Clinical trial results:
Immune Responses in Adults to Revaccination with Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (ADACEL®) 10 Years After a Previous Dose

Summary

EudraCT number	2015-005842-69
Trial protocol	Outside EU/EEA
Global end of trial date	03 September 2009

Results information

Result version number	v1 (current)
This version publication date	13 March 2016
First version publication date	13 March 2016

Trial information

Trial identification

Sponsor protocol code	Td526

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00712959
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur Inc.
Sponsor organisation address	1 Discovery Drive, Swiftwater, United States, 18370
Public contact	Director, Clinical Development, Sanofi Pasteur Inc., 570 957-3570, emilia.jordanov@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur Inc., 570 957-3570, emilia.jordanov@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To compare the diphtheria and tetanus seroprotection rates in Group 1 and Group 2 approximately one month post Tdap-vaccination

2) To compare the pertussis antibody geometric mean concentrations (GMCs) in Group 1 and Group 2 approximately one month post Tdap-vaccination

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Subjects from studies Td9707 and Td9805 who previously received Tdap or Tdap-vIPV vaccines were enrolled in study Td526. In Td526, subjects from the Td9707 and Td9805 studies either qualified for Tdap revaccination (Group 1) or were age-balanced vaccine-naive subjects who received Tdap vaccine at least 10 years after a previous tetanus, diphtheria and/or pertussis dose (Group 2).

Evidence for comparator:

Not applicable

Actual start date of recruitment	26 June 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 768
Worldwide total number of subjects	768
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	758
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 26 June 2008 to 27 February 2009 at 7 medical centers in Canada.

Pre-assignment

Screening details:

A total of 769 subjects who met all the inclusion and none of the exclusion criteria were enrolled, 768 subjects were vaccinated and evaluated.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Previous Tdap or Tdap-IPV Recipients

Arm description:

Subjects received Tdap or Tdap-Inactivated Poliomyelitis Vaccine (IPV) in a previous study (Td9707 or Td9805).

Arm type	Experimental
Investigational medicinal product name	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 dose of Tdap vaccine on Day 0.

Arm title	Group 2: Tdap Vaccine-naive

Arm description:

Age-balanced Tdap vaccine-naive subjects who received Tdap vaccine in the study at least 10 years after a previous tetanus, diphtheria and/or pertussis dose.

Arm type	Experimental
Investigational medicinal product name	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 dose of Tdap vaccine on Day 0.

Number of subjects in period 1	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive
Started	361	407
Completed	342	404
Not completed	19	3
Consent withdrawn by subject	3	-
Lost to follow-up	13	2
Protocol deviation	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: Previous Tdap or Tdap-IPV Recipients
Reporting group description:	
Subjects received Tdap or Tdap-Inactivated Poliomyelitis Vaccine (IPV) in a previous study (Td9707 or Td9805).	
Reporting group title	Group 2: Tdap Vaccine-naive
Reporting group description:	
Age-balanced Tdap vaccine-naive subjects who received Tdap vaccine in the study at least 10 years after a previous tetanus, diphtheria and/or pertussis dose.	

Reporting group values	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive	Total
Number of subjects	361	407	768
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	356	402	758
From 65-84 years	5	5	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	31.2	34.6	
standard deviation	± 14	± 12.5	-
Gender categorical Units: Subjects			
Female	194	264	458
Male	167	143	310

End points

End points reporting groups

Reporting group title	Group 1: Previous Tdap or Tdap-IPV Recipients
Reporting group description:	
Subjects received Tdap or Tdap-Inactivated Poliomyelitis Vaccine (IPV) in a previous study (Td9707 or Td9805).	
Reporting group title	Group 2: Tdap Vaccine-naive
Reporting group description:	
Age-balanced Tdap vaccine-naive subjects who received Tdap vaccine in the study at least 10 years after a previous tetanus, diphtheria and/or pertussis dose.	

Primary: Percentage of Subjects With Seroprotection Against Tetanus and Diphtheria Before and After Revaccination With ADACEL® 10 Years After a Previous Dose

End point title	Percentage of Subjects With Seroprotection Against Tetanus and Diphtheria Before and After Revaccination With ADACEL® 10 Years After a Previous Dose[1]
End point description:	
Diphtheria concentrations were determined by neutralization assay; tetanus concentrations were determined by enzyme-linked immunosorbent assay (ELISA).	
End point type	Primary
End point timeframe:	
Day 0 (pre-vaccination) and Day 30 post-vaccination	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	381		
Units: Percentage of subjects				
number (not applicable)				
Anti-Tetanus Pre-vaccination	45	49		
Anti-Tetanus Post-vaccination	100	100		
Anti-Diphtheria Pre-vaccination	74	66		
Anti-Diphtheria Post-vaccination	99	96		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-Pertussis Geometric Mean Concentrations Post-vaccination With ADACEL® 10 Years After a Previous Dose

End point title	Anti-Pertussis Geometric Mean Concentrations Post-vaccination

	With ADACEL® 10 Years After a Previous Dose[2]

End point description:

Post-vaccination geometric mean concentrations (GMCs) for pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM) were determined by enzyme-linked immunosorbent assay (ELISA).

End point type	Primary

End point timeframe:

Day 30 post-vaccination

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	381		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Pertussis Toxoid	116 (105 to 129)	89.2 (80.2 to 99.3)		
Filamentous hemagglutinin	214 (199 to 231)	249 (229 to 272)		
Pertactin	266 (243 to 292)	216 (188 to 247)		
Fimbriae Types 2 and 3	779 (720 to 843)	1015 (894 to 1154)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Achieving Booster Response of Anti-Tetanus and Anti-Diphtheria Following Revaccination With ADACEL® 10 Years After a Previous Dose

End point title	Percentage of Subjects Achieving Booster Response of Anti-Tetanus and Anti-Diphtheria Following Revaccination With ADACEL® 10 Years After a Previous Dose

End point description:

Anti-Diphtheria or anti-Tetanus booster responses were defined as:

Pre-vaccination antibody concentrations of < 0.1 IU/mL and post-vaccination levels ≥ 0.4 IU/mL; or a pre-vaccination antibody concentrations of ≥ 0.1 IU/mL to < 2 IU/mL and a 4-fold rise; or pre-vaccination antibody concentrations of ≥ 2.0 IU/mL and a 2-fold response.

End point type	Other pre-specified

End point timeframe:

Day 30 post-vaccination

End point values	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	381		
Units: Percentage of subjects				
number (not applicable)				
Anti-Tetanus	83	82		
Anti-Diphtheria	86	81		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Achieving Booster Response for Each Anti-Pertussis Antibody Following Revaccination With ADACEL® 10 Years After a Previous Dose

End point title	Percentage of Subjects Achieving Booster Response for Each Anti-Pertussis Antibody Following Revaccination With ADACEL® 10 Years After a Previous Dose

End point description:

Booster response for each anti-pertussis antibody was defined as a post-vaccination antibody concentration:

≥ 4 x the lower limit of quantitation (LLOQ), if the pre-vaccination concentration was < LLOQ; or
≥ 4 x the pre-vaccination antibody concentration, if the pre-vaccination concentration was ≥ LLOQ but < 4 x LLOQ; or
≥ 2 x the pre-vaccination antibody concentration, if the pre-vaccination concentration was ≥ 4 x LLOQ.

End point type	Other pre-specified

End point timeframe:

Day 30 post-vaccination

End point values	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	381		
Units: Percentage of subjects				
number (not applicable)				
Anti-Pertussis Toxoid	88	84		
Filamentous hemagglutinin	88	94		
Pertactin	90	93		
Fimbriae Types 2 and 3	84	93		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Concentrations Against Pertussis Antigens Before and Post-vaccination With ADACEL® 10 Years After a Previous Dose

End point title	Geometric Mean Concentrations Against Pertussis Antigens Before and Post-vaccination With ADACEL® 10 Years After a Previous Dose

End point description:

Post-vaccination geometric mean concentrations (GMCs) against pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM) were determined by enzyme-linked immunosorbent assay (ELISA).

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and Day 30 post-vaccination

End point values	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	381		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Pertussis Toxoid Pre-vaccination	15.1 (12.9 to 17.6)	9.42 (8.2 to 10.8)		
Pertussis Toxoid Post-vaccination	116 (105 to 129)	89.2 (80.2 to 99.3)		
Filamentous hemagglutinin Pre-vaccination	34.8 (31.2 to 38.7)	20 (17.7 to 22.5)		
Filamentous hemagglutinin Post-vaccination	214 (199 to 231)	249 (229 to 272)		
Pertactin Pre-vaccination	28.2 (24.4 to 32.7)	8.54 (7.41 to 9.85)		
Pertactin Post-vaccination	266 (243 to 292)	216 (188 to 247)		
Fimbriae Types 2 and 3 Pre-vaccination	124 (111 to 139)	37.8 (32.7 to 43.7)		
Fimbriae Types 2 and 3 Post-vaccination	779 (720 to 843)	1015 (894 to 1154)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Concentrations Against Tetanus and Diphtheria Antigens Before and Post-vaccination With ADACEL® 10 Years After a Previous Dose

End point title	Geometric Mean Concentrations Against Tetanus and Diphtheria Antigens Before and Post-vaccination With ADACEL® 10 Years After a Previous Dose

End point description:

Post-vaccination geometric mean concentrations (GMCs) for Diphtheria was determined by

neutralization assay; GMCs for Tetanus was determined by enzyme-linked immunosorbent assay (ELISA).

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and Day 30 post-vaccination

End point values	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	381		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Tetanus Pre-vaccination	0.835 (0.754 to 0.924)	0.778 (0.679 to 0.892)		
Anti-Tetanus Post-vaccination	8.79 (8.06 to 9.59)	9.64 (8.73 to 10.7)		
Anti-Diphtheria Pre-vaccination	0.283 (0.235 to 0.341)	0.198 (0.163 to 0.24)		
Anti-Diphtheria Post-vaccination	4.06 (3.49 to 4.71)	2.74 (2.36 to 3.18)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects Reporting at Least One Solicited Injection Site or Systemic Reaction Post-vaccination With ADACEL® 10 Years After a Previous Dose

End point title	Number of Subjects Reporting at Least One Solicited Injection Site or Systemic Reaction Post-vaccination With ADACEL® 10 Years After a Previous Dose

End point description:

Solicited Injection site reactions: Pain, Erythema, and Swelling. Solicited Systemic reactions: Fever (Temperature), Headache, Malaise, and Myalgia.

Grade 3 Injection site reactions: Pain, Incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism; Erythema and Swelling, ≥ 5 cm. Grade 3 Systemic reactions: Fever, > 39.0°C; Headache, Malaise, and Myalgia, Prevents daily activities.

End point type	Other pre-specified

End point timeframe:

Day 0 up to Day 7 post-vaccination

End point values	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	407		
Units: Number of subjects				
number (not applicable)				
Any Pain	309	341		
Grade 3 Pain	9	7		
Any Erythema	81	120		
Grade 3 Erythema	7	7		
Any Swelling	72	94		
Grade 3 Swelling	9	7		
Any Fever	15	20		
Grade 3 Fever	0	0		
Any Headache	142	152		
Grade 3 Headache	6	8		
Any Malaise	103	117		
Grade 3 Malaise	7	8		
Any Myalgia	211	216		
Grade 3 Myalgia	8	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collection from Day 0 (post-vaccination) up to 6 months post-vaccination.

Adverse event reporting additional description:

The diary cards for solicited safety data were not returned for some subjects; the total number for each event therefore represents those with available data for the indicated event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Group 1: Previous Tdap or Tdap-IPV Recipients

Reporting group description:

Subjects received Tdap or Tdap-Inactivated Poliomyelitis Vaccine (IPV) in a previous study (Td9707 or Td9805).

Reporting group title	Group 2: Tdap Vaccine-naive

Reporting group description:

Age-balanced Tdap vaccine-naive subjects who received Tdap vaccine in the study at least 10 years after a previous tetanus, diphtheria and/or pertussis dose.

Serious adverse events	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 361 (0.83%)	1 / 407 (0.25%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 361 (0.28%)	0 / 407 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arnold-Chiari malformation			
subjects affected / exposed	1 / 361 (0.28%)	0 / 407 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			

subjects affected / exposed	0 / 361 (0.00%)	1 / 407 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Vaginal haematoma			
subjects affected / exposed	1 / 361 (0.28%)	0 / 407 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 1: Previous Tdap or Tdap-IPV Recipients	Group 2: Tdap Vaccine-naive	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	309 / 361 (85.60%)	341 / 407 (83.78%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed[1]	142 / 350 (40.57%)	152 / 404 (37.62%)	
occurrences (all)	142	152	
General disorders and administration site conditions			
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed[2]	309 / 352 (87.78%)	341 / 404 (84.41%)	
occurrences (all)	309	341	
Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed[3]	81 / 351 (23.08%)	120 / 404 (29.70%)	
occurrences (all)	81	120	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed[4]	103 / 350 (29.43%)	117 / 404 (28.96%)	
occurrences (all)	103	117	
Injection site Swelling			
alternative assessment type: Systematic			

subjects affected / exposed[5]	72 / 351 (20.51%)	94 / 403 (23.33%)	
occurrences (all)	72	94	
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	14 / 361 (3.88%)	22 / 407 (5.41%)	
occurrences (all)	14	23	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed[6]	211 / 351 (60.11%)	216 / 404 (53.47%)	
occurrences (all)	211	216	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	30 / 361 (8.31%)	23 / 407 (5.65%)	
occurrences (all)	31	23	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which diary cards were returned and for which data were available for the event during the period.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which diary cards were returned and for which data were available for the event during the period.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which diary cards were returned and for which data were available for the event during the period.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which diary cards were returned and for which data were available for the event during the period.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which diary cards were returned and for which data were available for the event during the period.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2008	Provided explanation that the use of contraception was not required after Day 28 post-vaccination; non-standard study procedures, information on the handling of missing data, and non-standard lost to follow-up procedures were deleted; reporting of the vaccine batch number was clarified; and instructions for diary card as well as the calendar dates were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported