2 events; pain in limb and peripheral limb swelling), Skin and Subcutaneous Tissue Disorders (1 event; erythema), Gastrointestinal Disorders (1 event; nausea), and Vascular Disorders (1 event; flushing).

Solicited Local Reactions

A total of 80.41% (952/1184) and 73.99% (586/792) of all adolescent ADACEL™ and Td Vaccine participants experienced a solicited local adverse event during Days 0-14. The frequency and maximum intensity of solicited local reactions were comparable between the ADACEL™ and Td Vaccine groups for all intensities and at all time points, with slightly higher frequencies generally reported in the ADACEL™ group compared to the Td Vaccine group. As shown in Table 39 in Appendix 4, most solicited local adverse events were considered to be Mild at all time points. The durations of Erythema, Swelling and Pain were generally comparable between the groups. The mean duration of Any Erythema was 2.1 days for ADACEL™ recipients and 1.8 days for Td Vaccine recipients; for Any Swelling was 2.4 and 2.0 days; and the mean duration for Any Pain was 2.1 days for both groups.

The frequency and intensity of Erythema, Swelling and Pain were consistently higher in both vaccine groups among younger adolescents (11-13 years) compared to older adolescents (14-17). For the ADACEL™ group, the frequency rates of younger compared to older adolescents was 24.46% vs. 16.96% for Erythema; 21.94% vs. 19.90% for Swelling; and 78.73% vs. 76.82% for Pain. A similar profile was observed for younger compared to older adolescents in the Td Vaccine group.

Female participants in both vaccine groups consistently reported higher rates of any Erythema Swelling, and Pain, as well as higher rates of Moderate and Severe reactions, compared to male participants. Caucasians generally reported higher rates of any Erythema and Pain, while Blacks reported higher rates of any Swelling in both vaccine groups.

During Days 0-14, Underarm Lymph Node Swelling was reported by 6.64% (78/1175) and 5.34% (42/787) of ADACEL™ and Td Vaccine participants, respectively. Limb circumference changes from baseline at all time points were also comparable between ADACEL™ and Td Vaccine groups. During Days 0-14, mean limb circumference change was 1.25 cm and 1.35 cm in ADACEL™ and Td Vaccine participants, respectively.

Solicited Systemic Reactions

Most systemic adverse events reported were Mild in intensity (See Table 41 in Appendix 4). At each intensity and for each systemic adverse event, the percentages of participants reporting events were comparable between groups at all time points except for Fever and Vomiting. Although there was an almost two-fold difference in reporting of Any Fever in participants receiving ADACEL™ as compared to Td Vaccine (4.96% vs. 2.68%), the majority of these were Mild in intensity (See Table 41 in Appendix 4). The mean duration of Any Fever was 1.2 days for both groups. For Any Fever, the RR=1.85 (CI= 1.13, 3.02) for ADACEL™ compared to Td. For Any Vomiting, the rate was 4.60% compared with 2.80% RR= 1.64 (CI=1.01, 2.68) for ADACEL™ compared to Td. No differences in rates of Moderate & Severe Fever were observed between the two groups.

With the exception of Severe Headache that was reported by 1.96% of ADACEL™ and 1.52% of Td Vaccine recipients during Days 0-14, Severe systemic adverse events were uncommon, occurring in ≤1.3% of all ADACEL™ and Td Vaccine participants during Days 0-14 (See Table 41 in Appendix 4).

Hypothesis Testing

ADACEL™ was non-inferior to Td Vaccine for rates of Erythema, Swelling and Fever. Pain was somewhat more frequent in the adolescent group for Any intensity following administration of the ADACEL™ (77.79% compared with 71.03 % for Td Vaccine) and for the difference between the two groups, the upper limit of the 95% CI was 10.72% (outside the pre-specified margin of 10%; Table 27). Pain was mostly of mild intensity, the mean duration of Pain was 2.1 days for both groups and approximately 16% of subjects took medication but less than 0.5% sought medical attention for this reaction. Non-inferiority was achieved in adolescents for Moderate and Severe Pain.

Table 27: Td506 - Safety Endpoints Days 0-14 - Comparison of Rates ADACEL™ vs. Td (95% CI) for Adolescents, ITTS Population

Adverse Reaction	Rates of Any (%)					Rates of Moderate & Severe (%)				
	ADACEL™	Td	Diff%	LCL	UCL	ADACEL™	Td	Diff%	LCL	UCL
Erythema	20.77	19.70	1.07	-2.55	4.69	11.91	9.91	2.00	-0.79	4.79
Swelling	20.94	18.30	2.64	-0.93	6.20	12.85	11.18	1.67	-1.25	4.59
Pain	77.79	71.03	6.76	2.80	10.72	19.40	16.26	3.14	-0.29	6.57
Fever	4.96	2.68	2.28	0.59	3.96	1.03	0.77	0.26	-0.58	0.64

4.7.1.2 Td505- Lot Consistency Study

A total of 99.7% of 1811 participants were included in the safety analysis . A total of 1.1% (20/1811) of participants discontinued early from the trial, with one discontinuation as a result of an adverse event (death as a result of suicide).

Overall Safety Profile

Table 28 presents the overall safety profile for the ITTS population. Rates of solicited and unsolicited adverse events were generally comparable between groups. Statistical testing of the secondary hypothesis showed that all objectives were met for Erythema, Swelling, Pain and Fever for Any and Moderate & Severe intensities as shown in Table 29.

Immediate Reactions

Thirteen participants experienced 15 immediate adverse events: 6 participants for Lot 1, 4 participants for Lot 2, and 3 participants for Lot 3. Most events were of Mild intensity; 4 events were of Moderate intensity (injection site bruising and pain, vasovagal attack, and back pain).

Solicited Local Reactions

A total of 83.06% (1500/1806) of all participants experienced a solicited local adverse event during Days 0-14 and the reaction rates were similar among the three lots (See Table 28). Most of the local solicited adverse events reported were of Mild intensity. The only exception was Swelling, in which similar rates were reported for Mild, Moderate, and Severe intensities (See Table 39 in Appendix 4). Mild Swelling rates during Days 0–14 ranged from 6.04% (36/596) to 9.70% (58/598) for the three lots; The mean duration of Any Erythema was 2.2 days; for Any Swelling it was 2.4 days; and for Any Pain it was 2.1 days.

As in study Td506, female vaccine recipients had higher rates of any Erythema, Swelling and Pain compared to male recipients. Similarly, Caucasians generally reported higher rates of any Erythema and Pain, while Blacks reported higher rates of Any Swelling.

Underarm Lymph Node Swelling rates were similar among lots ranging from 7.72% (46/596) to 10.18% (61/599). The majority of participants reported <1 cm change in Limb Circumference.

Solicited Systemic Reactions

A total of 65.73% (1187/1806) of all participants experienced a systemic solicited event. Solicited adverse events at all time periods were similar between lots (See Table 28). At Days 0-14, a fever of ≥ 38.0°C was reported by 4.17-6.55% of participants in the three groups. The mean duration of Any Fever was 1.2 days. At each intensity and for each systemic adverse event, percentages of participants reporting events were similar between lots.

Most systemic adverse events reported were Mild in intensity. At each intensity and for each systemic adverse event, percentages of participants reporting events were similar between lots. Headache was the most common Severe systemic adverse event (See Table 41 in Appendix 4) and was experienced in 2.01% (12/596), 2.17% 13/599), and 2.84% (17/598) of participants in ADACEL™ lots 1, 2, and 3, respectively, during Days 0–14.

Table 28: Td505 - Overall Summary of Safety, ITTS Population

Type of Adverse Event	ADACEL™ 1		ADACEL™ 2		ADACEL™ 3		Total	
	n/N	%	n/N	%	n/N	%	n/N	%
Immediate Events (within 30 minutes)	6/600	1.00	4/604	0.66	3/602	0.50	13/1806	0.72
Any Solicited Local Reaction (Day 0–14)	500/600	83.33	499/604	82.62	501/602	83.22	1500/1806	83.06
Any Solicited Systemic Reaction (Day 0–14)	388/600	64.67	403/604	66.72	396/602	65.78	1187/1806	65.73
Solicited Reactions (Day 0–14)								
Erythema	141/596	23.66	145/599	24.21	150/598	25.08	436/1793	24.32
Swelling	125/596	20.97	133/599	22.20	146/598	24.41	404/1793	22.53
Pain	481/596	80.70	472/599	78.80	480/598	80.27	1433/1793	79.92
Fever (≥38.0°C or 100.4°F)	39/595	6.55	25/599	4.17	29/596	4.87	93/1790	5.20
Unsolicited Adverse Events	141/600	23.50	141/604	23.34	142/602	23.59	424/1806	23.48
Serious Adverse Events	1/600	0.17	2/604	0.33	1/602	0.17	4/1806	0.22

Hypothesis Testing

To evaluate consistency between the lots, rates of in Erythema, Swelling, Pain and Fever between groups receiving the 3 different lots of ADACEL™ were compared for 'Any' and 'Moderate & Severe' intensities for Days 0–14 using the 95% CI on the difference in rates between any 2 lots.

As shown in Table 29, the 95% CIs for the differences in Erythema, Swelling, Pain and Fever rates between any 2 lots are within the interval (–10%, 10%) for all intensity categories during Days 0–14.

Table 29: Td505 - Safety Endpoints Days 0-14 - Comparison of Rates for 3 Lots of ADACEL™, (95% CI), ITTS Population

Adverse Event	Groups Compared	Rates of Any (%)					Rates of Moderate & Severe (%)				
		Rate 1	Rate 2	Diff %	LCL	UCL	Rate 1	Rate 2	Diff %	LCL	UCL
Erythema	Lot 1 - Lot 2	23.66	24.21	-0.55	-5.41	4.32	12.08	11.02	1.06	-2.55	4.68
	Lot 1 - Lot 3	23.66	25.08	-1.43	-6.29	3.44	12.08	11.37	0.71	-2.91	4.33
	Lot 2 - Lot 3	24.21	25.08	-0.88	-5.74	3.98	11.02	11.37	-0.35	-3.97	3.26
Swelling	Lot 1 - Lot 2	20.97	22.20	-1.23	-5.97	3.51	13.59	12.85	0.74	-3.29	4.77
	Lot 1 - Lot 3	20.97	24.41	-3.44	-8.18	1.30	13.59	18.06	-4.47	-8.50	-0.44
	Lot 2 - Lot 3	22.20	24.41	-2.21	-6.94	2.52	12.85	18.06	-5.21	-9.23	-1.18
Pain	Lot 1 - Lot 2	80.70	78.80	1.91	-2.64	6.45	20.97	20.87	0.11	-4.63	4.84
	Lot 1 - Lot 3	80.70	80.27	0.44	-4.11	4.98	20.97	25.75	-4.78	-9.52	-0.04
	Lot 2 - Lot 3	78.80	80.27	-1.47	-6.01	3.07	20.87	25.75	-4.88	-9.62	-0.15
Fever	Lot 1 - Lot 2	6.55	4.17	2.38	-0.14	4.90	1.34	0.83	0.51	-0.74	1.76
	Lot 1 - Lot 3	6.55	4.87	1.69	-0.83	4.21	1.34	1.51	-0.17	-1.42	1.09
	Lot 2 - Lot 3	4.17	4.87	-0.69	-3.21	1.82	0.83	1.51	-0.68	-1.92	0.57

4.7.2 Safety Results in Adults (Study Td506)

4.7.2.1 Td506 - Safety of ADACEL™ vs. Td Vaccine (18-64 Years)

More than 96% of the 2427 enrolled participants were included in the safety analysis. There were no withdrawals due to adverse events.

Overall Safety Profile

Overall, the safety profile was acceptable and comparable between the two vaccine groups, although the reaction rates were generally slightly higher in the ADACEL™ group (See Table 30 and Appendix 4). The safety hypothesis of non-inferiority of ADACEL™ to Td Vaccine was achieved for all safety endpoints as shown in Table 31.

Table 30: Td506 - Summary of Safety of Adults (18-64 Years), ITTS Population

Type of Adverse Event	ADACEL™		Td	
	n/N	%	n/N	%
Immediate Reactions (within 30 minutes)	4/1752	0.23	1/573	0.17
Any Solicited Local Reactions Event (Days 0–14)	1199/1752	68.44	384/573	67.02
Any Solicited Systemic Reactions Events (Days 0–14)	881/1752	50.29	273/573	47.64
Solicited Reactions (Days 0–14)				
Erythema	420/1698	24.73	121/561	21.57
Swelling	356/1698	20.97	97/561	17.29
Pain	1115/1698	65.67	353/561	62.92
Fever (≥38.0°C or 100.4°F)	24/1688	1.42	6/551	1.09
Unsolicited AEs (Days 0–28)	375/1752	21.40	120/573	20.94
Unsolicited AEs (Onset After Day 28)	391/1752	22.32	106/573	18.50
Serious AEs	33/1752	1.88	11/573	1.92

Immediate Reactions

Five participants (4 ADACEL™ participants and 1 Td Vaccine participant; See Table 30) experienced 7 immediate adverse events. The majority of immediate reactions were systemic reactions and most events were Mild. All participants recovered without sequelae. Three of the 7 events were classified under Nervous System Disorders [3 events; hypoesthesia/paresthesia, Other events were General Disorders and Administration Site Conditions (2 events; injection site erythema), Skin and Subcutaneous Tissue Disorders (1 event; contusion), Gastrointestinal Disorders (1 event; dyspepsia).

Solicited Local Reactions

A total of 68.44% (1199/1752) and 67.02% (384/573) of all adult ADACEL™ and Td Vaccine participants experienced a solicited local adverse event during Days 0-14. The frequency and maximum intensity of solicited local reactions were comparable between the ADACEL™ and Td Vaccine groups for all intensities and at all time points except for Lymph Node Swelling: 6.48% compared with 4.10% RR= 1.58 (CI=1.02, 2.45) for ADACEL and Td, respectively (See Table 40 of Appendix 4). Pain was the most frequently reported local adverse event in both groups at all time points. The durations of Erythema, Swelling and Pain were generally comparable between the groups. The mean duration of Any Erythema was 2.6 days for ADACEL™ recipients and 2.2 days for Td Vaccine recipients; that for Any Swelling was 2.8 and 2.3 days; and that for Any Pain was 2.2 and 2.3 days.

Similar to adolescents, adult female recipients in both vaccine groups had higher rates of any Erythema, Swelling and Pain compared to male recipients. Adult Blacks also reported higher rates of Swelling in both vaccine groups but unlike adolescents, rates for Erythema and Pain were similar for Blacks and Caucasians.

Underarm Lymph Node Swelling was reported by 6.48% (110/1698) and 4.10% (23/561) of ADACEL™ and Td Vaccine participants, respectively, during Days 0-14 (See in Table 40 of

Appendix 4) and the majority were of mild intensity. Limb Circumference changes from baseline at all time points were also comparable between ADACEL™ and Td Vaccine groups. During Days 0-14, mean limb circumference changes were 1.51 cm and 1.29 cm in ADACEL™ and Td Vaccine participants, respectively.

Solicited Systemic Reactions

A total of 50.29% (881/1752) and 47.64% (273/573) of all adult ADACEL™ and Td Vaccine participants experienced a solicited systemic adverse event during Days 0-14. Most systemic adverse events reported were Mild (See Table 42 in Appendix 4). At each intensity and for each systemic adverse event, the percentages of participants reporting events were comparable between groups. Fever was reported by 1.42% (24/1688) and 1.09% (6/551) of ADACEL™ and Td Vaccine participants, respectively, during Days 0-14. The mean duration of Any Fever was 1.3 days in both groups.

With the exception of Severe Headache reported by 2.77% of ADACEL™ and 2.14% of Td recipients, during Days 0-14, Severe systemic adverse events were uncommon for all solicited systemic adverse events, generally occurring in ≤1.3% of all ADACEL™ and Td Vaccine participants at any time point.

Hypothesis Testing

To evaluate the non-inferiority of the ADACEL™ to the Td Vaccine during Days 0-14, the rates of Erythema, Swelling, Pain and Fever between groups were compared for Any and Moderate & Severe intensities for Days 0–14 using the 95% CI on the difference in rates between the ADACEL™ and Td Vaccine groups. ADACEL™ was non-inferior to Td Vaccine for all safety endpoints (Table 31).

Table 31: Td506 - Safety Endpoints Days 0-14 - Comparison of Rates ADACEL™ vs. Td (95% CI) for Adults, ITTS Population

Adverse Reaction	Any (%)					Moderate & Severe (%)				
	ADACEL™	Td	Diff	LCL	UCL	ADACEL™	Td	Diff	LCL	UCL
Erythema	24.73	21.57	3.17	-0.81	7.14	14.19	13.19	1.00	-2.25	4.26
Swelling	20.97	17.29	3.68	-0.00	7.36	13.37	10.87	2.50	-0.55	5.54
Pain	65.67	62.92	2.74	-1.85	7.33	16.20	11.05	5.14	2.01	8.27
Fever	1.42	1.09	0.33	-0.70	1.37	0.41	0.36	0.05	-0.54	0.64

4.7.3 Safety Results in Concomitant Vaccine Administration Studies (Td501 and Td502)

4.7.3.1 Td501 – Concomitant Administration of ADACEL™ with Hepatitis B Vaccine

Of the 410 participants that were enrolled and randomized in the study, 98.29% of participants were included for safety analyses (See Table 6). No participants discontinued due to an adverse event.

Overall Safety Profile

Table 32 provides the overall safety profile summary for the ITTS population by treatment group. ADACEL™ given concomitantly with Hepatitis B Vaccine was non-inferior to ADACEL™ alone for rates of Pain and Fever. Differences between the two groups were found for rates of Erythema and Swelling (see Table 33). These differences in tolerability need to be considered in conjunction with the advantages of concomitant administration of the two vaccines.

Table 32: Td501 - Summary of Safety for Adolescents 11-14 Years, ITTS Population

	Simultaneous Group ADACEL™+HepB		Sequential Group ADACEL™, HepB		Total N=403	
Type of Adverse Events	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Immediate Reactions (Within 30 Minutes)	1/202	0.5	4/201	2.0	5/403	1.2
Any Solicited Local Reaction (Day 0 to 14)	178/202	88.1	174/201	86.6	352/403	87.3
Any Solicited Systemic Reaction (Day 0 to 14)	160/202	79.2	150/201	74.6	310/403	76.9
Solicited Reactions (Day 0 to 14)						
Erythema	47/201	23.4	43/201	21.4	90/402	22.4
Swelling	48/201	23.9	36/201	17.9	84/402	20.9
Pain	172/201	85.6	171/201	85.1	343/402	85.3
Fever (≥38.0°C or 100.4°F)	11/201	5.5	12/200	6.0	23/401	5.7
Unsolicited Adverse Events (Day 0 – Day 150 or Day 180)	74/202	36.6	95/201	47.3	169/403	41.9
Serious Adverse Events (Day 0 – Day 150 or Day 180)	1/202	0.5	1/201	0.5	2/403	0.5

Immediate Reactions

In total, 5 immediate adverse events were observed in 5 participants following ADACEL™ administration. Three events were considered Mild (vomiting, stomach ache and itchy mouth), 1 event was classified as Moderate (syncope), and there was one Severe intensity event observed (erythema). The incidence of immediate adverse events was lower in the simultaneous group (1 in simultaneous group vs. 4 in sequential group). All participants recovered within 24 hours and without sequelae.

Solicited Local Reactions

Comparable proportions of participants from both study groups experienced at least one local adverse reaction during the 14-day post-vaccination observation period (88.1% [178/202] and 86.6% [174/201] for the simultaneous and sequential groups respectively (Table 32). Overall Swelling was higher in the simultaneous group than sequential group at Days 0-14 (23.88% [48/201] vs. 17.91%[36/201] (See Table 39 in Appendix 4). Pain was the most frequent local adverse reaction reported at any time period assessed.

Approximately one third of those reporting Erythema during Days 0-14 graded it as Severe Reports of Severe Pain were rare (7.96% and 7.46% in simultaneous and sequential groups, respectively). The mean duration of Any Erythema was 1.8 days; for Any Swelling it was 2.6 days; and for Any Pain it was 2.3 days.

Underarm Lymph Node Swelling rates were 8.96% in the simultaneous group vs. 8.46% in the sequential group (See Table 39 in Appendix 4) The majority of participants reported <1cm Change in Limb Circumference.

Solicited Systemic Reactions

Participants in the simultaneous reported a slightly higher incidence of solicited systemic adverse reactions during Days 0-14 post-Visit 1 vaccination than those in the sequential group (79.2% [160/202] vs. 74.6% [150/201] respectively. Most solicited systemic reactions were considered to be Mild, and Severe systemic reactions were uncommon (See Table 41 in Appendix 4). The mean duration of Any Fever was 1.0 days.

Headache was the most common systemic adverse reaction reported during Days 0-14, occurring in 54.00% and 47.25% of simultaneous and sequential groups, respectively. Generalized Body Ache and Tiredness were also common events reported during Days 0-14 (See Table 41 in Appendix 4).

Hypothesis Testing

Non-inferiority of the simultaneous group safety rates to the sequential group safety rates was to be concluded if the upper limit of the 2-sided 95% CI for the differences between simultaneous and sequential event rates was <10%.

Some of the comparisons of the local solicited reactions between the groups surpassed the upper limit of the 95% CI of 10% (See Table 33). The upper limit of 95% CI was 10.14% for Erythema of Any intensity at Days 0-14, 13.90% for Swelling of Any intensity, and 10.74% for Moderate & Severe intensity at Days 0-14. However, these events were short lived (most resolved by Day 3), the majority were graded as Mild, did not lead to taking medication or a physician visit, and were unlikely to have caused functional limitations of the participants. For Fever, the upper limit of the 95% CIs for the difference in Any and Moderate & Severe rates were <10% for all time points thus meeting the non-inferiority criteria (See Table 33).

Table 33: Td501 - Safety Endpoints Days 0-14 - Comparison of Rates in Simultaneous Group vs. Sequential Group (95% CI) for Adolescents Aged 11-14 Years, ITTS Population

Adverse Reaction	Rates of Any (%)					Rates of Moderate & Severe (%)				
	Simultaneous	Seque-ntial	Diff%	LCL	UCL	Simultaneous	Seque-ntial	Diff%	LCL	UCL
Erythema	23.38	21.39	1.99	-6.16	10.14	13.43	11.44	1.99	-4.46	8.44
Swelling	23.88	17.91	5.97	-1.96	13.90	15.92	11.94	3.98	-2.78	10.74
Pain	85.57	85.07	0.50	-6.42	7.42	19.90	23.38	-3.48	-11.53	4.56
Fever	5.47	6.0	-0.53	-5.08	4.02	1.49	1.50	-0.01	-2.38	2.37

4.7.3.2 Td502 – Concomitant Administration of ADACEL™ with Influenza Vaccine

Of the 720 participants that were enrolled and randomized in this study, 96.7% of participants were included in the ITTS population for safety analyses (See Table 6). No participants discontinued due to an adverse event.

Overall Safety Profile

Table 34 provides the overall safety profile summary for the ITTS population by treatment group. The secondary hypothesis of non-inferiority of ADACEL™ given concomitantly or separately from Influenza Vaccine was achieved for rates of Erythema, Swelling and Fever (See Table 35). Differences in rates of Pain were observed in that participants who received Concomitant vaccines reported more Pain. This difference in tolerability needs to be considered in conjunction with the advantages of concomitant administration of the two vaccines.

Table 34: Td502 – Summary of Safety for Adults Aged 19- 64 Years, ITTS Population

	Simultaneous Group ADACEL™+Flu		Sequential Group Flu, ADACEL™		Total N=696	
Type of Adverse Event	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Immediate Reactions (Within 30 Minutes)	3/356	0.84	1/340	0.29	4/696	0.57
Any Solicited Local Reaction (Day 0 to 14)	246/356	69.1	218/340	64.1	464/696	66.7
Any Solicited Systemic Reaction (Day 0 to 14)	219/356	61.5	191/340	56.2	410/696	58.9
Solicited Reactions (Day 0 to 14)						
Erythema	38/352	10.80	42/339	12.39	80/691	11.58
Swelling	54/352	15.34	35/339	10.32	89/691	12.88
Pain	235/353	66.57	206/339	60.77	441/692	63.73
Fever	15/352	4.26	8/336	2.38	23/688	3.30
Unsolicited Adverse Events (throughout the study)	123/356	34.55	108/340	31.76	231/696	33.19
Serious Adverse Events (throughout the study)	1/356	0.28	1/340	0.29	2/696	0.29

Immediate Reactions

A total of 4 immediate adverse reactions were observed, 3 in the simultaneous group and 1 in the sequential group. Three of the adverse events (dizziness, hypoesthesia, and vasovagal attack) were classified as Mild, while the other (haematoma) was not classified for severity. All participants recovered without sequelae.

Solicited Local Reactions

Comparable proportions of participants from both study groups experienced at least one local adverse reaction during the 14-day observation period post-ADACEL™ vaccination (69.1% [246/356] and 64.1% [218/340] for simultaneous and sequential groups, respectively (See Table 40 in Appendix 4). The rates of most reported local reactions were slightly higher for participants in the simultaneous group than for those in the sequential group, with the exception of 'Any' Erythema, which was slightly lower for the simultaneous group. Pain was the most frequent local adverse reaction reported at any time period assessed. Incidence of Severe intensity was low for all adverse reactions (See Table 40 in Appendix 4). The mean duration of Any Erythema was 2.6 days; for Any Swelling it was 2.5 days; and for Any Pain it was 2.2 days.

Reports of Underarm Lymphnode Swelling were 5.68% vs. 3.83% for the simultaneous and sequential groups, respectively (See Table 40 in Appendix 4). The majority of participants reported <1cm change in Limb Circumference, which was considered within measurement error.

Solicited Systemic Reactions

Overall, participants in the simultaneous group showed slightly higher rates of systemic adverse reactions than did those in the sequential group, who had received ADACEL™ alone. A total of 61.5% (219/365) participants in the simultaneous group and 56.2% (191/340) participants in the sequential group reported any systemic reaction during Days 0-14. Most solicited systemic reactions were reported to be Mild, and Severe systemic reactions were uncommon (See Table 42 in Appendix 4). At Days 0-14, Any Fever was reported by 4.26% vs. 2.38% participants in the simultaneous and sequential groups, respectively. The mean duration of Any Fever was 1.8 days

Headache was the most common systemic adverse reaction reported. Generalized Body Ache and Tiredness were also common reactions reported (See Table 42 in Appendix 4).

Hypothesis Testing

There were no statistical differences with respect to Erythema, Swelling, and Fever rates. Statistical testing for Pain surpassed the upper limit of the 95% CI of 10% difference in rates (the upper limit was 12.96% for Any Pain and 10.71% for Moderate and Severe Pain); See Table 35. The reports of Pain were short-lived (most resolved by Day 3), the majority were graded as Mild, did not lead to taking medication or a physician visit, and were unlikely to have caused functional limitations of the participants.

Table 35: Td502 - Safety Endpoints Days 0-14 - Comparison of Rates in Simultaneous Group vs. Sequential Group (95% CI) for Adults Aged 19-64 Years

Adverse Reaction	Rates of Any (%)					Rates of Moderate & Severe (%)				
	Simultaneous	Seque-ntial	Diff%	LCL	UCL	Simultaneous	Seque-ntial	Diff%	LCL	UCL
Erythema	10.8	12.39	-1.59	-6.37	3.18	5.68	6.49	-0.81	-4.38	2.76
Swelling	15.34	10.32	5.02	0.05	9.98	11.08	7.37	3.70	-0.60	8.01
Pain	66.57	60.77	5.81	-1.35	12.96	13.31	7.08	6.23	1.76	10.71
Fever	4.26	2.38	1.88	-0.79	4.55	1.99	0.60	1.39	-0.28	3.07

4.7.4 Unsolicited Adverse Events and Other Events of Interest

4.7.4.1 Unsolicited Adverse Events in Adolescents

The frequency of unsolicited adverse events over the entire follow-up period (i.e., to the end of each study) was lower in adolescent ADACEL™ recipients (in Td501, Td505, and Td506) compared to Td recipients: 35.87% compared to 50.51% (See Table 36). This however, may be artificial, due to the much shorter follow-up period of one month in Td505, which would tend to lower the unsolicited adverse event rates in the ADACEL™ group. Within study Td506, unsolicited adverse events were comparable between groups over 0-28 days (See Table 3 and Table 4) and over the entire study period.

The most frequently reported adverse event over the entire collection period in both vaccine groups was pharyngitis, for which a total of 220 events were reported by 5.92% (201/3393) of ADACEL™ recipients and a total of 69 events by 7.83% (62/792) of Td Vaccine participants (See **Table 36**).

Table 36: Unsolicited Adverse Events Reported Post-Vaccination ≥1% of Participants/Group Across Trials, ITTS Population - Adolescents (11-17 Years)

	ADACEL™ (N=3393)			Td (N=792)		
	Participants		%	Participants		%
Unsolicited AEs during entire collection period	1217		35.87	400		50.51
	Participants		Events	Participants		Events
SOC/Preferred Term	**N**	**%**	**n**	**n**	**%**	**n**
Infections and infestations						
Nasopharyngitis	121	3.57	122	39	4.92	41
Sinusitis nos	81	2.39	83	38	4.80	43
Upper respiratory tract infection nos	78	2.30	82	45	5.68	47
Pharyngitis streptococcal	65	1.92	73	31	3.91	32
Otitis media nos	48	1.41	51	27	3.41	30
Influenza	36	1.06	37	15	1.89	15
Viral infection nos	32	0.94	32	14	1.77	14
Pharyngitis viral nos	11	0.32	11	10	1.26	11
Upper respiratory tract infection viral nos	11	0.32	11	9	1.14	9
Respiratory, thoracic and mediastinal disorders						
Pharyngitis	201	5.92	220	62	7.83	69
Cough	92	2.71	96	23	2.90	23
Nasal congestion	62	1.83	69	8	1.01	8
Rhinitis allergic nos	6	0.18	7	9	1.14	9
Injury, poisoning and procedural complications						
Limb injury nos	37	1.09	40	20	2.53	21
Joint sprain	33	0.97	33	18	2.27	18
Laceration	29	0.85	29	9	1.14	9
Nervous system disorders						
Dizziness	31	0.91	33	9	1.14	9
Headache nos	24	0.71	26	12	1.52	15
Gastrointestinal disorders						
Abdominal pain upper	40	1.18	44	4	0.51	8
Musculoskeletal and connective tissue disorders						
Arthralgia	35	1.03	35	12	1.52	13
Reproductive system and breast disorders						
Dysmenorrhoea	32	0.94	34	10	1.26	10
Immune system disorders						
Multiple allergies	26	0.77	27	8	1.01	8
Eye disorders						
Conjunctivitis	18	0.53	18	8	1.01	8
Skin and subcutaneous tissue disorders						
Contusion	17	0.50	17	11	1.39	11
Acne nos	15	0.44	15	10	1.26	10

4.7.4.2 Unsolicited Adverse Events in Adults

The frequency of unsolicited adverse events over the entire collection period (i.e., to the end of each study) was comparable between ADACEL™ recipients and Td Vaccine recipients and was lower than in adolescents.

Unsolicited events were reported by 35.50% of ADACEL™ recipients and 33.16% of Td Vaccine recipients (See Table 37). The most frequently reported adverse event over the entire collection period in both vaccine groups was Sinusitis that was reported by 3.47% (85/2448) of ADACEL™ recipients and 3.14% (18/573) of Td Vaccine recipients. The next most frequently reported events were Nasopharyngitis and Upper Respiratory Tract Infections (See Table 37).

Table 37: Unsolicited Adverse Events Reported Post-Vaccination ≥1% of Participants/Group Across Trials, ITTS Population - Adults (18-64 Years)

	ADACEL™ (N=2448)			Td (N=573)		
	Participants	%		Participants	%	
Unsolicited AEs during entire collection period	869	35.50		190	33.16	
	Participants		Events	Participants		Events
SOC/Preferred Term	**n**	**%**	**n**	**n**	**%**	**n**
Infections and infestations						
Sinusitis nos	85	3.47	95	18	3.14	22
Nasopharyngitis	83	3.39	88	12	2.09	12
Upper respiratory tract infection nos	51	2.08	55	11	1.92	11
Bronchitis nos	37	1.51	39	5	0.87	5
Urinary tract infection nos	26	1.06	30	10	1.75	11
Pharyngitis streptococcal	12	0.49	13	6	1.05	6
Respiratory, thoracic and mediastinal disorders						
Pharyngitis	62	2.53	67	12	2.09	12
Cough	44	1.80	44	9	1.57	9
Musculoskeletal and connective tissue disorders						
Back pain	33	1.35	36	8	1.40	8
Pain in limb	24	0.98	26	8	1.40	10
Arthralgia	19	0.78	20	9	1.57	10
Neck pain	8	0.33	8	7	1.22	7
Reproductive system and breast disorders						
Dysmenorrhoea	25	1.02	27	7	1.22	7

A description of unsolicited adverse events reported in the Supportive Trials is provided in Appendix 5.

4.7.4.3 Events of Special Interest

The safety data were analyzed for occurrences of new onset diabetes, seizures, autoimmune disorders and whole arm swelling within 30 days of vaccination. Information on pregnancy occurring in these trials was also assessed.

Diabetes

Within 30 days post-vaccination, there were two cases of new onset of diabetes mellitus, one in the adolescent age group and one in the adult age group, both received ADACEL™. At Day 23 post-vaccination, an 11-year-old male ADACEL™ recipient, who had a sibling with IDDM, was diagnosed with a recent history of polyuria, polydipsia, and an approximately 10-lb weight loss. The other case was a 56-year-old male ADACEL™ recipient in whom NIDDM was found incidentally during hospitalization for accidental injury 13 days after vaccination. Both these events were classified as unrelated to study vaccine. Additionally, there was a case of an 11-year-old male Td recipient who was admitted to the hospital 105 days post-vaccination due to development of new onset diabetes.

Seizures

Three cases of seizure (two adolescents and one adult) were reported during these studies. Both adolescent cases had a medical history of seizure disorder, one received ADACEL™ and the other received Td Vaccine. The third case occurred in a 51-year-old female in the ADACEL™ group 22 days post-vaccination and resolved without sequelae. The investigators classified all events as unrelated to study vaccine.

Autoimmune Disorders

No occurrences of autoimmune disorders were reported in any of the studies.

Whole Arm Swelling

No occurrences of whole arm swelling were reported in any of the studies.

Pregnancies

Thirty (30) women (total of 31 pregnancies) in study Td506 became pregnant during trial participation. The outcome was known in all but 2 participants. There were 5 spontaneous abortions and 1 therapeutic abortion. There were 4 early deliveries (3 by Cesarean section), all with delivery of normal newborns. All other pregnancies went to term. The rate of 5 miscarriages in a total of 31 pregnancies in 30 women can be expected (76). There was one case of pregnancy in study Td502, this participant (randomized to the Sequential group) had received Influenza Vaccine, but had not received ADACEL™ because she discontinued after she was found to be pregnant. The final outcome is unknown because the participant dropped out of the study.

Events of Special Interest in Supportive Trials

A new case of diabetes mellitus-type II in an adult in the ADACEL™ group was reported within 30 days of vaccination, and was considered to be non-vaccine related by the Investigator. No reports of new onset of seizures or autoimmune disease following any vaccine were reported during these studies. Spontaneous reporting of three cases of whole arm swelling was recorded in the same trials. Two of these cases were reported by participants who had received ADACEL™,

and one by a participant who had received Td Vaccine. All three participants were females between 24 and 32 years of age. The onset date of the event was the same as the vaccination date, the duration was between 2 and 3 days and the subjects recovered without sequelae.

4.7.5 Serious Adverse Events

In all four trials, serious adverse events (SAEs) were collected for the duration of the trial. However as summarized in Table 24, the duration of collection varied among trials. The collection period for Td501 lasted for five or six months, depending on the group; Td502 for one or two months, depending on the group; Td505 for one month; and Td506 for six months.

Across the four trials, a total of 87 SAEs were reported by 71 study participants in the analysis population. Of these 87 SAEs, 30 events were reported in adolescents (21 events in 17 (0.50%) ADACEL™ recipients and 9 events in 8 (1.01%) Td recipients; See Table 3) and 57 in adults (45 events in 35 (1.43%) ADACEL™ recipients and 12 events in 11 (1.92%) Td recipients; See Table 4). Of the 71 participants who reported SAEs, 25 were adolescents (17 ADACEL™ and 8 Td recipients), and 46 were adults (35 ADACEL™ and 11 Td recipients). There were proportionally more SAEs reported by adults compared to adolescents, and proportionally more reported by Td recipients compared to ADACEL™ recipients. The higher percentage of adults appears to be due to a high frequency of hospitalizations for pre-existing conditions and conditions unrelated to vaccination.

All but two of the reported SAEs were evaluated by the investigators as not related to vaccine administration. Of the two that were considered possibly related, both were female participants in study Td506, who had received ADACEL™. One was a 23-year-old female, hospitalized one-day after vaccination for a Severe Migraine equivalent with unilateral facial paralysis. The subject recovered without sequelae and was discharged two days later. The other was a 49-year-old female, hospitalized 12 days after vaccination with radiating pain in the upper extremity and a diagnosis of Nerve Compression, and discharged one day later. Follow-up examination revealed no neurological abnormalities, symptoms were reported as resolved, and no further investigation was done; differential diagnosis was cervical radiculopathy or brachial plexopathy. There were no other serious adverse events relating to a neuropathy in either age group.

The most common SAEs were psychiatric disorders and appendicitis. A total of 8 participants (5 adolescents and 3 adults) reported a total of 9 SAEs classified under Psychiatric Disorders. The five adolescents comprised 4 ADACEL™ recipients and one Td Vaccine recipient. All of the Psychiatric Disorder events were classified by the investigators as unrelated to study vaccine.

Five cases of appendicitis were reported within 37 days post-vaccination: four in 11- to 13-year-old male ADACEL™ participants (3 in Td505 and one case in Td501), and one in a 27-year-old female ADACEL™ recipient in study Td506. All five of these events were classified as unrelated to study vaccine.

Serious Adverse Events in Supportive Trials

Among 962 adolescent and adult ADACEL™ participants in the Supportive trials, three (0.3%) experienced an SAE during the study (two fractures and one case of cholelithiasis). All three participants had received ADACEL™. Two participants were in study TD9805 and one was in study TC9704. None of the reported SAEs were considered as vaccine-related.

4.8 Safety Conclusions

A total of 5841 ADACEL™ recipients were evaluated for safety in the four main studies. Safety data from 962 recipients in the three supportive studies were also assessed. ADACEL™ was found to be safe and well tolerated in both adolescents and adults.

Overall, the injection site reactions of Erythema, Swelling, and Pain were brief in duration and Mild to Moderate in intensity. The majority of ADACEL™ recipients experienced no injection site Erythema or Swelling but did experience injection site Pain, with most Pain reported as Mild. The rates for Erythema, Swelling and Pain were higher for ADACEL™ compared to Td Vaccine recipients in Td506, although only for Any Pain did this reach statistical significance. ADACEL™ was non-inferior to Td Vaccine with respect to Erythema and Swelling. Non-inferiority of ADACEL™ vs. Td Vaccine was also established for adults with respect to Pain. In adolescents, however, the frequency of Any Pain was marginally higher for ADACEL™ recipients (77.79%) compared to Td recipients (71.03%). This difference in 'Any' Pain is accounted by the higher frequency of 'Mild' Pain reported by the ADACEL™ participants. The mean duration for all three measures of injection site local reactions was less than three days across all studies. Fever was an uncommon occurrence in any vaccine group in these studies. When Fever did occur, it was rated as Mild and occurred within the first 3 days after vaccination with a mean duration of ≤1.6 days. Among ADACEL™ recipients, only one adolescent and no adults had Severe Fever (≥39.5°C). In Td506, adolescents who received ADACEL™ had higher rates of Fever (4.98%) than Td Vaccine recipients (2.68%) although most Fever was reported as Mild in intensity and the mean duration of any Fever was 1.2 days for both groups.

For all other solicited local and systemic events, there were no clinically significant differences observed between the ADACEL™ and Td Vaccine groups. Overall, in adolescents, the rates of unsolicited adverse events were lower in the ADACEL™ group compared to the Td Vaccine group, and may be explained by the variable duration of follow-up. In Td506, however, the rates of unsolicited adverse events were comparable among adolescents receiving ADACEL™ and Td Vaccine. In adults these rates were comparable between the two vaccine groups.

Across four studies, increased rates of reactogenicity were seen in adolescents compared to adults, and in younger adolescents as compared to older ones. Td booster immunization has been reported to be moderately more reactogenic in adolescents 11 to 12 years of age than in adolescents 14 to16 years of age (77). In the comparison of ADACEL™ given concomitantly with Hepatitis B Vaccine versus ADACEL™ given alone, slightly higher rates of Erythema and Swelling were seen in the group that received the vaccines concomitantly. Similarly, in the comparison of ADACEL™ given concomitantly with Influenza Vaccine versus ADACEL™ given alone, higher rates of Injection Site Pain were seen in the group that received the vaccines concomitantly. However, in both cases the differences in tolerability must be considered in light of the benefits of co-administration.

Specific safety conclusions that can be made from the data are as follows:

- The safety profile of ADACEL™ is comparable to that of Td Vaccine, the US standard of care. Slightly increased reactogenicity was observed with respect to Any Pain and Any Fever in adolescents, however, these were mainly mild in intensity and of short duration. This is not unexpected due to the addition of pertussis antigens in the vaccine.

- The safety profile of ADACEL™ is consistent across studies, with no clinically important differences in reactogenicity or tolerability.
- ADACEL™ may safely be given concomitantly with either Hepatitis B Vaccine or Influenza Vaccine. The slight increase in reactogenicity seen with concomitant administration of ADACEL™ with either of these vaccines is acceptable given the benefits of co-administration such as compliance and cost-savings.

ADACEL™ offers the advantage of protection against pertussis while maintaining a safety profile that is comparable to that of Td Vaccine, and can be safely given concomitantly with either of the licensed vaccines that were evaluated in this clinical program.

5 Overall Conclusions

The recent increase in pertussis reports, particularly among adolescents and adults, suggests a need for an adolescent and adult booster vaccine. ADACEL™ was formulated especially for these populations. The most important benefit of ADACEL™ is to provide protection against pertussis while maintaining protection against diphtheria and tetanus. In addition to directly benefiting the vaccinee, ADACEL™ is expected to reduce the risk of pertussis among infants and others at high risk of severe disease, by reducing the likelihood that the vaccinee would transmit pertussis infection. The evidence suggests that ADACEL™ will contribute to reversing the recent trend of increasing incidence of pertussis. In Canada, a dramatic decrease in pertussis has been reported in one province and one territory following the introduction of ADACEL™ in an adolescent vaccine program.

Efficacy of ADACEL™ against pertussis was established by the achievement of higher anti-pertussis GMTs than those following a 3-dose infant series demonstrating 84.9% efficacy. This comparative bridging of immunogenicity data after administration of ADACEL™ in adolescents and adults to efficacy data in infants obtained from a controlled study with a vaccine that contains the same licensed components, DAPTACEL®, is consistent with the FDA Guidelines for the Evaluation of Combination Vaccines for Preventable Diseases, April 1997 (16) and the recommendations made at the 5 June 1997 VRBPAC meeting (17). Based on the non-inferiority of the antibody analyses, it is expected that a single booster dose of ADACEL™ will provide clinical efficacy in adolescents and adults that is non-inferior to the clinical efficacy observed in the Sweden I study.

The combination ADACEL™ Vaccine was shown to be as immunogenic as Td Vaccine, the licensed standard of care, for both diphtheria and tetanus. Thus, individuals who received the combination vaccine were as protected against diphtheria and tetanus as those who received Td Vaccine alone. ADACEL™ was found to be protective for participants with a wide range of pre-immunization titers, and can be considered an appropriate booster in older as well as younger individuals**.** Furthermore, data from interaction studies show that ADACEL™ can be given concomitantly with either Hepatitis B Vaccine or Influenza Vaccine.

There were no unexpected safety issues observed in the large number of participants who received ADACEL™ Vaccine. The safety profile of ADACEL™ was acceptable in all age groups and

was similar to that of Td Vaccine with slightly increased reactogenicity in adolescents as compared to Td Vaccine.

In conclusion, the data provided in this document demonstrate that in adolescents and adults aged 11-64 years, ADACEL™ Vaccine adds protection against pertussis in addition to protection against diphtheria and tetanus and a safety and tolerability profile comparable to Td Vaccine, the standard of care. These data support the replacement of Td Vaccine by ADACEL™ in adolescents and adults.

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Appendix 1: Tetanus and Diphtheria Epidemiology

Tetanus

Tetanus is an acute illness caused by a potent neurotoxin produced by *Clostridium tetani*, an organism that contaminates and replicates in an anaerobic environment found in severe wounds. The disease is characterized by severe, painful muscle contractions, accompanied by hypersensitivity, hyperreflexia, and increased autonomic stimulation of the affected body part(s). Mild stimuli may cause severe reflex muscle spasms. Fever due to extreme muscle spasm may be present. Tetanus may be either generalized, involving the face, neck, abdomen, and trunk, or localized to a specific body part (injury site). Involvement of the masseter muscle of the face results in trismus or lockjaw, giving rise to the classical facial expression known as "risus sardonicus"(78). Treatment of tetanus disease is mainly supportive and may include respiratory support, administration of tetanus antitoxin, and careful cleaning of infected wounds (78). Despite modern medical care, the case fatality rates still run as high as 30%–90% (79), particularly in the elderly. Natural infection does not always produce immunity from further infection.

Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level (78) (73). A level of ≥0.1 IU/mL has been considered as a safe estimation of protection (73).

A tetanus vaccine composed of Tetanus Toxoid first became available in 1938, but was not widely used until routine immunization of the US military began in 1941 (78). Currently, recommendations in the United States and Canada are that all children receive 5 doses of tetanus toxoid given as a component of a combination diphtheria-tetanus-acellular pertussis vaccine (DTaP), consisting of a 3-dose primary series given at 2, 4, and 6 months of age, followed by a first booster in the second year of life (15 to 18 months of age) and a second booster dose at school entry (4 to 6 years of age) (80) (81). In Canada, the recommended age for the first adolescent booster vaccination is 14 to 16 years (80). In the US, the recommended age for the first adolescent booster vaccination against tetanus (typically given in combined formulation with a reduced dosage of diphtheria toxoid [Td]) has been lowered from 14 to 16 years of age to 11 to 12 years of age for adolescents who have not otherwise been given a dose of tetanus toxoid within the preceding 5 years (81). Subsequent boosters are recommended every 10 years. Td is recommended for adults from age 19-≥65 years as a booster every 10 years (82).

The incidence of tetanus in Canada and the United States has fallen throughout the past century. Following routine use of tetanus toxoid vaccines in the US, the occurrence of tetanus disease decreased dramatically from 560 reported cases in 1947 to an average of 43 cases reported annually during 1998 to 2000 (83). Among patients with known outcome, the case-fatality ratio during 1998-2000 was 18%, 5 times lower than the case-fatality ratio of 91% reported in 1947. In the mid- to late 1990s, the age distribution of reported cases shifted to a younger age group, in part due to an increased number of cases among injection drug users in California (83). Among cases reported during 1998-2000, 9% were <20 years of age, 55% were 20 to 59 years of age, and 36% were ≥60 years of age. Adults, ≥60 years of age continue to have the highest rates of tetanus

and tetanus-related deaths (83) (84). In the US, tetanus occurs almost exclusively among unvaccinated or inadequately vaccinated persons (83) (85).

Diphtheria

Corynebacterium diphtheriae may cause both localized and generalized disease. The systemic intoxication is caused by diphtheria exotoxin, an extracellular protein of toxigenic strains of *C. diphtheriae.* Both toxigenic and nontoxigenic strains of *C. diphtheriae* cause disease, but only strains that produce toxin cause myocarditis and neuritis. Toxigenic strains are more often associated with severe or fatal respiratory infections (11) (86) than with cutaneous infections. The clinical presentation may vary from asymptomatic infection to fulminant, multisystemic disease, and death. Natural infection does not always produce immunity. The only reservoir for *C. diphtheriae* is man (86).

Toxigenic strains of diphtheria bacilli are still detected (pharynx, skin and ear) each year in carriers, sometimes associated with mild clinical symptoms. Asymptomatic carriage of *C. diphtheriae* is far more common than clinical diphtheria (11) and occasional cases of mild clinical diphtheria do occur in apparently fully immunized persons.

A diphtheria vaccine was first licensed in 1921, but did not become widely used in the United States until the early 1930s (87). The adsorbed form of Diphtheria Toxoid (adsorbed to alum) was licensed in 1948 (11). Diphtheria can be prevented through active immunization with this vaccine. A serum antitoxin level of 0.01 IU/mL is the lowest level providing basic clinical immunity against the disease. Serum antitoxin levels of at least 0.1 IU/mL are generally regarded as providing full protection (74).

Universal vaccination is recommended for all infants in the United States, with a 3-dose primary series of Diphtheria and Tetanus Toxoids given at 2, 4, and 6 months of age, followed by a booster dose 15 to 18 months of age, and another booster dose at 4 to 6 years of age (81) (87). A combination DTaP vaccine is now the preferred vehicle for childhood immunization against diphtheria (75). As with tetanus, it is now recommended in the US that the first adolescent booster of Diphtheria Toxoid following the five-dose childhood series (a reduced dosage of Diphtheria Toxoid given in combined formulation with Tetanus Toxoid [Td]) be administered at 11 to 12 years of age (81). Subsequent boosters are recommended every 10 years. Td is recommended for adults from age 19-≥65 years as a booster every 10 years (82).

Despite the recommendations for Td Vaccine in adults, there is incomplete coverage of this vaccine. A serosurvey of healthy adult populations in Toronto, Canada indicates that approximately 20% of those surveyed do not have antibody levels ≥ 0.01 IU/mL to diphtheria (88). The actual proportion of susceptible individuals in the general adult population may be even higher. In a recent seroepidemiologic study conducted by CDC it was observed that only 60.5% of the population had fully protective levels of diphtheria antibody (≥0.10 IU/mL) (18).

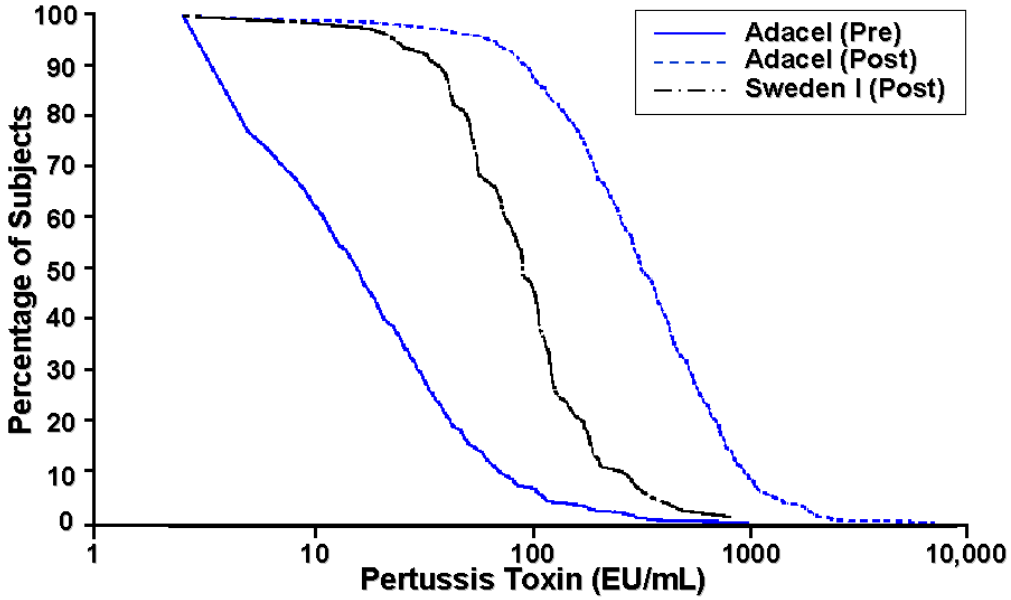
Prior to the widespread use of diphtheria toxoid in the late 1940s, diphtheria disease was common in the US (11). More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5%-10% of cases were fatal; the highest case-fatality rates were in the very young and the elderly. More recently, reported cases of diphtheria declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state. From 1980 through 2000, only 51 cases of diphtheria were reported in the US, of which 6 were fatal. The case fatality rate

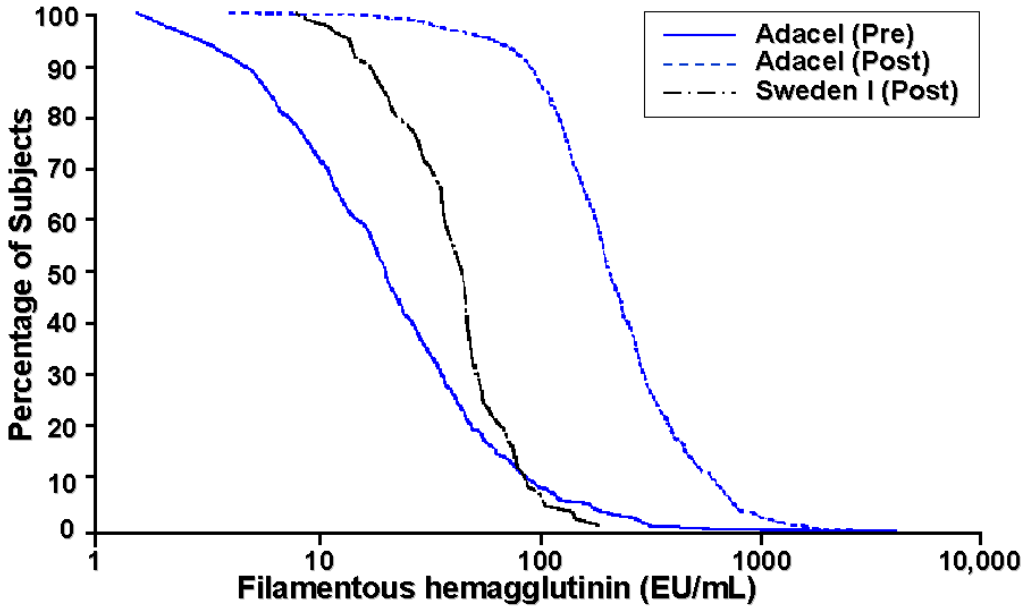
for diphtheria has changed very little since the 1950s. Of 49 reported cases with known age during the period of 1980 to 2000, 55% were in persons ≥20 years of age, and 43% were in persons ≥40 years of age (87). Most cases have occurred in unimmunized or inadequately immunized persons. Although diphtheria disease is rare in the US, it appears that *C. diphtheriae* continues to circulate in areas of the country with previously endemic diphtheria (87).

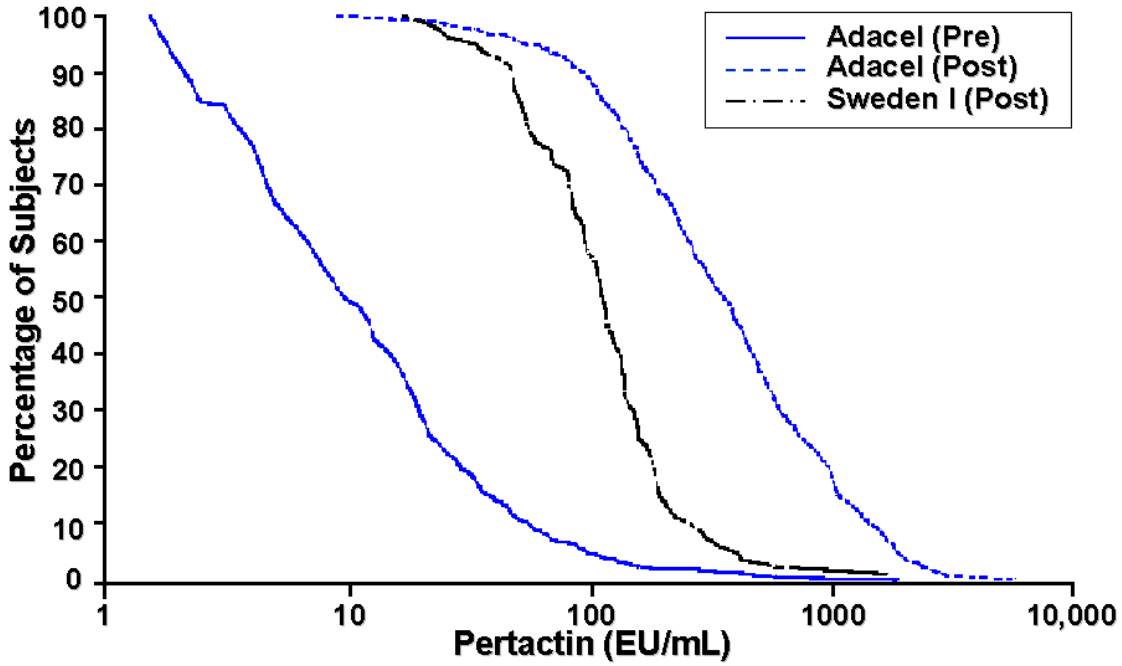
Diphtheria continues to occur in other parts of the world. A major epidemic of diphtheria occurred in the newly independent states of the former Soviet Union beginning in 1990 (89). This epidemic resulted in approximately 150,000 cases and 5,000 deaths during the years 1990-1997. The outbreak is believed to have been due to several factors, including a lack of routine immunization of adults in these countries. In 2003, a reported case of fatal respiratory diphtheria occurred in a 63-year-old male US traveler to Haiti where the disease is endemic (90).

Appendix 2: Reverse Cumulative Distribution Curves - ADACEL™ vs. DAPTACEL®

Figure 5: Td506, Adolescents (11-17 Years): Reverse Cumulative Distribution Curves for PT, FHA, FIM and PRN: Pre- and Post-ADACEL™ Vaccination by Study Population and Post- DAPTACEL® Vaccination (Sweden I Efficacy Trial)






Adacel (Pre)
Adacel (Post)
Sweden I (Post)
Percentage of Subjects
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10,000
Pertactin (EU/mL)

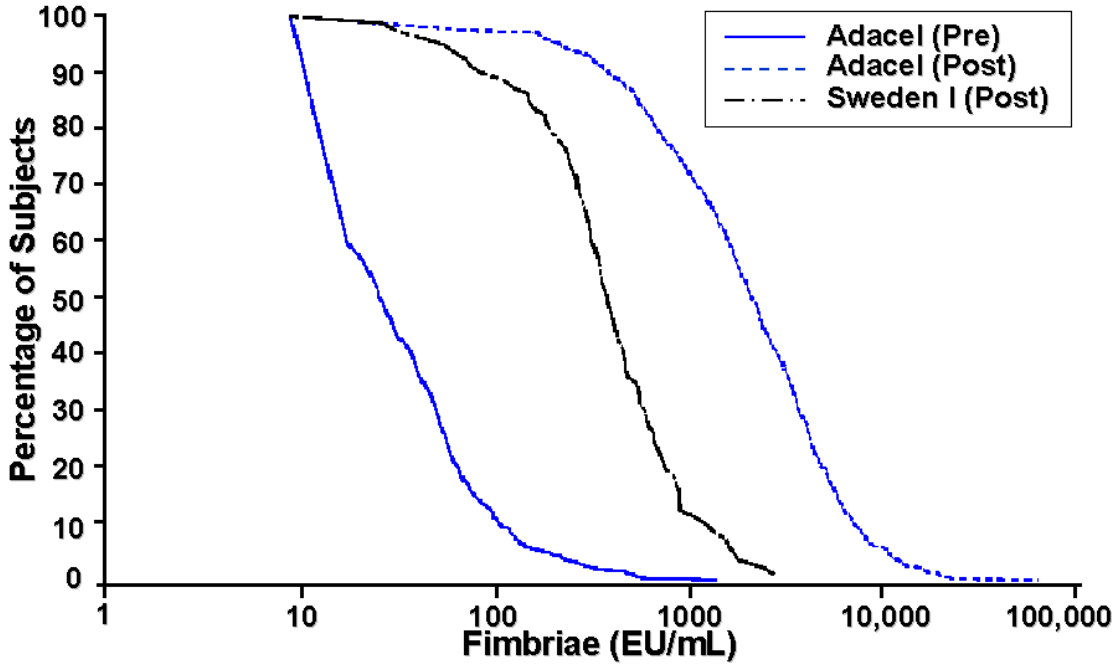
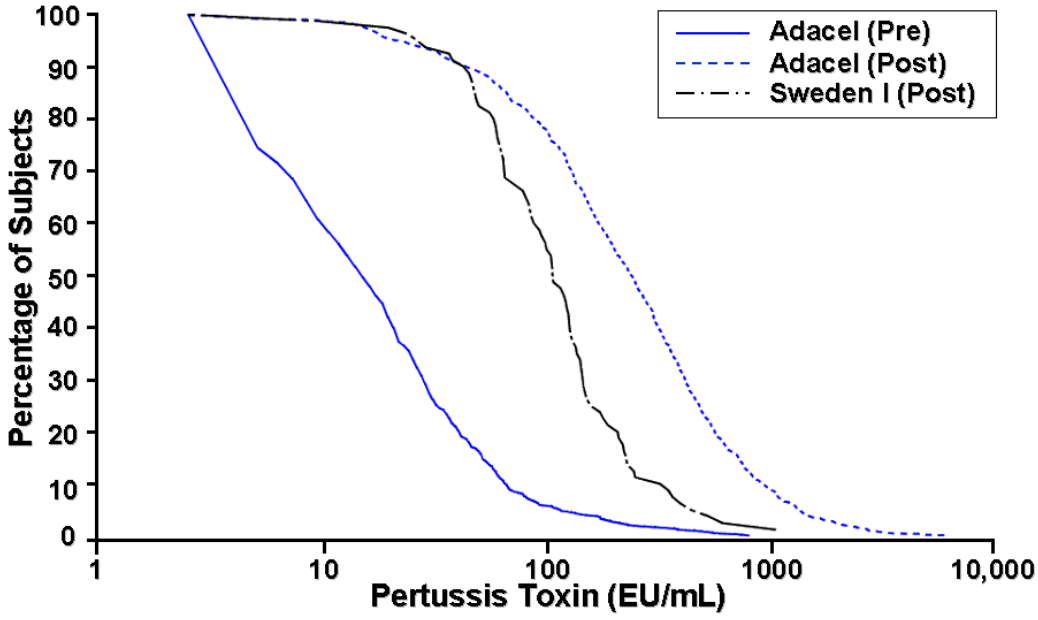
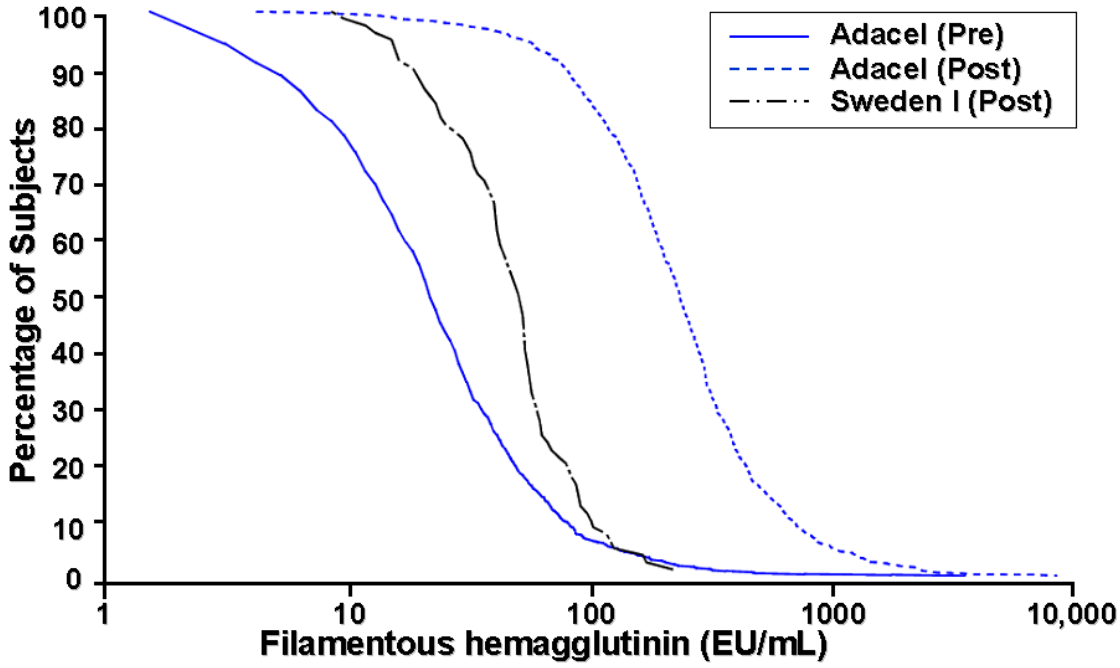
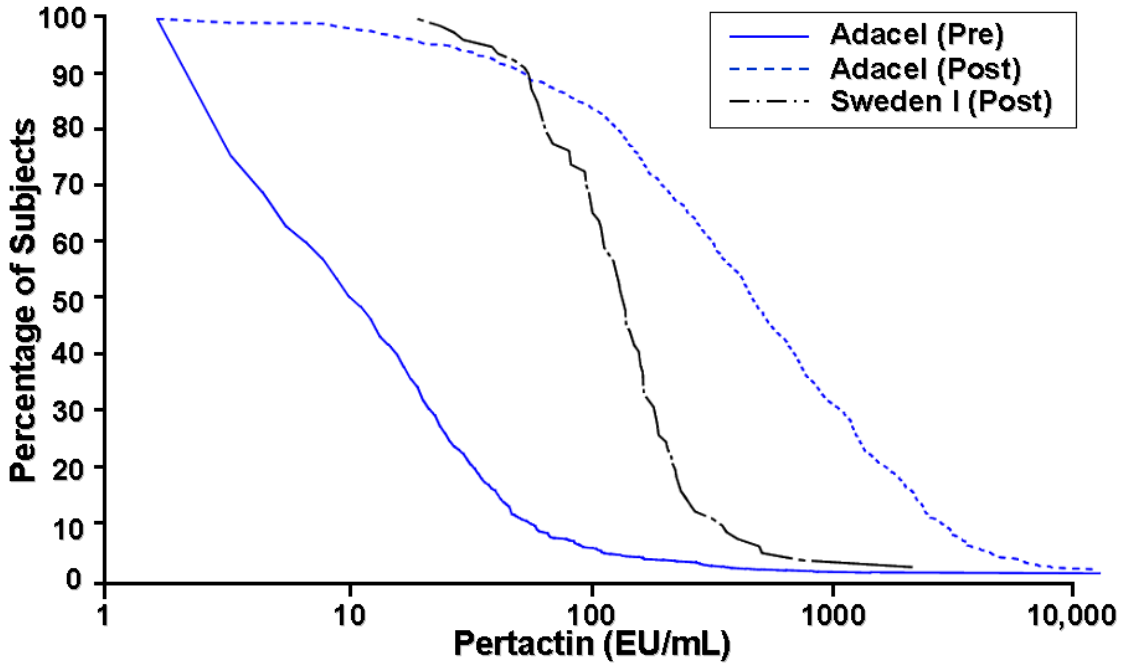

Adacel (Pre)
Adacel (Post)
Sweden I (Post)
Percentage of Subjects
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10,000
100,000
Fimbriae (EU/mL)

Figure 6: Td506, Adults (18-64 Years): Reverse Cumulative Distribution Curves for PT, FHA, FIM and PRN: Pre- and Post-ADACEL™ Vaccination by Study Population and Post-DAPTACEL® Vaccination (Sweden I Efficacy Trial)






Adacel (Pre)
Adacel (Post)
Sweden I (Post)
Percentage of Subjects
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10,000
Pertactin (EU/mL)

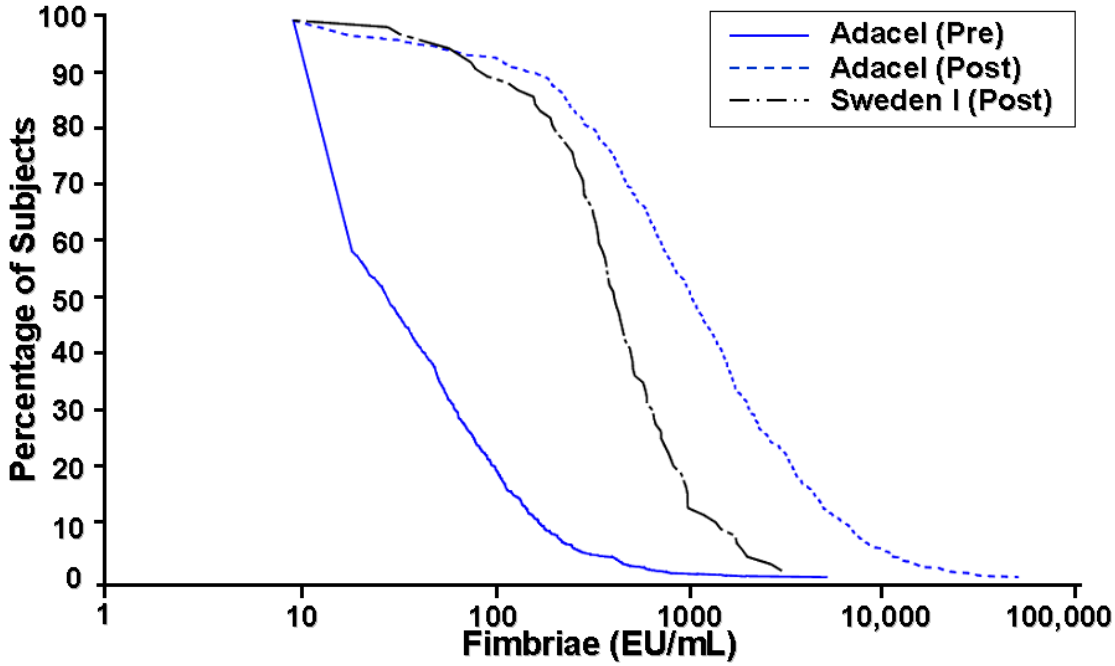
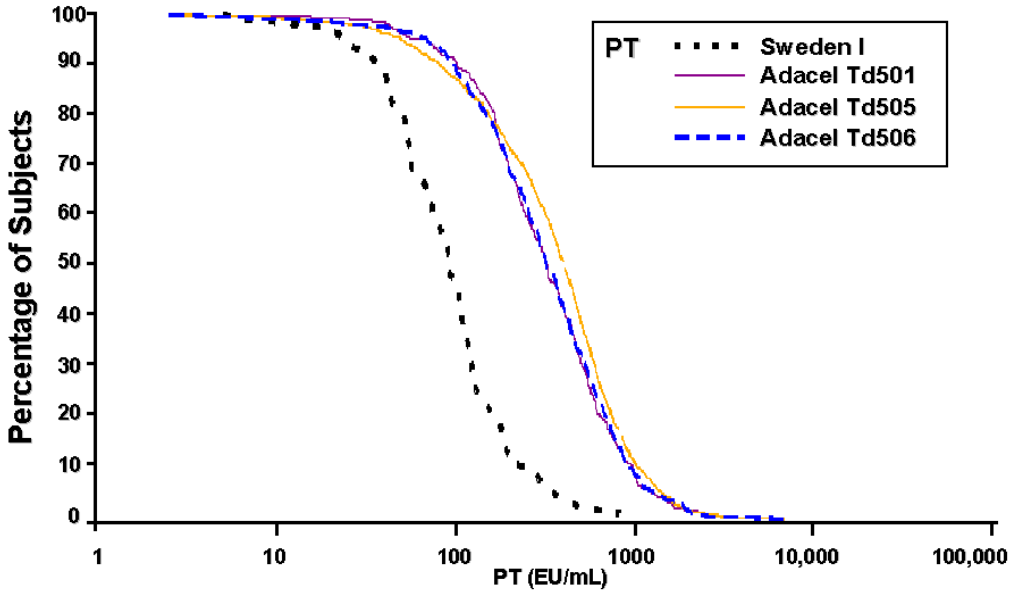
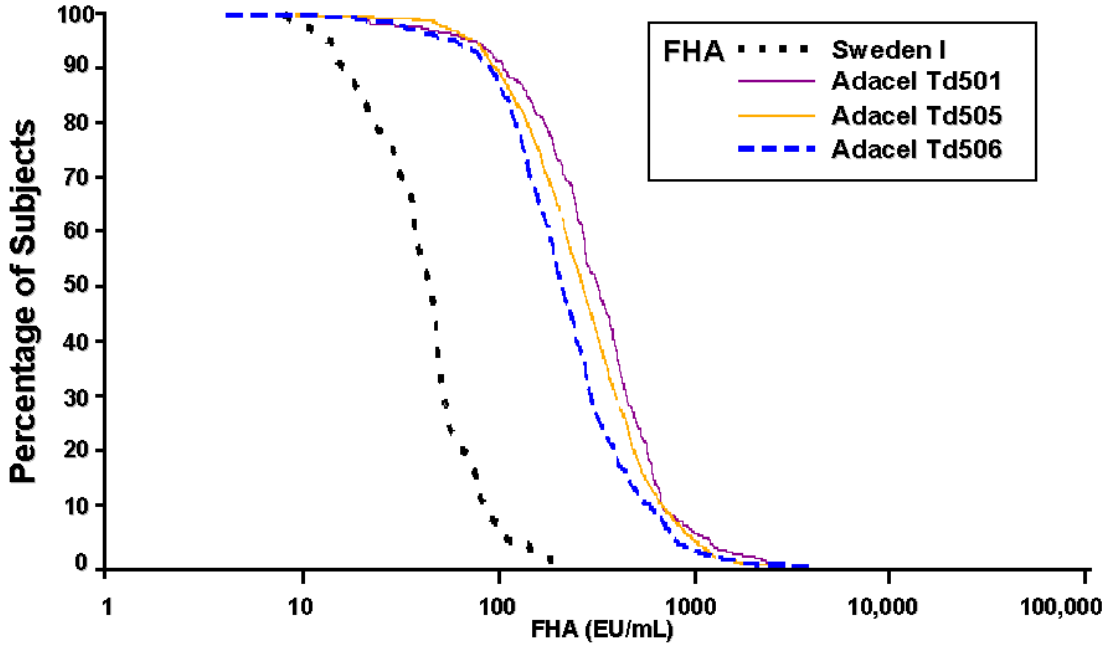
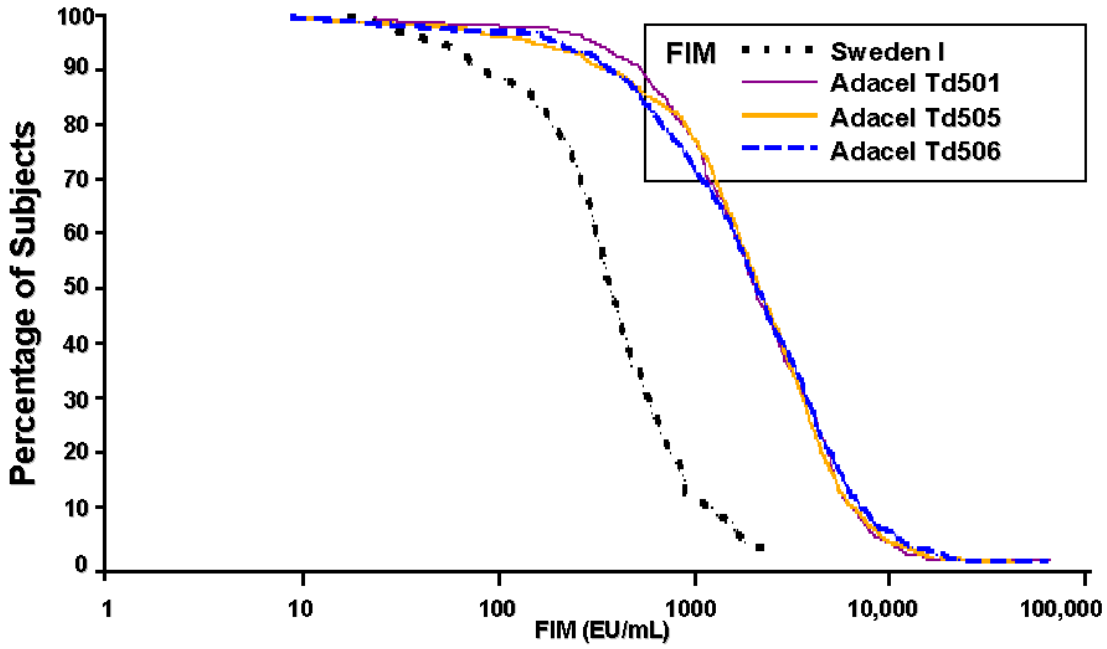

Adacel (Pre)
Adacel (Post)
Sweden I (Post)
Percentage of Subjects
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10,000
100,000
Fimbriae (EU/mL)

Figure 7: Adolescents 11 to 17 Years: Reverse Cumulative Distribution Curves for PT, FHA, FIM, and PRN: Post-ADACEL™ Vaccination by Study Population (Td506, Td505 and Td501) and Post- DAPTACEL® Vaccination (Sweden I Efficacy Trial)






FIM
Sweden I
Adacel Td501
Adacel Td505
Adacel Td506
Percentage of Subjects
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10,000
100,000
FIM (EU/mL)

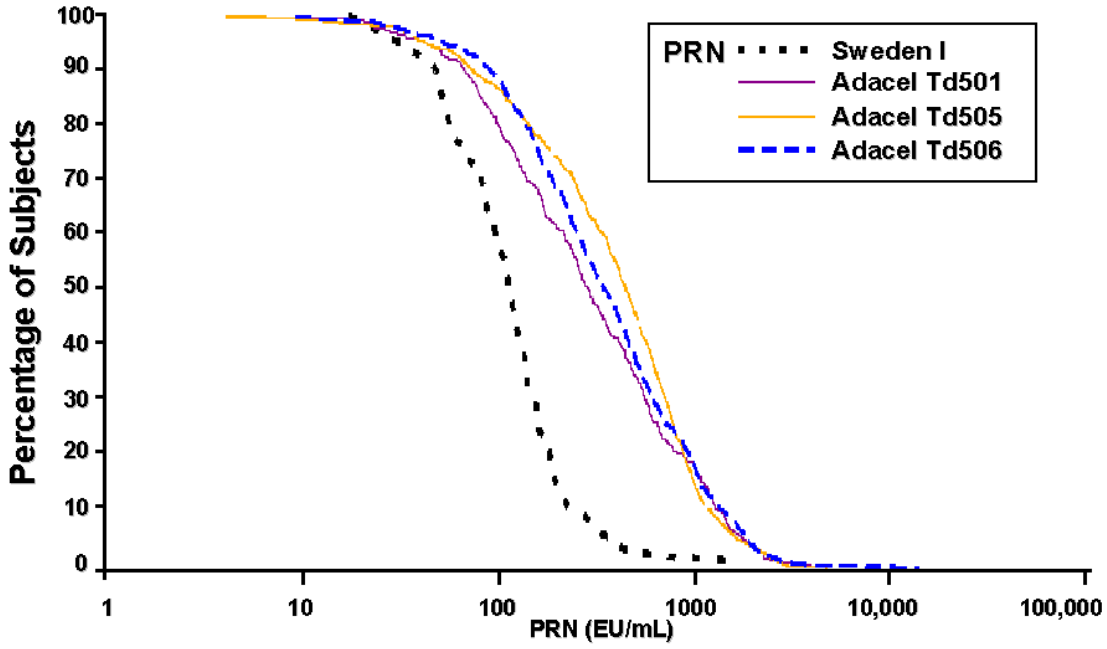
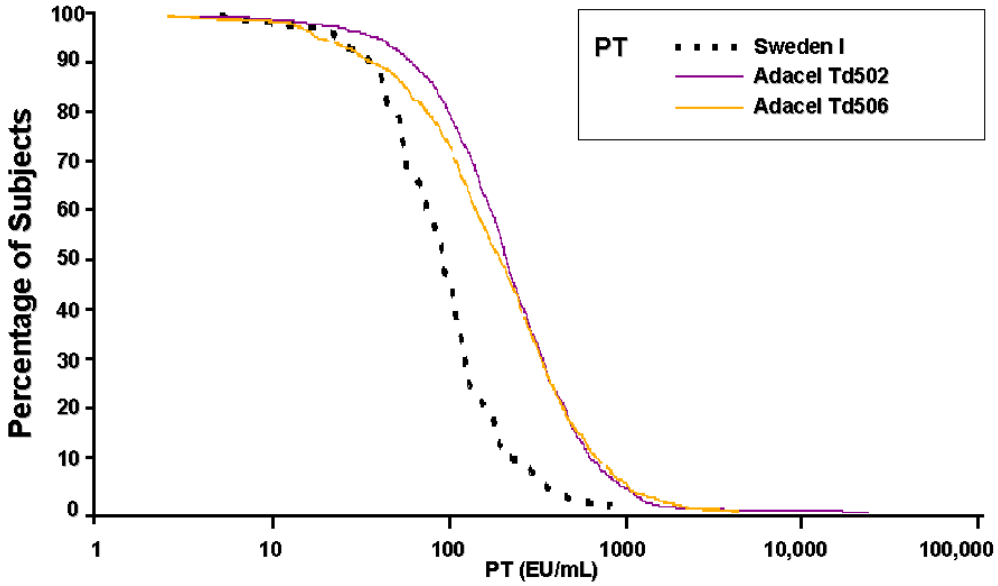
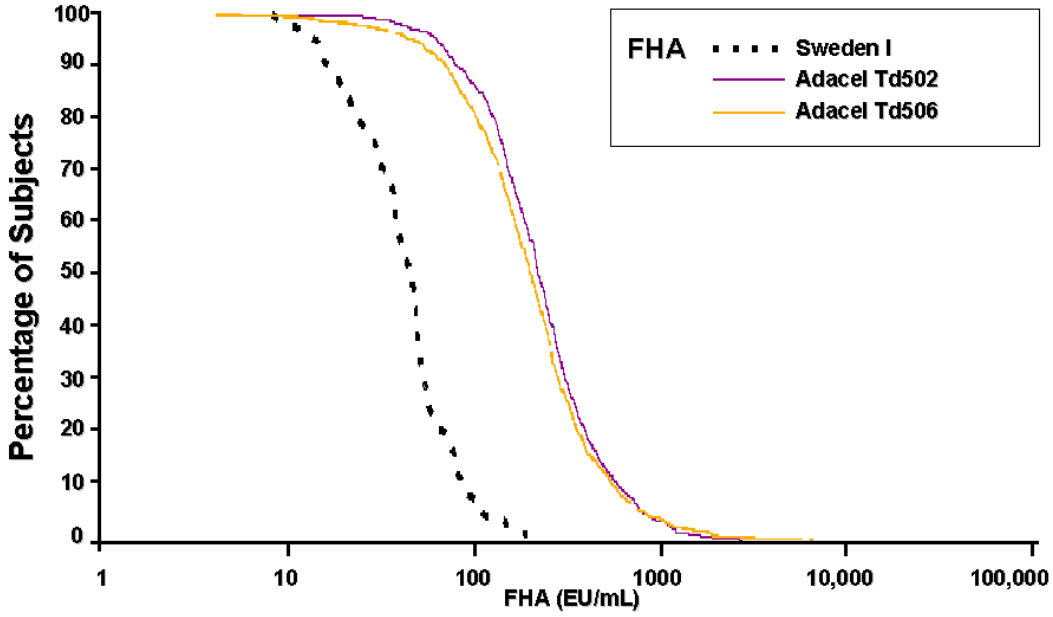
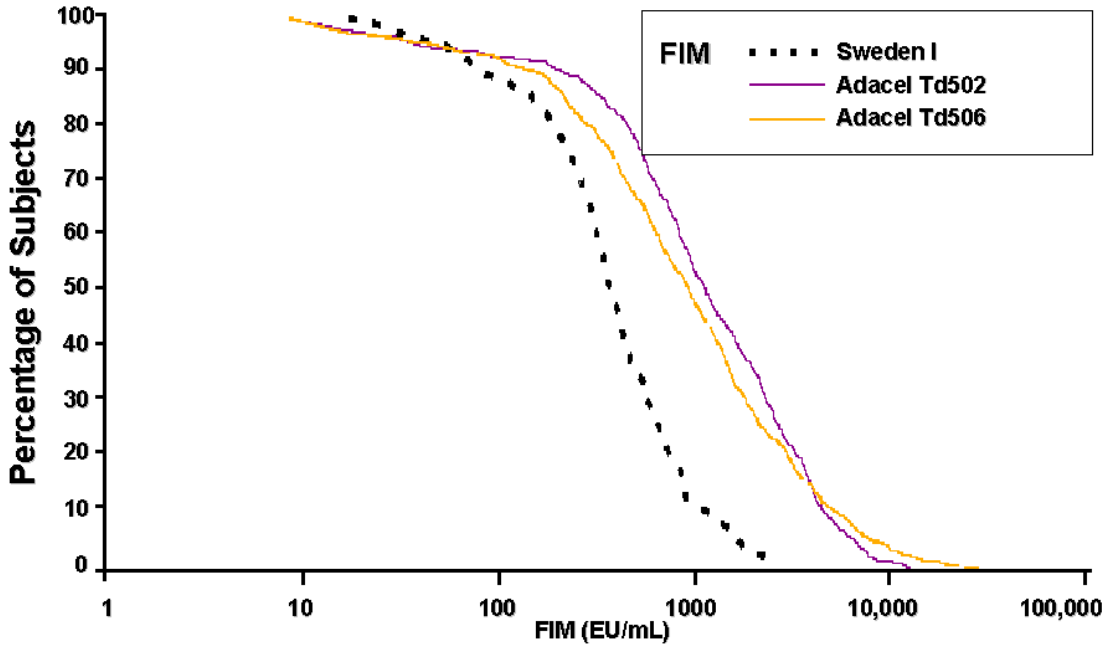
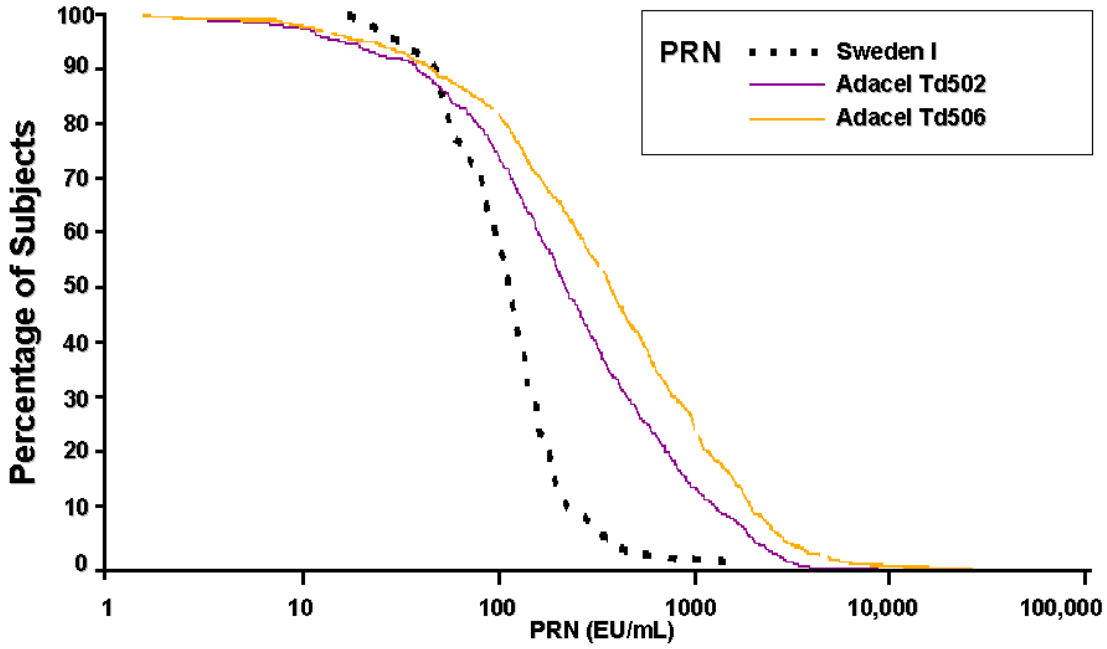

PRN
Sweden I
Adacel Td501
Adacel Td505
Adacel Td506
Percentage of Subjects
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10,000
100,000
PRN (EU/mL)

Figure 8: Adults 18-64 Years: Reverse Cumulative Distribution Curves for PT, FHA, FIM and PRN: Post-ADACEL™ Vaccination by Study Population (Td506 and Td502) and Post-DAPTACEL® Vaccination (Sweden I Efficacy Trial)






FIM
Sweden I
Adacel Td502
Adacel Td506
Percentage of Subjects
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10,000
100,000
FIM (EU/mL)


PRN
Sweden I
Adacel Td502
Adacel Td506
Percentage of Subjects
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10,000
100,000
PRN (EU/mL)

Appendix 3: Safety Parameters of Four Clinical Trials for US Licensure

Immediate Adverse Events

All participants were observed for 30 minutes after administration of the study vaccines. Any immediate adverse reaction arising within the first 30 minutes post-vaccination (e.g., hives, difficulty breathing, anaphylaxis, and any other event) was recorded as an Immediate Adverse Event on the Adverse Events page of the CRF.

Solicited Local and Systemic Events

The selected solicited local and systemic adverse events of Erythema, Swelling, local Pain, and Fever were recorded on the CRFs (for each day of the 0–14 days) as Mild, Moderate, or Severe (See Table 38). Other Solicited local adverse events that were collected included in the change in Limb Circumference and Underarm Lymph Node Swelling. Besides Fever, the other solicited systemic adverse events that were collected included Chills, Rash, Headache, Generalized Body Ache and/or Muscle Weakness, Tiredness and/or Decreased Energy, Nausea, Vomiting, Sore and Swollen Joints, and Diarrhea (See Table 38 for definitions of Mild, Moderate, and Severe for each local and systemic event).

With respect to maximum intensity categories, for the purpose of the data evaluation, two new categories (in addition to the maximum intensity categories recorded on the CRF) were defined: 'Any' and 'Moderate & Severe'. 'Any' was defined as the sum of events classified as Mild, Moderate, or Severe, and 'Moderate & Severe' was defined as the sum of events classified as either Moderate or Severe. Moderate or Severe events were also considered to be clinically significant. In addition to these intensity categories for Erythema and Swelling, measurements of ≥50 mm are also included as a maximum intensity category.

Table 38: 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]	≥ 38.0 to ≤ 38.7°C ≥100.4 to ≤ 101.9°F	≥ 38.8 to ≤ 39.4°C ≥ 102.0 to ≤ 103.0°F	≥ 39.5°C ≥ 103.1°F
Any of the Following: • **Pain at injection site** • **Chills** • **Headache** • **Generalized bodyache (and/or Muscle weakness)** • **Tiredness (and/or Decreased energy**	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

Adverse Event	Mild	Moderate	Severe
• **Nausea** • **Vomiting** • **Diarrhea** • **Sore (and/or swollen) joints** • **Lymph Node Swelling**			
Rash[3]	no = None	yes = Presence of welts (large, red, swollen patches)	
Limb circumference	Daily measurement in centimeters (cm)		

[1]Parent or participant was to record exact measurement daily.
[2]Temperatures were obtained orally.
[3]A "rash" reaction was intended to capture those participants with an allergic reaction to the vaccine that was manifested by rash. Therefore, it excludes other obvious causes of rash, for example, poison ivy.
[4]Prior to vaccination with ADACEL™, a baseline measurement of the circumference of the limb where ADACEL™ was to be administered was performed. Limb circumference was measured and recorded by the participant every day for the 14 days following vaccination with ADACEL™

Unsolicited Adverse Events

Any adverse event other than those listed on the diary card and that according to the participant represented a change in health status or was possibly associated with the vaccine was collected from Day 0 post-immunization until Day 14. After Day 14, all health events reported by the participant or parent that elicited any contact with a physician (telephone or office visit) or resulted in an emergency room visit or hospitalization or other vaccine-related events as determined by the investigator were collected until Visit 2. Any unexpected visits to a physician's office or emergency room, hospitalizations, onset of serious illness and/or death were collected between Visit 2 and the duration of safety follow-up.

The investigator defined the intensity and the relationship of all adverse events to the study vaccine according to the following definitions:

Severity:

- Mild (noticeable but did not interfere with activities, easily tolerated)
- Moderate (interfered with activities but did not require medical care or absenteeism)
- Severe (incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism).

Relationship to vaccine:

- Not related
- Possibly related
- Probably related
- Definitely related

This information was actively surveyed at every telephone contact or site visit with the participant or the parent or guardian.

Serious Adverse Events (SAEs)

Participant or their parents/legal guardians were instructed to call the study site to report Serious Adverse Events (SAEs) at any time during the study period, from the time of first vaccination until termination from the study. Any SAE, whether deemed vaccine-related or not, was to be reported immediately to the Sanofi Pasteur Pharmacovigilance Department and the medical monitor. In addition, active collection of SAEs was performed at every scheduled site visit, telephone call, or review of computerized records.

An SAE was defined as any adverse drug experience occurring at any dose that resulted in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. An important medical event that did not result in death, was not life-threatening, or did not require hospitalization may have been considered a serious adverse drug experience if, based upon appropriate medical judgment, it could have jeopardized the participant and could have required medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs were coded using Version 5.0 of the MedDRA medical dictionary.

Appendix 4: Additional Safety Results for Solicited Local and Systemic Reactions from Four Principal Trials

Table 39: Overall Summary of Local Solicited Reactions – Adolescents 11 -17 Years (Days 0-14)

			Maximum Intensity											
			None		Mild		Moderate		Severe[3]		Any[2]		Moderate & Severe	
Study	Vaccine	M[1]	n[2]	%	n	%	n	%	n	%	n	%	n	%
Erythema									≥35mm (≥50mm)	≥35mm (≥50mm)				
Td506	Adacel	1175	931	79.23	101	8.60	69	5.87	71 (32)	6.04 (2.72)	244	20.77	140	11.91
	Td	787	632	80.30	76	9.66	36	4.57	42 (23)	5.34 (2.92)	155	19.70	78	9.91
Td505	Adacel	1793	1357	75.68	228	12.72	109	6.08	97 (57)	5.41 (3.18)	436	24.32	206	11.49
Td501	Simultaneous	201	154	76.62	20	9.95	11	5.47	16 (9)[3]	7.96 (4.48)[3]	47	23.38	27	13.43
	Sequential	201	158	78.61	18	8.96	8	3.98	15 (8)	7.46 (3.98)	43	21.39	23	11.44
Swelling									≥35mm (≥50mm)	≥35mm (≥50mm)				
Td506	Adacel	1175	929	79.06	76	6.47	76	6.47	75 (33)	6.38 (2.81)	246	20.94	151	12.85
	Td	787	643	81.70	48	6.10	45	5.72	43 (28)	5.46 (3.56)	144	18.30	88	11.18
Td505	Adacel	1793	1389	77.47	128	7.14	131	7.31	135 (82)	7.53 (4.57)	404	22.53	266	14.84
Td501	Simultaneous	201	153	76.12	10	4.98	15	7.46	17 (14)	8.46 (6.97)	48	23.88	32	15.92
	Sequential	201	165	82.09	7	3.48	5	2.49	19 (14)	9.45 (6.97)	36	17.91	24	11.94
Pain														
Td506	Adacel	1175	261	22.21	686	58.38	211	17.96	17	1.45	914	77.79	228	19.40
	Td	787	228	28.97	431	54.76	123	15.63	5	0.64	559	71.03	128	16.26
Td505	Adacel	1793	360	20.08	1029	57.39	379	21.14	25	1.39	1433	79.92	404	22.53
Td501	Simultaneous	201	29	14.43	132	65.67	37	18.41	3	1.49	172	85.57	40	19.90
	Sequential	201	30	14.93	124	61.69	46	22.89	1	0.50	171	85.07	47	23.38
Underarm Lymph Node Swelling														
Td506	Adacel	1175	1097	93.36	65	5.53	12	1.02	1	0.09	78	6.64	13	1.11
	Td	787	745	94.66	37	4.70	4	0.51	0	0.00	42	5.34	4	0.51
Td505	Adacel	1806	1633	91.13	129	7.20	28	1.56	2	0.11	159	8.87	30	1.67
Td501	Simultaneous	202	183	91.04	15	7.46	0	0.00	1	0.50	18	8.96	1	0.50
	Sequential	201	184	91.54	12	5.97	4	1.99	0	0.00	17	8.46	4	1.99

1-M represents the number of subjects with available data from ITTS population.
2-n, % - Number and percent of subjects. The percent value is based on the ITTS population excluding Missing. Any includes events with missing intensity.
3-Number (n) and % represent Severe erythema and swelling at ≥35mm and the Number (n) and % in parentheses represent intense severity data at ≥50mm

Table 40: Overall Summary of Local Solicited Reactions – Adults 18 -64 Years (Days 0-14)

			Maximum Intensity											
			None		Mild		Moderate		Severe[3]		Any[2]		Moderate & Severe	
Study	Vaccine	M	n	%	n	%	n	%	n	%	n	%	n	%
Erythema (Redness)									≥35mm (≥50mm)	≥35mm (≥50mm)				
Td506	Adacel	1698	1278	75.27	166	9.78	136	8.01	105 (67)	6.18 (3.95)	420	24.73	241	14.19
	Td	561	440	78.43	45	8.02	47	8.38	27 (17)	4.81 (3.03)	121	21.57	74	13.19
Td502	Simultaneous	352	314	89.20	16	4.55	9	2.56	11 (7)	3.13 (1.99)	38	10.80	20	5.68
	Sequential	339	297	87.61	20	5.90	11	3.24	11 (6)	3.24 (1.77)	42	12.39	22	6.49
Swelling									≥35mm (≥50mm)	≥35mm (≥50mm)				
Td506	Adacel	1698	1342	79.03	93	5.48	129	7.60	98 (54)	5.77 (3.18)	356	20.97	227	13.37
	Td	561	464	82.71	28	4.99	30	5.35	31 (15)	5.53 (2.67)	97	17.29	61	10.87
Td502	Simultaneous	352	298	84.66	10	2.84	16	4.55	23 (11)	6.53 (3.13)	54	15.34	39	11.08
	Sequential	339	304	89.68	9	2.65	11	3.24	14 (6)	4.13 (1.77)	35	10.32	25	7.37
Pain														
Td506	Adacel	1698	583	34.33	835	49.18	256	15.08	19	1.12	1115	65.67	275	16.20
	Td	561	208	37.08	291	51.87	57	10.16	5	0.89	353	62.92	62	11.05
Td502	Simultaneous	353	118	33.43	188	53.26	45	12.75	2	0.57	235	66.57	47	13.31
	Sequential	339	133	39.23	182	53.69	21	6.19	3	0.88	206	60.77	24	7.08
Underarm Lymph Node Swelling														
Td506	Adacel	1698	1588	93.52	83	4.89	21	1.24	2	0.12	110	6.48	23	1.35
	Td	561	538	95.90	20	3.57	3	0.53	0	0.00	23	4.10	3	0.53
Td502	Simultaneous	356	332	94.32	18	5.11	2	0.57	0	0.00	20	5.68	2	0.57
	Sequential	340	326	96.17	13	3.83	0	0.00	0	0.00	13	3.83	0	0.00

1-M represents the number of subjects with available data from ITTS population.
2-n, % - Number and percent of subjects. The percent value is based on the ITTS population excluding Missing. Any includes events with missing intensity.
3-Number (n) and % represent Severe erythema and swelling at ≥35mm and the Number (n) and % in parentheses represent intense severity data at ≥50mm

Table 41: Overall Summary of Systemic Solicited Adverse Events - Adolescents 11-17 Years (Days 0-14)

			Maximum Intensity										
			Missing		Any			Moderate & Severe			Severe		
Systemic AE	Study	Vaccine	n1	n2 (%)	n	%	95% CI	n	%	95% CI	n	%	95% CI
Fever	Td506	Adacel	14	0 0.00	58	4.96	3.79, 6.36	12	1.03	0.53, 1.78	2	0.17	0.02, 0.62
		Td	9	0 0.00	21	2.68	1.67, 4.07	6	0.77	0.28, 1.66	1	0.13	0.00, 0.71
	Td505	Adacel	16	0 0.00	93	5.20	4.21, 6.33	22	1.23	0.77, 1.85	3	0.17	0.03, 0.49
	Td501	Simultaneous	1	0 0.00	11	5.47	2.76, 9.58	3	1.49	0.31, 4.30	0	0.00	0.00, 1.82
		Sequential	1	0 0.00	12	6.00	3.14, 10.25	3	1.50	0.31, 4.32	1	0.50	0.01, 2.75
Chills	Td506	Adacel	9	2 0.17	177	15.06	13.07, 17.24	43	3.66	2.66, 4.90	6	0.51	0.19, 1.11
		Td	5	2 0.25	99	12.58	10.34, 15.10	21	2.67	1.66, 4.05	1	0.13	0.00, 0.71
	Td505	Adacel	13	0 0.00	230	12.83	11.31, 14.46	64	3.57	2.76, 4.54	9	0.50	0.23, 0.95
	Td501	Simultaneous	2	0 0.00	34	17.00	12.07, 22.94	5	2.50	0.82, 5.74	1	0.50	0.01, 2.75
		Sequential	0	1 0.50	27	13.43	9.04, 18.94	6	2.99	1.10, 6.38	0	0.00	0.00, 1.82
Headache	Td506	Adacel	9	2 0.17	514	43.74	40.88, 46.64	190	16.17	14.11, 18.40	23	1.96	1.24, 2.92
		Td	5	3 0.38	318	40.41	36.96, 43.93	99	12.58	10.34, 15.10	12	1.52	0.79, 2.65
	Td505	Adacel	13	1 0.06	793	44.23	41.91, 46.56	291	16.23	14.55, 18.02	42	2.34	1.69, 3.15
	Td501	Simultaneous	2	0 0.00	108	54.00	46.83, 61.05	35	17.50	12.50, 23.49	3	1.50	0.31, 4.32
		Sequential	0	0 0.00	95	47.26	40.20, 54.41	30	14.93	10.30, 20.62	5	2.49	0.81, 5.71
Generalized Body Ache	Td506	Adacel	9	2 0.17	357	30.38	27.76, 33.10	115	9.79	8.15, 11.63	15	1.28	0.72, 2.10
		Td	5	1 0.13	235	29.86	26.68, 33.19	61	7.75	5.98, 9.85	7	0.89	0.36, 1.82
	Td505	Adacel	13	0 0.00	545	30.40	28.27, 32.58	161	8.98	7.70, 10.40	16	0.89	0.51, 1.45
	Td501	Simultaneous	2	0 0.00	103	51.50	44.35, 58.61	25	12.50	8.26, 17.90	1	0.50	0.01, 2.75
		Sequential	0	0 0.00	82	40.80	33.93, 47.93	22	10.95	6.99, 16.10	0	0.00	0.00, 1.82
Tiredness	Td506	Adacel	9	1 0.09	355	30.21	27.60, 32.93	129	10.98	9.25, 12.91	14	1.19	0.65, 1.99
		Td	5	1 0.13	215	27.32	24.23, 30.58	67	8.51	6.66, 10.69	8	1.02	0.44, 1.99
	Td505	Adacel	13	0 0.00	562	31.34	29.20, 33.55	185	10.32	8.95, 11.82	33	1.84	1.27, 2.58
	Td501	Simultaneous	2	1 0.50	102	51.00	43.85, 58.12	25	12.50	8.26, 17.90	3	1.50	0.31, 4.32
		Sequential	0	0 0.00	90	44.78	37.78, 51.93	29	14.43	9.88, 20.06	1	0.50	0.01, 2.74
Nausea	Td506	Adacel	9	1 0.09	156	13.28	11.39, 15.35	49	4.17	3.10, 5.48	12	1.02	0.53, 1.78
		Td	5	1 0.13	97	12.33	10.11, 14.83	30	3.81	2.59, 5.40	5	0.64	0.21, 1.48
	Td505	Adacel	14	0 0.00	209	11.66	10.21, 13.24	66	3.68	2.86, 4.66	11	0.61	0.31, 1.10
	Td501	Simultaneous	2	0 0.00	31	15.50	10.78, 21.27	4	2.00	0.55, 5.04	1	0.50	0.01, 2.75
		Sequential	0	0 0.00	30	14.93	10.30, 20.62	2	1.00	0.12, 3.55	0	0.00	0.00, 1.82
Vomiting	Td506	Adacel	9	0 0.00	54	4.60	3.47, 5.95	20	1.70	1.04, 2.62	6	0.51	0.19, 1.11
		Td	0	1 0.50	5	2.49	0.81, 5.71	3	1.49	0.31, 4.30	0	0.00	0.00 1.82
	Td505	Adacel	14	0 0.00	66	3.68	2.86, 4.66	27	1.51	1.00, 2.18	9	0.50	0.23, 0.95

			Maximum Intensity										
			Missing		Any			Moderate & Severe			Severe		
Systemic AE	**Study**	**Vaccine**	**n1**	**n2 (%)**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
	Td501	Simultaneous	2	1 0.50	13	6.50	3.51, 10.86	0	0.00	0.00, 1.83	0	0.00	0.00, 1.83
		Sequential	0	1 0.50	5	2.49	0.81, 5.71	3	1.49	0.31, 4.30	0	0.00	0.00, 1.82
Diarrhea	Td506	Adacel	9	0 0.00	121	10.30	8.62, 12.18	26	2.21	1.45, 3.23	4	0.34	0.09, 0.87
		Td	5	0 0.00	80	10.17	8.14, 12.49	16	2.03	1.17, 3.28	0	0.00	0.00, 0.47
	Td505	Adacel	14	0 0.00	191	10.66	9.27, 12.18	34	1.90	1.32, 2.64	2	0.11	0.01, 0.40
	Td501	Simultaneous	2	0 0.00	24	12.00	7.84, 17.33	4	2.00	0.55, 5.04	0	0.00	0.00, 1.83
		Sequential	0	0 0.00	19	9.45	5.79, 14.37	2	1.00	0.12, 3.55	0	0.00	0.00, 1.82
Sore Joints	Td506	Adacel	9	0 0.00	133	11.32	9.56, 13.27	34	2.89	2.01, 4.02	3	0.26	0.05, 0.74
		Td	5	0 0.00	92	11.69	9.53, 14.14	21	2.67	1.66, 4.05	1	0.13	0.00, 0.71
	Td505	Adacel	14	0 0.00	251	14.01	12.43, 15.70	78	4.35	3.46, 5.40	7	0.39	0.16, 0.80
	Td501	Simultaneous	2	0 0.00	45	22.50	16.91, 28.92	9	4.50	2.08, 8.37	1	0.50	0.01, 2.75
		Sequential	0	0 0.00	36	17.91	12.87, 23.92	14	6.97	3.86, 11.41	0	0.00	0.00, 1.82
Rash	Td506	Adacel	10	0 0.00	32	2.73	1.87, 3.83	0	0.00	0.00, 0.31	0	0.00	0.00, 0.31
		Td	5	0 0.00	16	2.03	1.17, 3.28	0	0.00	0.00, 0.47	0	0.00	0.00, 0.47
	Td505	Adacel	13	0 0.00	62	3.46	2.66, 4.41	0	0.00	0.00, 0.21	0	0.00	0.00, 0.21
	Td501	Simultaneous	2	0 0.00	9	4.50	2.08, 8.37	0	0.00	0.00, 1.83	0	0.00	0.00, 1.83
		Sequential	0	0 0.00	9	4.48	2.07, 8.33	0	0.00	0.00, 1.82	0	0.00	0.00, 1.82

Missing n1 - Number of subjects from the ITTS population with events not evaluated.
Missing (n2 %) - Number and percent of subjects who experienced the event but did not evaluate the intensity.
n, % - Number and percent of subjects. The percent value is based on the ITTS population excluding Missing (n1).
95% CI - Two-sided 95% confidence interval for the proportion.

Table 42: Overall Summary of Systemic Solicited Adverse Events - Adults 18-64 Years (Days 0-14)

			Maximum Intensity										
			Missing		Any			Moderate & Severe			Severe		
Systemic AE	Study	Vaccine	n1	(n2 %)	n	%	95% CI	n	%	95% CI	n	%	95% CI
Fever	Td506	Adacel	64	0 0.00	24	1.42	0.91, 2.11	7	0.41	0.17, 0.85	0	0.00	0.00, 0.22
		Td	22	0 0.00	6	1.09	0.40, 2.35	2	0.36	0.04, 1.30	1	0.18	0.00, 1.01
	Td502	Simultaneous	4	0 0.00	15	4.26	2.40, 6.93	7	1.99	0.80, 4.05	4	1.14	0.31, 2.88
		Sequential	4	0 0.00	8	2.38	1.03, 4.64	2	0.60	0.07, 2.13	0	0.00	0.00, 1.09
Chills	Td506	Adacel	54	4 0.24	138	8.13	6.87, 9.53	34	2.00	1.39, 2.79	12	0.71	0.37, 1.23
		Td	13	0 0.00	37	6.61	4.69, 8.99	12	2.14	1.11, 3.71	3	0.54	0.11, 1.56
	Td502	Simultaneous	4	1 0.28	51	14.49	10.98, 18.61	11	3.13	1.57, 5.52	3	0.85	0.18, 2.47
		Sequential	1	0 0.00	46	13.57	10.11, 17.68	16	4.72	2.72, 7.55	3	0.88	0.18, 2.56
Headache	Td506	Adacel	54	4 0.24	575	33.86	31.61, 36.17	241	14.19	12.57, 15.94	47	2.77	2.04, 3.66
		Td	13	1 0.18	191	34.11	30.18, 38.20	71	12.68	10.04, 15.72	12	2.14	1.11, 3.71
	Td502	Simultaneous	4	1 0.28	140	39.77	34.62, 45.10	56	15.91	12.25, 20.16	6	1.70	0.63, 3.67
		Sequential	1	1 0.29	128	37.76	32.58, 43.16	57	16.81	12.99, 21.23	12	3.54	1.84, 6.10
Generalized Body Ache	Td506	Adacel	55	2 0.12	371	21.86	19.92, 23.91	123	7.25	6.06, 8.59	20	1.18	0.72, 1.81
		Td	13	0 0.00	105	18.75	15.60, 22.23	37	6.61	4.69, 8.99	5	0.89	0.29, 2.07
	Td502	Simultaneous	4	0 0.00	103	29.26	24.56, 34.32	35	9.94	7.02, 13.56	3	0.85	0.18, 2.47
		Sequential	1	0 0.00	74	21.83	17.55, 26.61	26	7.67	5.07, 11.04	8	2.36	1.02, 4.60
Tiredness	Td506	Adacel	54	4 0.24	413	24.32	22.30, 26.44	139	8.19	6.93, 9.59	22	1.30	0.81, 1.96
		Td	13	0 0.00	116	20.71	17.43, 24.31	37	6.61	4.69, 8.99	3	0.54	0.11, 1.56
	Td502	Simultaneous	4	2 0.57	115	32.67	27.79, 37.84	42	11.93	8.74, 15.78	7	1.99	0.80, 4.05
		Sequential	1	0 0.00	107	31.56	26.65, 36.80	38	11.21	8.06, 15.06	7	2.06	0.83, 4.21
Nausea	Td506	Adacel	54	1 0.06	156	9.19	7.86, 10.66	57	3.36	2.55, 4.33	14	0.82	0.45, 1.38
		Td	13	1 0.18	44	7.86	5.77, 10.40	13	2.32	1.24, 3.94	3	0.54	0.11, 1.56

			Maximum Intensity											
			Missing		Any			Moderate & Severe			Severe			
Systemic AE	**Study**	**Vaccine**	**n1**	**(n2 %)**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	
	Td502	Simultaneous	4	0 0.00	47	13.35	9.98, 17.36	12	3.41	1.77, 5.88	2	0.57	0.07, 2.04	
		Sequential	1	0 0.00	47	13.86	10.37, 18.01	19	5.60	3.41, 8.61	4	1.18	0.32, 2.99	
Vomiting	Td506	Adacel	54	0 0.00	51	3.00	2.24, 3.93	26	1.53	1.00, 2.24	9	0.53	0.24, 1.00	
		Td	13	0 0.00	10	1.79	0.86, 3.26	6	1.07	0.39, 2.32	1	0.18	0.00, 0.99	
	Td502	Simultaneous	4	0 0.00	12	3.41	1.77, 5.88	7	1.99	0.80, 4.05	4	1.14	0.31, 2.88	
		Sequential	1	0 0.00	13	3.83	2.06, 6.47	8	2.36	1.02, 4.60	3	0.88	0.18, 2.56	
Diarrhea	Td506	Adacel	55	0 0.00	175	10.31	8.91, 11.86	47	2.77	2.04, 3.67	9	0.53	0.24, 1.00	
		Td	13	0 0.00	63	11.25	8.75, 14.16	18	3.21	1.92, 5.03	3	0.54	0.11, 1.56	
	Td502	Simultaneous	4	1 0.28	53	15.06	11.49, 19.23	12	3.41	1.77, 5.88	0	0.00	0.00, 1.04	
		Sequential	1	1 0.29	39	11.50	8.31, 15.39	12	3.54	1.84, 6.10	3	0.88	0.18, 2.56	
Sore Joints	Td506	Adacel	55	2 0.12	155	9.13	7.81, 10.61	50	2.95	2.19, 3.87	8	0.47	0.20, 0.93	
		Td	13	0 0.00	39	6.96	5.00, 9.40	15	2.68	1.51, 4.38	3	0.54	0.11, 1.56	
	Td502	Simultaneous	4	1 0.28	44	12.50	9.23, 16.42	7	1.99	0.80, 4.05	0	0.00	0.00, 1.04	
		Sequential	1	0 0.00	32	9.44	6.55, 13.06	6	1.77	0.65, 3.81	2	0.59	0.07, 2.11	
Rash	Td506	Adacel	55	0 0.00	34	2.00	1.39, 2.79	0	0.00	0.00, 0.22	0	0.00	0.00, 0.22	
		Td	13	0 0.00	13	2.32	1.24, 3.94	0	0.00	0.00, 0.66	0	0.00	0.00, 0.66	
	Td502	Simultaneous	4	0 0.00	1	0.28	0.01, 1.57	0	0.00	0.00, 1.04	0	0.00	0.00, 1.04	
		Sequential	1	0 0.00	5	1.47	0.48, 3.41	0	0.00	0.00, 1.08	0	0.00	0.00, 1.08	

Missing n1 - Number of subjects from the ITTS population with events not evaluated.
Missing (n2 %) - Number and percent of subjects who experienced the event but did not evaluate the intensity.
n, % - Number and percent of subjects. The percent value is based on the ITTS population excluding Missing (n1).
95% CI - Two-sided 95% confidence interval for the proportion.

Appendix 5: Safety Results from Supportive Canadian Trials

ADACEL™ was used in three Phase 3 clinical trials (TC9704, TD9707, and TD9805) that were the basis of licensure of Tdap Vaccine as ADACEL™ in Canada in May 1999 and COVAXiS™ in Germany in July 2001. These studies included a comparative trial of ADACEL™ versus Td Adsorbed Vaccine in adolescents and adults aged 12 to 54 years (TC9704), and in adults aged 19 to 60 years (TD9707), as well as a comparative trial of ADACEL™ either given Concomitantly with or separately from Hepatitis B Vaccine in adolescents aged 11 to 12 years (TD9805). These studies provided additional safety data to the eBLA for 962 participants that were enrolled to receive ADACEL™.

The analysis population for safety for these studies was derived as a combined population of participants assessed for safety in the individual studies. The population described in the supportive data is for the entire study population of adolescents and adults, 11-60-years of age.

Table 43 shows the distribution and disposition of participants enrolled in the supportive trials. In total, 973 participants were enrolled to receive ADACEL™ as the first vaccination. Adults outnumbered adolescents by 2:1: 66.4% (646/973) versus 33.6% (327/973). The percentage completing the studies was similar for both age groups, with 97.6% completion (319/327) for adolescents and 97.2% completion (628/646) for adults. There were no discontinuations as a result of an adverse event. A total of 278 participants were enrolled to receive Td Vaccine as the first vaccination. Adults vastly outnumbered adolescents: 92.8% (258/278) versus 7.2% (20/278). Of the Td Vaccine population, 277 (99.6%) were included in the safety population, and 270 (97.1%) completed the study.

Table 43: Summary of Participant Enrollment, ADACEL™ and Td Vaccine Recipients in the Supportive Trials

	TC9704		TD9707		TD9805	Total	
	ADACEL™	Td	ADACEL™	Td	ADACEL™	ADACEL™	Td
Enrolled and Randomized	453	152	248	126	272	**973**	**278**
Discontinued	8	3	10	5	8	**26**	**8**
Completed Participants	445	149	238	121	264	**947**	**270**
Excluded from Analysis Population	4	1	4	0	3	**11**	**1**
Analysis Population	449	151	244	126	269	**962**	**277**

Safety Parameters for Supportive Canadian Trials

Immediate Reactions

Immediate reactions were defined as events reported within either the first 15 minutes or 30 minutes post-vaccination. In the TC9704 and TD9707 studies, immediate reactions were reported within the first 15 minutes post-vaccination and included local reactions, whereas in the TD9805 study, they were reported within the first 30 minutes post-vaccination and did not include local reactions.

Although immediate reactions are summarized for these studies, a compilation of immediate reaction data across these three studies is of limited value, due to differences in collection methods and inter-study differences.

Solicited Adverse Events

Solicited adverse events were recorded on the CRF for each time point following vaccination as described above, and were classified as local or systemic and as Mild, Moderate, or Severe. The categories of intensity were the same as those defined in Table 38. Solicited local adverse events included Injection Site Redness (Erythema), Swelling, Pain, and Underarm Lymph Node Swelling. Solicited systemic adverse events included Fever, Chills, Headache, Generalized Body Ache and/or Muscle Weakness, Tiredness and/or Decreased Energy, Nausea, Vomiting, and Diarrhea.

With respect to maximum intensity categories, for the purpose of the data evaluation, two new categories (in addition to the maximum intensity categories recorded on the CRF) were defined: 'Any' and 'Moderate & Severe'. 'Any' was defined as the sum of events classified as Mild, Moderate, or Severe, and 'Moderate & Severe' was defined as the sum of events classified as either Moderate or Severe. Moderate or Severe events were also considered to be clinically significant. In addition to these intensity categories for Erythema and Swelling, measurements of ≥50 mm were also included as a maximum intensity category.

For solicited local and systemic adverse events, the focus is on those events that occurred on Days 0–3, due to the difference in the data collection timing across studies.

Unsolicited Adverse Events

An unsolicited adverse event was defined as either a new adverse event or the worsening of a pre-existing (i.e., solicited) adverse event in which a start date, stop date, and duration could be determined. The event was assessed by a nurse and, if neccessary, the Site Investigator, as *Definitely, Probably*, *Possibly, or Unrelated* to the study vaccine. *Definite* was applied to those adverse events which had a timely relation to the study vaccine and for which no alternative etiology was present. These events were defined as events that occurred within a reasonable temporal sequence of the vaccine administration, were reasonably explained, and followed a known pattern of response. *Probably* related events had a timely relation to the study vaccine; but a potential etiology was not apparent. *Possibly* related events had a timely relation to the study vaccine; however, a potential alternative etiology existed which may have been responsible for the symptom. *Unrelated* events were those for which evidence existed that the symptom was definitely related to an etiology other than the study vaccine.

The unsolicited AEs were summarized as the number of events, and number and percent of unique participants reporting at least one unsolicited AE, summarized by body system, preferred term and relationship to vaccine over Days 0–3 and Days 0–14 (for the TC9704 study, on Days 0–8) as well as during the whole period of the study and by maximum intensity.

Serious Adverse Events (SAEs)

SAEs were collected at any time throughout the study. SAEs are summarized by body system and preferred term, as well as relationship to vaccine.

Reporting of serious events was in compliance with the Canadian Therapeutic Products Directorate Guidelines and ICH Tripartite guidelines. A Serious Adverse Event is any untoward medical occurrence that at any dose:

1) resulted in death
2) was life-threatening
3) resulted in persistent or significant disability/incapacity
4) required inpatient hospitalization
5) prolonged existing inpatient hospitalization
6) resulted in a congenital anomaly/birth defect.

Criteria for Safety Endpoints

The categories of safety information that were collected and the duration of follow-up for safety variables in the supportive trial are summarized in Table 44

Table 44: Summary of Safety Variables and Follow-Up Duration for Supportive Trials

Safety Parameters	TC9704	TD9707	TD9805
Immediate Reactions	15 minutes post-vaccination		30 minutes post-vaccination
Solicited Local Reactions	0-24 hrs, >24-72 hrs, >72 hrs to 8 days (up to 10 days in same cases) post-vaccination	0-24 hrs, >24-72 hrs, >72 hrs to 14 days post-vaccination	
Solicited Systemic Reactions	0-24 hrs, >24-72 hrs, >72 hrs to 8 days (up to 10 days in same cases) days post-vaccination	0-24 hrs, >24-72 hrs, >72 hrs to 14 days post-vaccination	
Unsolicited Adverse Events	Collected any time during the study (1-2 months)		Any time during the study (up to 8 months)
Serious Adverse Events	Collected any time during the study (1-2 months)		Any time during the study (up to 8 months)

For the supportive trials, the solicited adverse events were recorded on the CRF for each time point following vaccination, and were classified as local or systemic and as Mild, Moderate, or Severe. The definitions of intensity were the same as those for the main trials (See Appendix 3).

Solicited local adverse events included Injection Site Redness (Erythema), Swelling, Pain, and Underarm Lymph Node Swelling. Solicited systemic adverse events included Fever, Chills, Headache, Generalized Body Ache and/or Muscle Weakness, Tiredness and/or Decreased Energy, Nausea, Vomiting, and Diarrhea. For solicited local and systemic adverse events, the focus is on those events that occurred on Days 0–3, due to the difference in the data collection timing across studies.

To address the safety objective for the supportive studies, data are presented only for those participants who received either ADACEL™ or Td Vaccine as the first vaccine in the study. Comparisons of the two vaccines are made using descriptive methods only. No tests for statistical significance were performed.

Safety Results from Supportive Trials

The safety database for these studies comprised a total of 962 adolescents and adults that received ADACEL™, and 277 adolescents and adults that received the Td Vaccine.

Overall Safety Profile

The overall safety profile of ADACEL™ compared to Td Vaccine is summarized in Table 45. Data are presented only for the period Day 0–3 post-vaccination. Since the time period for collection of local solicited events varied across studies (0–8 days for TC9704 and 0–14 days for TD9707 and TD9805), the data for Days 0 to 14 are not comparable and are not presented here.

Table 45: Overall Safety Profile of Three Supportive Trials (TC9704, TD9707 and TD9805)

	ADACEL™ Participants (N= 962)			Td Participants (N=277)		
	11-17 yrs N= 324	**18-60 yrs N=638**	**11-60 yrs N=962**	**11-17 yrs N= 20**	**18-60 yrs N=257**	**11-60 yrs N=277**
	%	%	%	%	%	%
Solicited Reactions (Days 0–3):						
Erythema	18.5	15.2	16.3	0.0	14.4	13.4
Swelling	23.5	14.8	17.7	20.0	12.5	13.0
Pain	79.6	86.0	83.9	80.0	87.5	87.0
Fever >38.0°C	2.8	2.8	2.8	0.0	0.8	0.7
Unsolicited AEs (entire study period)	54.0	44.4	47.6	55.0	39.7	40.8
SAEs (entire study period)	0.6	0.2	0.3	0.0	0.0	0.0

Immediate Reactions

A total of 63 (6.5%) ADACEL™ recipients reported 79 immediate events, compared with 18 (6.3%) Td Vaccine recipients reporting 23 events. Among adolescents, 23 (7.1%) ADACEL™ recipients reported 25 events and 40 (6.3%) adult ADACEL™ recipients reported 54 events.

There were no reports in any trial of anaphylaxis occurring post-immunization and most of the immediate events reported were local reactions.

Solicited Local Reactions

Table 46 presents the data for solicited local reactions. Overall, the rates of local adverse events for the combination ADACEL™ were clinically comparable to those of Td Vaccine.

Table 46: Percent of Participants Reporting Solicited Local Reactions (Days 0-3) in 3 Supportive Trials (TC9704, TD9707 and TD9805), 11-60 yrs

Adverse Event	Vaccine	N	Maximum Intensity				
			Any (%)	Mild (%)	Moderate & Severe (%)	Severe (%)	
						≥35mm	≥50mm
Erythema	ADACEL™	961	16.3	8.4	7.9	4.8	3.3
	Td	277	13.4	7.6	5.8	2.5	0.7
Swelling	ADACEL™	961	17.7	3.9	13.7	10.7	7.4
	Td	277	13.0	3.6	8.7	6.9	4.3
Pain	ADACEL™	961	83.9	61.9	22.0	1.5	-
	Td	277	87.0	73.3	13.7	0.7	-
UnderArm Lymphnode Swelling	ADACEL™	324	4.1	4.1	0.0	0.0	-
	Td	277	NC	NC	NC	NC	-

More than 80% of participants aged 11 to 60 years in both vaccination groups reported 'Any' Pain within 3 days following vaccination. In both the ADACEL™ and Td Vaccine groups, Pain was the most frequently reported solicited local reaction (83.9% and 87.0%, respectively),with most Pain reported as Mild intensity (61.9% and 73.3%) respectively.. Erythema ≥50 mm was reported by 3.3% (32/961) and 0.7% (2/277) of the ADACEL™ and Td Vaccine groups, respectively, and Injection Site Swelling ≥50 mm by 7.4% (71/961) and 4.3% (12/277), respectively; See Table 46.

For adolescents, the frequency of Erythema, Swelling, and Pain reported by ADACEL™ recipients for Days 0–3 in the supportive studies were comparable to those reported in the main trials. For adults, the rates of Erythema and Swelling were comparable, but the rates of Pain were higher in the supportive studies (86.0%) than in the main studies (65.6% and 60.8% in Td506 and Td502, respectively). Similar to the main studies, for the majority of participants with Pain, intensity was Mild.

Solicited Systemic Reactions

Table 47 presents the data on solicited systemic reactions. Overall, the rates of systemic adverse events for the combination ADACEL™ were clinically comparable to those of Td Vaccine.

The incidence of Fever >38.0ºC was uncommon in the ADACEL™ and Td Vaccine groups, reported by 2.8% and 0.7% participants, respectively. Rates of Moderate & Severe and Severe

Fever were rare, occurring in 0.6% of the ADACEL™ group, and in no participants in the Td Vaccine group. (See Table 47)

The incidence of Chills, Nausea, Vomiting, Diarrhea, and Sore/Swollen Joints was consistently higher in the ADACEL™ group compared to the Td Vaccine group. However, the majority of all of these reactions were considered Mild and <1.2% reported Severe reactions (See Table 47).

Table 47: Percent of Participants Reporting Solicited Systemic Reactions (Days 0-3) in 3 Supportive Trials (TC9704, TD9704 and TD9805), 11-60 yrs

Adverse Event	Vaccine	Maximum Intensity							
		Any (%)		Mild (%)		Moderate & Severe (%)		Severe (%)	
		n	%	n	%	n	%	n	%
Fever	ADACEL™	27	2.8	21	2.2	6	0.6	2	0.2
	Td	2	0.7	2	0.7	0	0.0	0	0.0
Chills	ADACEL™	99	10.3	80	8.3	19	2.0	4	0.4
	Td	13	4.7	11	4.0	2	0.7	1	0.4
Headache	ADACEL™	265	27.6	199	20.7	66	6.9	7	0.7
	Td	69	24.9	56	20.2	13	4.7	1	0.4
Body Ache/ Muscle Weakness	ADACEL™	190	19.8	140	14.6	50	5.2	11	1.1
	Td	38	13.7	31	11.2	7	2.5	0	0.0
Tiredness	ADACEL™	254	26.4	186	19.4	68	7.1	11	1.1
	Td	60	21.7	46	16.6	14	5.1	2	0.7
Nausea	ADACEL™	105	10.9	92	9.6	13	1.4	2	0.2
	Td	24	8.7	21	7.6	3	1.1	0	0.0
Vomiting	ADACEL™	9	0.9	5	0.5	4	0.4	2	0.2
	Td	2	0.7	2	0.7	0	0.0	0	0.0
Diarrhea	ADACEL™	52	5.4	44	4.6	8	0.8	2	0.2
	Td	12	4.3	10	3.6	2	0.7	1	0.4
Sore/Swollen Joints	ADACEL™	102	10.6	77	8.0	25	2.6	5	0.5
	Td	17	6.1	13	4.7	4	1.4	0	0.0

Unsolicited Adverse Events

A total of 1569 unsolicited adverse events were reported over the entire study periods by 70.2% (675/962) of the ADACEL™ participants, compared to a total of 644 reported by 78.3% (217/277) of the Td Vaccine participants. Of these unsolicited events, 44.1% in the ADACEL™ group and 30.3% in the Td Vaccine group were considered to be possibly, probably, or definitely related to vaccination. Review of the line listings of unsolicited adverse events with onset within the 8-14 days post-vaccination follow-up period showed that several solicited local and systemic adverse events were also tabulated with the unsolicited events, and thus were double-counted. Solicited events were considered related to the vaccination. The unsolicited adverse events most frequently reported over the study periods were General Disorders and Administrative Site Conditions, reported by 22.5% and 23.8 of ADACEL™ and Td Vaccine recipients, respectively;

Respiratory, Thoracic and Mediastinal Disorder, reported by 21.7% and 24.5%, respectively; and Infections and Infestations, reported by 19.4% and 27.8%, respectively.

Events of Special Interest

One case of diabetes mellitus-type II and three cases of whole arm swelling were reported in these trials; a description of events of special interest in the Supportive trials is presented in Section 4.7.4.3.

Serious Adverse Events

Three SAEs (two fractures and one case of cholelithiasis) were reported among ADACEL™ participants in the Supportive trials (See Section 4.7.5 for details)

Safety Conclusions

The safety findings from these three studies demonstrate that ADACEL™ was well tolerated in persons 11 to 60 years of age. Combining Td Vaccine with acellular pertussis vaccine did not result in an overall increase in reactogenicity, as evidenced by comparable rates of local and systemic reactions. The safety findings from these studies are consistent with the safety profile of ADACEL™ in the four principal studies.

Injection site Pain during the first three days post-vaccination was seen in the majority of both ADACEL™ and Td participants (83.9% and 87.0%, respectively) and was generally Mild (69.1% and 73.3%, respectively). For adolescents, the frequency of Erythema, Swelling, and Pain reported by ADACEL™ for Days 0–3 in the supportive studies were comparable to those reported in the four principal trials. For adults, the rates of Erythema and Swelling were comparable, but the rates of Pain were higher in the supportive studies (86.0%) than in the principal studies (63.96% and 64.59% in Td506 and Td502, respectively).

In these studies, as expected, there was a trend for adolescents to have a higher incidence of injection site Erythema and Swelling, particularly severe (≥ 50mm) reactions compared to adults; however, they had a lower incidence of injection site Pain than adults receiving either ADACEL™ or Td Vaccine. Injection Site Swelling ≥50 mm was reported by 13.3% of adolescents and 4.4% of adults, and Erythema ≥50 mm was reported by 6.2% of adolescents versus 1.9% of adults. These rates were higher than those seen in the principal studies (See Table 43 and 45 in Appendix 5).

Regardless of vaccine group or age group, the most frequently reported solicited systemic reactions during the first 3 days post-vaccination were Headache, Tiredness, and Body Ache/Muscle Weakness. These reactions occurred in approximately 25.0% of all study participants, and were assessed as being of Mild intensity. The overall incidence of Fever was very uncommon, reported by 2.8% of the ADACEL™ group and 0.7% of the Td participants during the first 3 days post-vaccination. These findings are consistent with the findings from the principal ADACEL™ studies.