Safety and Immunogenicity in Adults of Revaccination with Adacel® Vaccine 8-12 Years after a Previous Dose

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Rationale

- Long-term serology follow-up studies indicate anti-pertussis antibody (esp. anti-PT and anti-FIM) concentrations decline 5-10 years after the initial Tdap dose
- Data from observational studies have shown that protection against pertussis following Tdap vaccination of adolescents wanes over time, placing them at potential risk of infection, if exposed
- Boosting protection against tetanus, diphtheria, and pertussis would represent a meaningful clinical benefit
- The current Adacel vaccine label limits vaccination to a single dose; no revaccination[1]
- Under various scenarios, clinicians may want to vaccinate persons whose prior history of Tdap receipt is unknown and the HCP has Tdap on hand but not Td:
  - When tetanus prophylaxis is appropriate for wound management
  - Adults living in an area of a pertussis outbreak or when taking care of infants

Ref: 1. Adacel vaccine [Prescribing Information]. Sanofi Pasteur Inc.

Background: Adacel Vaccine Indication

- In Canada[1] and most other countries, Adacel vaccine is indicated for active booster immunization in persons 4 years of age and older
  - Re-vaccination with Adacel can be used to boost immunity to tetanus, diphtheria, and pertussis at 5- to 10-year intervals (supported by Canadian studies)
  - Can be used for tetanus-prone wound management
- In the US[2], Adacel vaccine is currently approved as a single booster dose for persons 10–64 years of age
  - For tetanus-prone wound-management, Adacel may be given if no previous Tdap vaccine has been administered

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Ref: 1. Adacel vaccine [Product Monograph]. Sanofi Pasteur Limited. 2. Adacel vaccine [Prescribing Information]. Sanofi Pasteur Inc.

Study Populations and Goals: Adacel Revaccination

- Study Td537 accessed two population sources for enrollment:
  - In the US, Adacel vaccine recipients in pivotal phase III trial (Study Td506)
    - Earliest US cohort available to revaccinate
  - In Canada, Adacel vaccine was routinely administered to adolescents in Newfoundland and Nova Scotia beginning in 2000
- Primary Goals of Study Td537:
  - Characterize the safety and immunogenicity of Adacel vaccine when given approximately 8-12 years following a prior Adacel dose
  - Generate data to support repeat-dose indication for Adacel vaccine in the US

Td537: Study Design

- Observer-blinded, randomized, multi-center study to describe safety and immunogenicity of repeat administration of Adacel vaccine, 8-12 years following initial administration.
  - US cohort: received Adacel 8-12 years previously in study Td506
    - Subjects were 21-64 years of age at enrollment in study Td537
  - Canada: received Adacel 8-12 years previously in school at 11-14 years of age
    - Subjects 18-24 years of age at enrollment in Td537
- Subjects randomized in a 3:1 ratio to receive either Adacel or Tenivac (Td) vaccine:
  - Group 1: Repeat dose of Adacel (999 subjects)
  - Group 2: Td (Tenivac; 333 subjects)

Study Vaccines

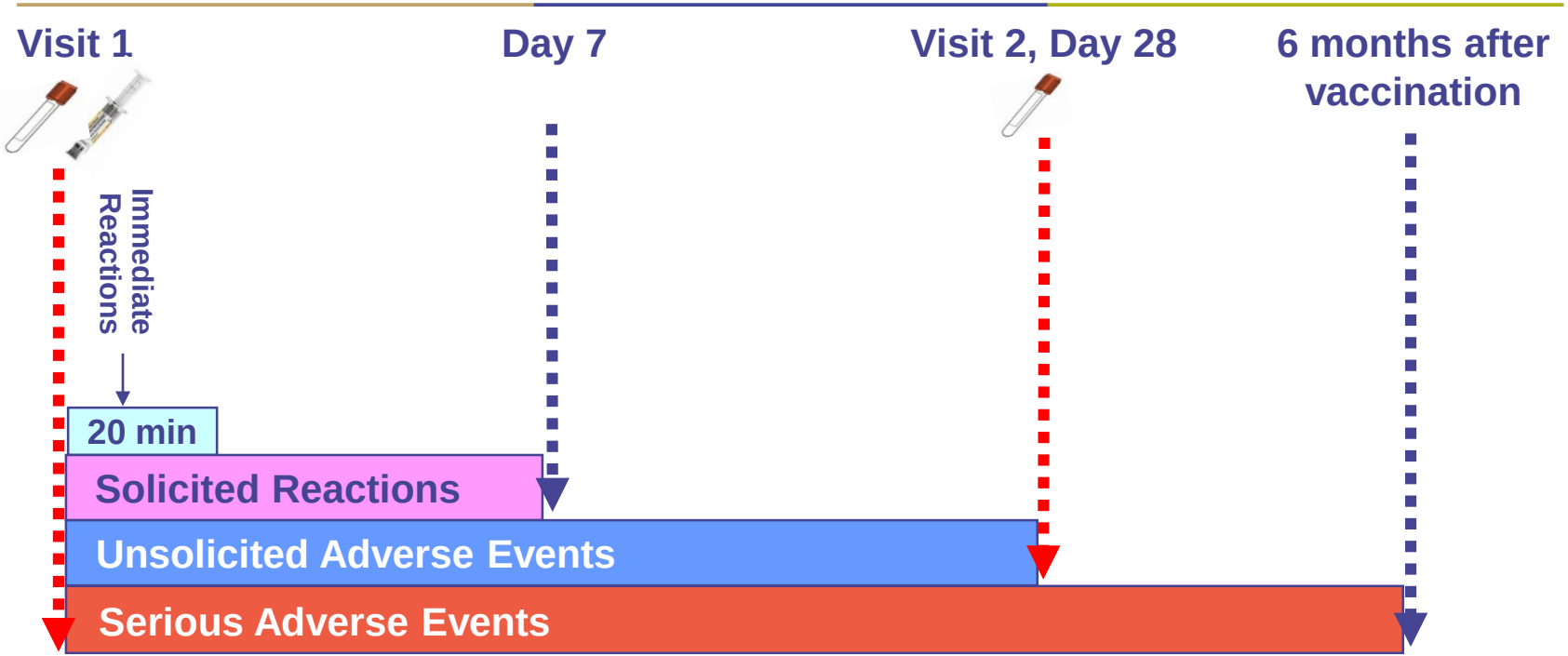
Antigen	Adacel Vaccine[1]	Tenivac Vaccine[2]
Diphtheria toxoid	5 Lf	5 Lf
Tetanus toxoid	2 Lf	2 Lf
Pertussis toxoid (PT)	2.5 mcg	
Filamentous hemagglutinin (FHA)	5 mcg	
Pertactin (PRN)	3 mcg	
Fimbriae types 2 and 3 (FIM)	5 mcg	
Aluminum phosphate (adjuvant)	1.5 mg	1.5 mg
2-phenoxyethanol	0.6% v/v	0.6% v/v

Refs: 1. Adacel vaccine [Prescribing Information]. Sanofi Pasteur Inc. **2.** Tenivac vaccine [Prescribing Information]. Sanofi Pasteur Inc.

Primary and Secondary Objectives

- Primary Objectives:
  - To compare seroprotection rates (≥ 0.1 IU/mL) to tetanus and diphtheria toxoids induced by Adacel vaccine to those induced by Td vaccine
  - To compare booster response rates (defined in back-up slides) to tetanus and diphtheria toxoids induced by Adacel vaccine to those induced by Td vaccine
  - To compare anti-pertussis geometric mean antibody concentrations (GMCs) induced by Adacel vaccine to the those induced by Daptacel vaccine in historical trials
  - To compare booster response rates (defined in back-up slides) to pertussis antigens following revaccination with Adacel vaccine to those induced in historical controls
- Secondary Objective:
  - To evaluate anti-pertussis GMCs by age strata (18 to < 49 years and 49 to < 65 years) following revaccination with Adacel vaccine

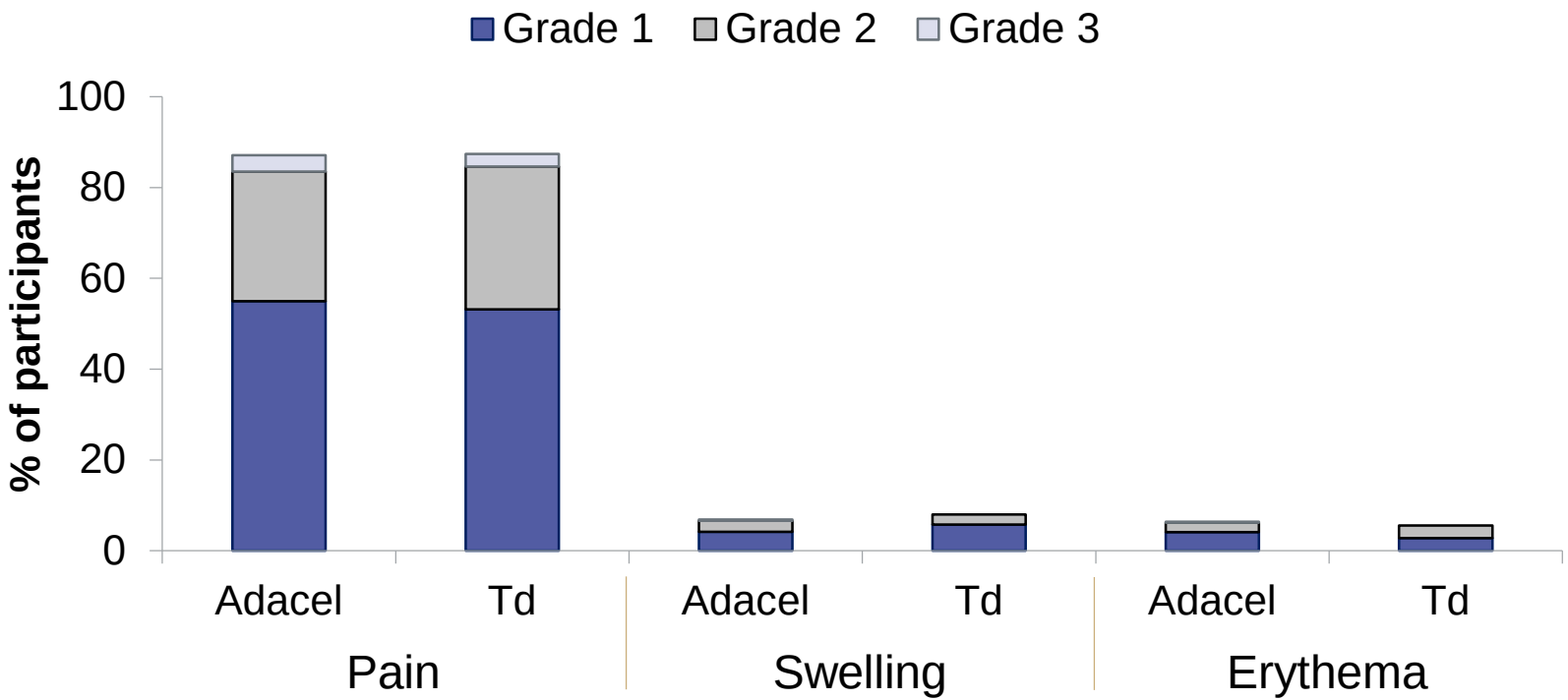
Safety Data and Sera Collection



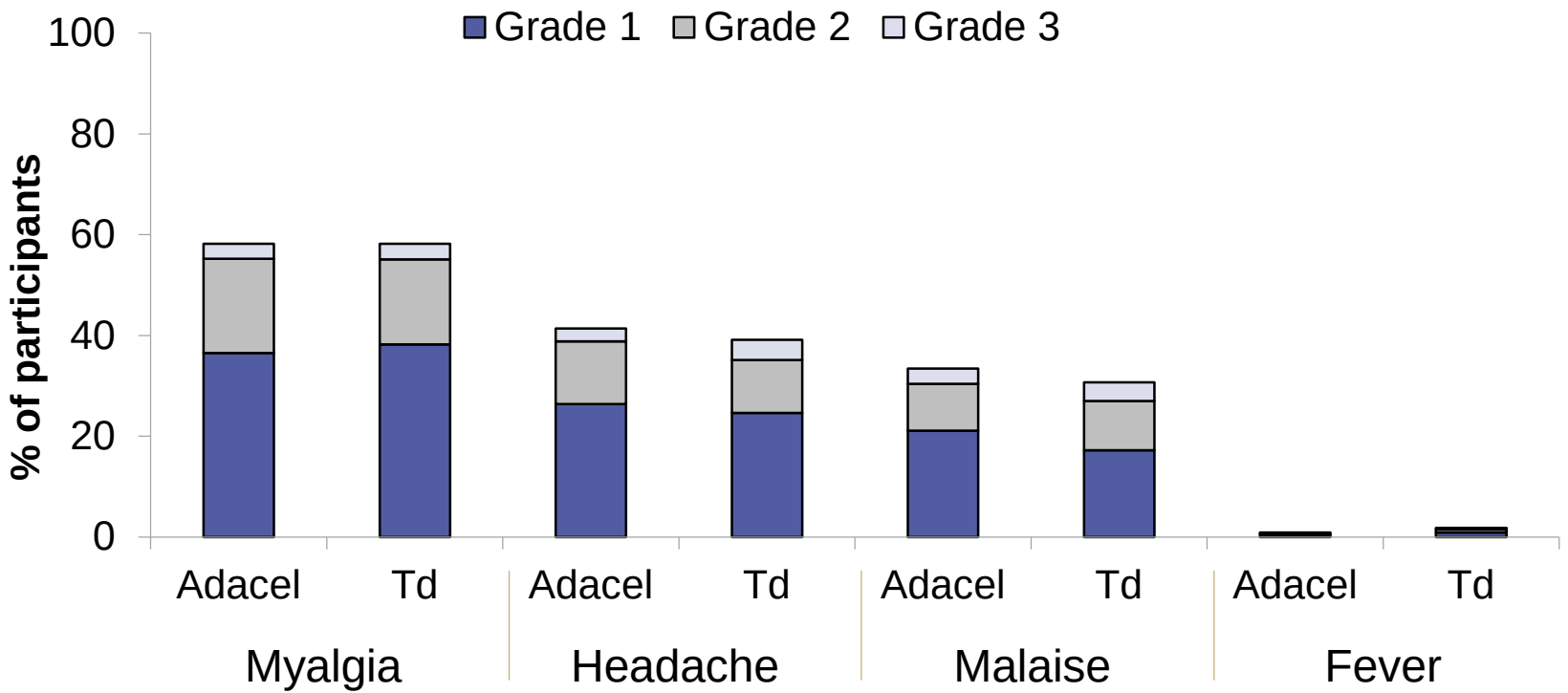
Demographic Characteristics

	Adacel (N=1002)	Td (N=328)
Sex: n (%)		
Male	356 (35.5)	116 (35.4)
Female	646 (64.5)	212 (64.6)
Age (years)		
Mean (SD)	28.9 (10.0)	29.2 (10.6)
Min; Max	18.3; 64.9	21.8; 64.5
Age group: n (%)		
18-< 49 years	917 (91.5)	297 (90.5)
49-< 65 years	85 (8.5)	31 (9.5)
Racial origin: n (%)		
Asian	6 (0.6)	3 (0.9)
Black or African American	23 (2.3)	8 (2.4)
White	956 (95.4)	310 (94.5)
American Indian or Alaska Native	1 (0.1)	2 (0.6)
Native Hawaiian or other Pacific Islander	1 (0.1)	0 (0.0)
Mixed origin	15 (1.5)	5 (1.5)
Ethnicity		
Hispanic or Latino	10 (1.0)	3 (0.9)
Not Hispanic or Latino	992 (99.0)	325 (99.1)

Solicited Injection-site Reactions, Days 0-7, by Severity



Solicited Systemic Reactions, Days 0-7, by Severity



Additional Safety Data

	Adacel (N=999)	Td (N=328)
Immediate reactions	0	0
Unsolicited adverse events	26.2%	25.9%
Unsolicited adverse reactions*	6.1%	5.5%
Serious adverse events†	0.8%	0.3%
Deaths	0	0

* Unsolicited adverse reactions were unsolicited adverse events considered by the investigator to be related to study vaccine. † All SAEs were considered by the investigator not to be related to study vaccine

Seroprotection Rates: Tetanus and Diphtheria Toxoids

	Adacel (N=948)		Td (N=317)		Adacel minus Td		
Toxin	n/M	%	n/M	%	Difference (%)	(95% CI)	Non-inferiority
Tetanus	948/948	100.0	317/317	100.0	0.00	(-0.4; 1.2)	**Yes**
Diphtheria	946/948	99.8	315/317	99.4	0.42	(-0.3; 2.1)	**Yes**

Seroprotection is defined as post-dose concentration >= 0.1 IU/mL.

Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the difference of seroprotection rates between groups is > -10% (-5% if the seroprotection percentage of the Td group is > 95%) for each toxin.

Booster Response Rates: Tetanus and Diphtheria Toxoids

	Adacel (N=948)		Td (N=317)		Adacel minus Td		
Toxin	n/M	%	n/M	%	Difference (%)	(95% CI)	Non-inferiority
Tetanus	703/944	74.5	257/315	81.6	-7.12	(-12.0; -1.7)	**No**
Diphtheria	786/945	83.2	265/315	84.1	-0.95	(-5.4; 4.0)	**Yes**

Booster response is defined as a minimum rise in antibody concentration from pre- to post-vaccination. The minimum rise is at least 2 times, if the pre-vaccination concentration is above the cutoff value, or at least 4 times if it is at or below the cutoff value

The cutoff values for tetanus and diphtheria toxins are 2.7 IU/mL and 2.56 IU/mL, respectively

Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the difference of booster response rates between groups is > -10% (-5% if the booster response percentage of the Td group is >95%) for each toxin

Anti-Pertussis GMCs

	Adacel (N=948)		Historical Group		Adacel / Historical Group		
Antigen	M	GMC	M	GMC	GMC ratio	(95% CI)	Non-inferiority
PT	935	102	366	98.1	1.04	(0.92; 1.18)	**Yes**
FHA	948	209	80	39.9	5.22	(4.51; 6.05)	**Yes**
PRN	948	318	80	108	2.94	(2.46; 3.51)	**Yes**
FIM	948	745	80	341	2.18	(1.84; 2.60)	**Yes**

Historical group: GMC responses to Daptacel vaccine in historical studies.

Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the ratio of GMCs between groups is > 0.66 for each antigen.

Booster Response Rates: Pertussis Antigens

	Adacel (N=948)		Expected Booster Response Rates Based on Td506	Adacel minus Expected Booster Response Rates Based on Td506		
Antigen	n/M	%	%	Difference (%)	(95%CI)	Non-inferiority
PT	693/894	77.5	61.4	16.12	(13.27; 18.73)	**Yes**
FHA	651/945	68.9	73.1	-4.21	(-7.23; -1.34)	**Yes**
PRN	617/945	65.3	83.9	-18.61	(-21.7; -15.6)	**No**
FIM	537/945	56.8	75.9	-19.07	(-22.3; -16.0)	**No**

Booster response is defined as a minimum rise in antibody concentration from pre- to post-vaccination. The minimum rise is at least 2 times, if the pre-vaccination concentration is above the cut-off value, or at least 4 times if it is at or below the cut-off value.

The cut-off values for the pertussis antigens are 93 EU/mL for PT, 170 EU/mL for FHA, 115 EU/mL for PRN, and 285 EU/mL for FIM.

Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the difference of booster response rates between subjects receiving Adacel in Td537 and expected booster response rates derived from subjects in study Td506 is > -10% for each antigen.

Summary and Conclusions: Tetanus and Diphtheria

- Post-vaccination tetanus and diphtheria seroprotection rates (≥ 0.1 IU/mL) of subjects in the Adacel group were non-inferior to those of subjects in the Td group
- Booster response to tetanus and diphtheria toxoids:
  - Adacel-induced booster response rate to diphtheria was non-inferior to that of the Td group
  - For tetanus, non-inferiority of Adacel vaccine was not achieved compared to Td vaccine
    - The lower limit of the 2-sided 95% CI of the difference in the booster response rates was -12.0%, which is below the non-inferiority margin of > -10%
    - However, 100% of Adacel recipients achieved seroprotective tetanus antibody concentrations (≥ 0.1 IU/mL) and Adacel induced a robust anti-tetanus GMC of 10.1 IU/mL (8.6-fold increase pre- to post-vaccination); therefore, the non-inferiority comparison should have no clinical relevance

Summary and Conclusions: Pertussis Antigens

- Post-vaccination anti-pertussis GMCs in the Adacel group were non-inferior compared with those induced by Daptacel vaccine among historical controls
- The booster response rates to 2 pertussis antigens (PT and FHA) were non-inferior in Adacel subjects compared to pre-specified response rates derived from Study Td506; non-inferiority was not met for 2 antigens (PRN and FIM), however:
  - Pre-vaccination FIM and PRN antibody concentrations in subjects in this trial were 5- to 10-fold higher than in participants in study Td506
  - The missed non-inferiority results should not impact the protection provided by Adacel vaccine against pertussis because the post-vaccination GMCs to PRN and FIM met non-inferiority testing and they were 2.9- and 2.2-fold higher, respectively, in the Adacel group compared to the historical Daptacel vaccine control group
  - Adacel vaccine induced 6.4- and 5.2-fold rises (post- to pre-vaccination ratios) in PRN and FIM antibodies, respectively.

Summary and Conclusions: Safety

- There were no immediate unsolicited AEs or ARs reported in this study
- For both vaccine groups, the most frequently reported solicited injection-site reactions were pain, swelling, and erythema, and the most frequently reported solicited systemic reactions were myalgia, headache, and malaise
- The majority of solicited injection-site and systemic reactions were Grade 1 or 2 in intensity
- Unsolicited AEs between Visit 1 and Visit 2 were reported by similar proportions of subjects in the Adacel and Td groups
- Nine subjects (Adacel group, 8 subjects; Td group, 1 subject) experienced an SAE during the study. All SAEs were considered unrelated to vaccination.
- There were no deaths reported in this study

Discussion

- The data from Td537 suggest that Adacel vaccine should be safe and effective when administered 8-12 years following prior Adacel vaccination[1]
  - Additional studies not reviewed today suggest the safety of shorter revaccination intervals
- Sanofi Pasteur seeks approval from the FDA for the repeat administration of Adacel vaccine
- HCPs often ask if Tdap is acceptable under the following scenarios (and others) when it is unknown whether the patient has ever received a prior dose of Tdap and the HCP has Tdap on hand but not Td:
  - Wound management
  - Persons living in an area of a pertussis outbreak
  - Adults directly caring for or living in the same household with an infant
- Approval of repeat dose administration may improve the efficiency for HCPs who prefer avoiding storage of both Adacel and Td vaccines

Ref: **1**. Halperin et al, J Pediatric Infect Dis Soc. 2018

THANK YOU