Clinical trial results:
Safety Among Adolescents and Adults of Revaccination with Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (ADACEL®) 4 to 5 Years After a Previous Dose

Summary

EudraCT number	2015-005590-20
Trial protocol	Outside EU/EEA
Global end of trial date	12 October 2007

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	18 February 2016

Trial information

Trial identification

Sponsor protocol code	Td518

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00347958
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., 1 570-957-5647, oladayo.oyelola@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur Inc., 1 570-957-5647, oladayo.oyelola@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?	Yes
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	11 November 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 October 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide safety data on revaccination with ADACEL vaccine

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 in this study received a previous dose of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (ADACEL®) vaccine as part of Sanofi Pasteur trial Td501, Td502, or Td505.

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 August 2006
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	United States: 194
Country: Number of subjects enrolled	Canada: 350
Worldwide total number of subjects	544
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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	169

Adults (18-64 years)	368
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 21 August 2006 to 12 April 2007 in 6 clinical centers in the US and 6 clinical centers in Canada.

Pre-assignment

Screening details:

A total of 545 subjects were enrolled and vaccinated in the study. Data on 544 subjects that met the inclusion and exclusion criteria were analyzed and reported. One subject who did not receive Adacel® vaccine in one of the previous studies was excluded from the Safety Analysis Set.

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

Arm title	Adacel® Vaccine Group

Arm description:

Subjects 15 to 69 years of age who received a dose of Adacel vaccine in one of three previous studies (Td501, Td502, or Td505) and revaccinated in Study Td518.

Arm type	Experimental
Investigational medicinal product name	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Adacel®)
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 injection on Day 0.

Number of subjects in period 1	Adacel® Vaccine Group
Started	544
Completed	540
Not completed	4
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Adacel® Vaccine Group
Reporting group description:	
Subjects 15 to 69 years of age who received a dose of Adacel vaccine in one of three previous studies (Td501, Td502, or Td505) and revaccinated in Study Td518.	

Reporting group values	Adacel® Vaccine Group	Total	
Number of subjects	544	544	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	169	169	
Adults (18-64 years)	368	368	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	31.7		
standard deviation	± 15.7	-	
Gender categorical Units: Subjects			
Female	284	284	
Male	260	260	

End points

End points reporting groups

Reporting group title	Adacel® Vaccine Group

Reporting group description:

Subjects 15 to 69 years of age who received a dose of Adacel vaccine in one of three previous studies (Td501, Td502, or Td505) and revaccinated in Study Td518.

Primary: Percentage of Subjects With at Least 1 Solicited Injection Site and Systemic Reaction Post-Vaccination

End point title	Percentage of Subjects With at Least 1 Solicited Injection Site and Systemic Reaction Post-Vaccination[1]

End point description:

Solicited injection site reactions: Pain, Erythema, Swelling. Solicited systemic reactions: Fever (Temperature), Headache, Myalgia, and Malaise. Grade 3 Injection site reactions: Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥5 cm. Grade 3 Solicited systemic reactions: Fever (Temperature), >39.0°C (>102.2°F), Headache, Myalgia, and Malaise, Prevents daily activities.

End point type	Primary

End point timeframe:

Day 0 to Day 14 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	Adacel® Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	544			
Units: Percentage of subjects				
number (not applicable)				
Any Solicited Injection Site Reaction	89			
Any Injection site Pain	88			
Grade 3 Injection site Pain; Post-Injection 3	2			
Any Injection site Erythema	29			
Grade 3 Injection site Erythema	3			
Any Injection site Swelling	26			
Grade 3 Injection site Swelling	3			
Any Fever	7			
Grade 3 Fever	1			
Any Headache	53			
Grade 3 Headache	3			
Any Myalgia	61			
Grade 3 Myalgia	4			
Any Malaise	38			
Grade 3 Malaise	3			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers (GMTs) of Tetanus and Diphtheria Antibodies Pre- and Post-Vaccination

End point title	Geometric Mean Titers (GMTs) of Tetanus and Diphtheria Antibodies Pre- and Post-Vaccination

End point description:

Pre- and post-vaccination GMTs and their 95% confidence intervals for diphtheria were determined by toxin neutralizing testing. Tetanus antibody levels were determined by enzyme-linked immunosorbent assay testing.

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and Day 28 post-vaccination

End point values	Adacel® Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	451			
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Tetanus (IU/mL); Pre-dose	1.41 (1.27 to 1.56)			
Tetanus (IU/mL); Post-dose	9.62 (9.06 to 10.2)			
Diphtheria (IU/mL); no Menactra; Pre-dose	0.133 (0.11 to 0.162)			
Diphtheria (IU/mL); no Menactra; Post-dose	2.17 (1.84 to 2.56)			
Diphtheria (IU/mL); with Menactra; Pre-dose	4.45 (2.77 to 7.15)			
Diphtheria (IU/mL); with Menactra; Post-dose	8.7 (6.59 to 11.5)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers (GMTs) of Pertussis Antibodies Pre- and Post-Vaccination

End point title	Geometric Mean Titers (GMTs) of Pertussis Antibodies Pre- and Post-Vaccination

End point description:

Pre- and post-vaccination GMTs and their 95% confidence intervals for Pertussis were determined by enzyme-linked immunosorbent assay testing.

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and Day 28 post-vaccination

End point values	Adacel® Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	451			
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Pertussis PT (EU/mL); Pre-dose	21.3 (19.4 to 23.5)			
Pertussis PT (EU/mL); Post-dose	104 (97 to 112)			
Pertussis FHA (EU/mL); Pre-dose	34.6 (31.9 to 37.5)			
Pertussis FHA (EU/mL); Post-dose	201 (189 to 215)			
Pertussis PRN (EU/mL); Pre-dose	37.3 (32.7 to 42.6)			
Pertussis PRN (EU/mL); Post-dose	218 (201 to 236)			
Pertussis FIM (EU/mL); Pre-dose	165 (145 to 187)			
Pertussis FIM (EU/mL); Post-dose	749 (697 to 806)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Tetanus and Diphtheria Antibody Titers ≥ 0.1 Pre- and Post-Vaccination with Adacel®

End point title	Percentage of Subjects With Tetanus and Diphtheria Antibody Titers ≥ 0.1 Pre- and Post-Vaccination with Adacel®

End point description:

Seroprotection was defined as tetanus or diphtheria titers ≥ 0.1 after Adacel® vaccination. Tetanus titers were determined by an enzyme-linked immunosorbent assay; diphtheria titers were determined by a toxin neutralization assay.

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccinatino) and Day 28 post-vaccination

End point values	Adacel® Vaccine Group			
Subject group type	Reporting group			
Number of subjects analysed	451			
Units: Percentage of subjects				
number (not applicable)				
Tetanus (IU/mL); Pre-dose	96			

Tetanus (IU/mL); Post-dose	100			
Diphtheria (IU/mL); without Menactra; Pre-dose	61			
Diphtheria (IU/mL); without Menactra; Post-dose	95			
Diphtheria (IU/mL); Menactra; Pre-dose	95			
Diphtheria (IU/mL); Menactra; Post-dose	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from the day of vaccination to 6 months post-vaccination.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Adacel® Vaccine Group

Reporting group description:

Subjects 15 to 69 years of age who received a dose of Adacel vaccine in one of three previous studies (Td501, Td502, or Td505) and revaccinated in Study Td518.

Serious adverse events	Adacel® Vaccine Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 544 (1.29%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour of the appendix			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Pyelonephritis			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 544 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Adacel® Vaccine Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	479 / 544 (88.05%)		
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed[1]	287 / 539 (53.25%)		
occurrences (all)	287		
General disorders and administration site conditions			
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed[2]	472 / 539 (87.57%)		
occurrences (all)	472		
Injection site Erythema			

alternative assessment type: Systematic			
subjects affected / exposed[3]	154 / 539 (28.57%)		
occurrences (all)	154		
Injection site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[4]	138 / 539 (25.60%)		
occurrences (all)	138		
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[5]	35 / 538 (6.51%)		
occurrences (all)	35		
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed[6]	206 / 539 (38.22%)		
occurrences (all)	206		
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	35 / 544 (6.43%)		
occurrences (all)	35		
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed[7]	329 / 539 (61.04%)		
occurrences (all)	329		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	44 / 544 (8.09%)		
occurrences (all)	44		

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 14 days after vaccination; the total number (N) reflects those subjects for which the 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 14 days after vaccination; the total number (N) reflects those subjects for which the 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 14 days after vaccination; the total number (N) reflects those subjects for which the 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 14 days after vaccination; the total number (N) reflects those subjects for which the 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 14 days after vaccination; the total number (N) reflects those subjects for which the 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 14 days after vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[7] - 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 14 days after vaccination; the total number (N) reflects those subjects for which the 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
07 March 2006	Changes were made to indicate the delay in the start of the trial, the increase in age limit for prospective subjects to 15 to ≤69 years of age, the planned locations, changes in personnel, and clarification regarding pregnancy test for all females prior to enrollment.
05 June 2006	Changes included an increase in planned sample size, inclusion of comparative analyses of demographics and safety outcomes from previous studies, collection of sera from all subjects, stratification of enrollment by pre-specified age groups, expanded monitoring time period and reporting procedures for solicited and unsolicited events, revised Informed Consent Form, updated thresholds and fold-rises for pertussis, and the revaccination approach was refined.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported