Clinical trial results:
A pivotal open label, two-arm, multi-center trial to evaluate the safety and immunogenicity of a single dose of Adacel® vaccine in persons 10 to <11 years of age with the intent to extend the licensure of Adacel vaccine for use in children 10 years of age.

Summary

EudraCT number	2015-005627-84
Trial protocol	Outside EU/EEA
Global end of trial date	28 June 2011

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	20 April 2016

Trial information

Trial identification

Sponsor protocol code	Td519

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01311557
WHO universal trial number (UTN)	U1111-1115-6619

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur Inc.
Sponsor organisation address	1 Discovery Drive, Swiftwater, United States, 18370
Public contact	Medical Team Leader, Sanofi Pasteur Inc., 1 570-957-3289, david.greenberg@sanofipasteur.com
Scientific contact	Medical Team Leader, Sanofi Pasteur Inc., 1 570-957-3289, david.greenberg@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 September 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To compare pertussis antibody responses induced by Adacel in persons 10 to <11 years of age to those induced by Adacel in persons 11 to <12 years of age.

2) To compare the booster responses against pertussis antigens induced by Adacel in persons 10 to <11 years of age to those induced by Adacel in persons 11 to <12 years of age.

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:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	07 March 2011
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: 1302
Worldwide total number of subjects	1302
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)	1302

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 07 March 2011 to 19 May 2011 at 36 clinical centers in the United States.

Pre-assignment

Screening details:

A total of 1302 subjects who met all inclusion criteria and none of the exclusion criteria were enrolled and vaccinated.

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	Subjects 10 to <11 Years of Age

Arm description:

Subjects received 1 dose of Adacel® vaccine at Visit 1.

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	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection on Day 0 (Visit 1).

Arm title	Subjects 11 to <12 Years of Age

Arm description:

Subjects received 1 dose of Adacel® vaccine at Visit 1.

Arm type	Active comparator
Investigational medicinal product name	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Adacel®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection on Day 0 (Visit 1).

Number of subjects in period 1	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age
Started	651	651
Completed	646	645
Not completed	5	6
Consent withdrawn by subject	1	2
Serious adverse event	-	1
Lost to follow-up	-	1
Protocol deviation	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Subjects 10 to <11 Years of Age
Reporting group description:	
Subjects received 1 dose of Adacel® vaccine at Visit 1.	
Reporting group title	Subjects 11 to <12 Years of Age
Reporting group description:	
Subjects received 1 dose of Adacel® vaccine at Visit 1.	

Reporting group values	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age	Total
Number of subjects	651	651	1302
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)	651	651	1302
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	10.5	11.4	
standard deviation	± 0.3	± 0.3	-
Gender categorical Units: Subjects			
Female	305	315	620
Male	346	336	682

End points

End points reporting groups

Reporting group title	Subjects 10 to <11 Years of Age
Reporting group description: Subjects received 1 dose of Adacel® vaccine at Visit 1.	
Reporting group title	Subjects 11 to <12 Years of Age
Reporting group description: Subjects received 1 dose of Adacel® vaccine at Visit 1.	

Primary: Summary of Geometric Mean Titers of Anti-Pertussis Titers Following a Single Dose of Adacel® Vaccine

End point title	Summary of Geometric Mean Titers of Anti-Pertussis Titers Following a Single Dose of Adacel® Vaccine
End point description: Anti-Pertussis titers (Pertussis toxoid [PT], Filamentous hemagglutinin [FHA], Pertactin [PRN], Fimbriae types 2 and 3 [FIM] geometric mean titers were assessed by enzyme-linked immunosorbent assay (ELISA).	
End point type	Primary
End point timeframe: Day 30 post-vaccination	

End point values	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	613	608		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Pertussis toxoid	30.1 (28 to 32.4)	32 (29.6 to 34.7)		
Anti-Filamentous hemagglutinin	232 (218 to 247)	225 (211 to 239)		
Anti-Pertactin	464 (426 to 506)	444 (408 to 482)		
Anti-Fimbriae types 2 and 3	477 (413 to 550)	540 (478 to 611)		

Statistical analyses

Statistical analysis title	Non-inferiority (PT; GMT Ratio)
Statistical analysis description: Non-inferiority comparison of post-vaccination anti-Pertussis geometric mean titers between groups.	
Comparison groups	Subjects 10 to <11 Years of Age v Subjects 11 to <12 Years of Age

Number of subjects included in analysis	1221
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	GMT Ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.843
upper limit	1.05

Notes:

[1] - A two-sided 95% confidence interval (CI) was constructed around each of the ratios: Pertussis toxoid (PT) GMT Group 1/GMT Group 2. The GMT hypothesis was supported by the data if the lower bound of the calculated 95% CI was > 0.67. This was the equivalent of testing the null hypothesis using a one-sided type I error rate of 0.025. The post-vaccination anti-PT GMTs in Adacel recipients in Group 1 were non-inferior to the post-vaccination GMTs in Adacel recipients in Group 2.

Statistical analysis title	Non-inferiority (FHA; GMT Ratio)

Statistical analysis description:

Non-inferiority comparison of post-vaccination anti-Filamentous hemagglutinin geometric mean titers between groups.

Comparison groups	Subjects 10 to <11 Years of Age v Subjects 11 to <12 Years of Age
Number of subjects included in analysis	1221
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	GMT Ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.944
upper limit	1.13

Notes:

[2] - A two-sided 95% confidence interval (CI) was constructed around each of the ratios: Filamentous hemagglutinin (FHA) GMT Group 1/GMT Group 2. The GMT hypothesis was supported by the data if the lower bound of the calculated 95% CI was > 0.67. This was the equivalent of testing the null hypothesis using a one-sided type I error rate of 0.025. The post-vaccination anti-FHA GMTs in Adacel recipients in Group 1 were non-inferior to the post-vaccination GMTs in Adacel recipients in Group 2.

Statistical analysis title	Non-inferiority (PRN; GMT Ratio)

Statistical analysis description:

Non-inferiority comparison of post-vaccination anti-Pertactin geometric mean titers between groups.

Comparison groups	Subjects 10 to <11 Years of Age v Subjects 11 to <12 Years of Age
Number of subjects included in analysis	1221
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	GMT Ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.928
upper limit	1.18

Notes:

[3] - A two-sided 95% confidence interval (CI) was constructed around each of the ratios: Pertactin (PRN) GMT Group 1/GMT Group 2. The GMT hypothesis was supported by the data if the lower bound of the calculated 95% CI was > 0.67. This was the equivalent of testing the null hypothesis using a one-sided type I error rate of 0.025. The post-vaccination anti-PRN GMTs in Adacel recipients in Group 1 were non-inferior to the post-vaccination GMTs in Adacel recipients in Group 2.

Statistical analysis title	Non-inferiority (FIM; GMT Ratio)

Statistical analysis description:

Non-inferiority comparison of post-vaccination anti-Fimbriae types 2 and 3 geometric mean titers between groups.

Comparison groups	Subjects 10 to <11 Years of Age v Subjects 11 to <12 Years of Age
Number of subjects included in analysis	1221
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	GMT Ratio
Point estimate	0.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.731
upper limit	1.06

Notes:

[4] - A two-sided 95% confidence interval (CI) was constructed around each of the ratios: Fimbriae types 2 and 3 (FIM) GMT Group 1/GMT Group 2. The GMT hypothesis was supported by the data if the lower bound of the calculated 95% CI was > 0.67. This was the equivalent of testing the null hypothesis using a one-sided type I error rate of 0.025. The post-vaccination anti-FIM GMTs in Adacel recipients in Group 1 were non-inferior to the post-vaccination GMTs in Adacel recipients in Group 2.

Primary: Summary of Anti-Pertussis Booster Response Following a Booster Dose of Adacel® Vaccine

End point title	Summary of Anti-Pertussis Booster Response Following a Booster Dose of Adacel® Vaccine[5]

End point description:

Anti-Pertussis booster responses were assessed by enzyme-linked immunosorbent assay (ELISA). For pertusiss antigens (Pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae types 2 and 3 [FIM], a booster response rate was defined as a four-fold increase in pre- to post-vaccination titers for subjects with pre-vaccination titers ≤ 93 ELISA Unit (EU)/mL for PT, ≤ 170 EU/mL for FHA, ≤ 115 EU/mL for PRN, and ≤ 285 EU/mL for FIM. If the pre-vaccination titers were > 93 EU/mL for PT, > 170 EU/mL for FHA, > 115 EU/mL for PRN, or > 285 EU/mL for FIM then a two-fold increase in the antibody titer was defined as a booster response.

End point type	Primary

End point timeframe:

30 days post-vaccination

Notes:

[5] - 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	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	613	608		
Units: Percentage of subjects				
number (not applicable)				
Anti-Pertussis toxoid	56.7	56.1		

Anti-Filamentous hemagglutinin	84.2	84.8		
Anti-Pertactin	98	97.5		
Anti-Fimbriae types 2 and 3	93.7	97.1		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Anti-Tetanus and Anti-Diphtheria Booster Response Following a Booster Dose of Adacel® Vaccine

End point title	Summary of Anti-Tetanus and Anti-Diphtheria Booster Response Following a Booster Dose of Adacel® Vaccine[6]

End point description:

Anti-Tetanus booster responses were assessed by enzyme-linked immunosorbent assay (ELISA). Anti-Diphtheria booster responses were assessed by a toxin neutralization test. Booster response rate was defined as a four-fold increase in pre- to post-vaccination titers for subjects with pre-vaccination titers ≤ 2.56 EU/mL for diphtheria and ≤ 2.7 EU/mL for tetanus. If the pre-vaccination titers were > 2.56 EU/mL for diphtheria or > 2.7 EU/mL for tetanus, then a two-fold increase in response rate was defined as a booster response.

End point type	Primary

End point timeframe:

30 days post-vaccination

Notes:

[6] - 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	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	613	608		
Units: Percentage of subjects				
number (not applicable)				
Anti-Tetanus	98.5	98.8		
Anti-Diphtheria	97.7	98		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroprotection To Tetanus and Diphtheria Following a Single Dose of Adacel® Vaccine

End point title	Percentage of Subjects With Seroprotection To Tetanus and Diphtheria Following a Single Dose of Adacel® Vaccine

End point description:

Anti-tetanus seroprotection rates were assessed by enzyme-linked immunosorbent assay (ELISA). Anti-diphtheria seroprotection was assessed by toxin neutralization test. Seroprotection was defined as post-vaccination antibody titers ≥ 0.1 IU/mL.

End point type	Secondary

End point timeframe:

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

End point values	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	613	608		
Units: Percentage of subjects				
number (not applicable)				
Anti-Tetanus (Pre-vaccination)	90.3	91.2		
Anti-Tetanus (Post-vaccination)	99.7	100		
Anti-Diphtheria (Pre-vaccination)	83.6	75.9		
Anti-Diphtheria (Post-vaccination)	99.7	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Anti-Pertussis Geometric Mean Titers Before and Post-vaccination With a Single Dose of Adacel® Vaccine

End point title	Summary of Anti-Pertussis Geometric Mean Titers Before and Post-vaccination With a Single Dose of Adacel® Vaccine

End point description:

Anti-Pertussis titers (Pertussis toxoid [PT], Filamentous hemagglutinin [FHA], Pertactin [PRN], Fimbriae types 2 and 3 [FIM]) geometric mean titers were assessed by enzyme-linked immunosorbent assay (ELISA).

End point type	Secondary

End point timeframe:

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

End point values	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	613	608		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Pertussis toxoid; Day 0	4.96 (4.54 to 5.42)	4.85 (4.41 to 5.34)		
Anti-Pertussis toxoid; Day 30	30.1 (28 to 32.4)	32 (29.6 to 34.7)		
Anti-Filamentous hemagglutinin; Day 0	22.1 (20.1 to 24.2)	20.3 (18.5 to 22.3)		
Anti-Filamentous hemagglutinin; Day 30	232 (218 to 247)	225 (211 to 239)		

Anti-Pertactin; Day 0	15.6 (14.2 to 17.1)	14.8 (13.5 to 16.2)		
Anti-Pertactin; Day 30	464 (426 to 506)	444 (408 to 482)		
Anti-Fimbriae types 2 and 3; Day 0	6.77 (6.05 to 7.57)	7.07 (6.33 to 7.89)		
Anti-Fimbriae types 2 and 3; Day 30	477 (413 to 550)	540 (478 to 611)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following A Single Dose of Adacel® Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions Following A Single Dose of Adacel® Vaccine

End point description:

Solicited injection-site: Pain, Erythema and Swelling. Solicited systemic reactions: Fever, Headache, Malaise, and Myalgia.

Grade 3 Solicited Injection-site reactions: Pain, Incapacitating, unable to perform usual activities; Erythema and Swelling, ≥ 50 mm. Grade 3 Solicited systemic reactions: Fever, ≥ 39.0°C or ≥ 102.1°F; Headache, Malaise, and Myalgia, Significant, prevents daily activity.

End point type	Secondary

End point timeframe:

Day 0 up to Day 7 post-vaccination

End point values	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	650	649		
Units: Percentage of subjects				
number (not applicable)				
Injection-site Pain	80.9	80.9		
Grade 3 Injection-site Pain	3.3	2.2		
Injection-site Erythema	39.4	38.4		
Grade 3 Injection-site Erythema	7.9	7.4		
Injection-site Swelling	35.2	33.5		
Grade 3 Injection-site Swelling	8.4	7.3		
Fever	1.6	0.6		
Grade 3 Fever	0	0.2		
Headache	33.1	37.6		
Grade 3 Headache	2	1.9		
Malaise	26.2	29.3		
Grade 3 Malaise	1.9	2.8		
Myalgia	49.1	56.4		
Grade 3 Myalgia	3.3	1.7		

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 Day 0 up to Day 30 post-vaccination.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13

Reporting groups	
Reporting group title	Subjects 10 to <11 Years of Age
Reporting group description:	
Subjects received 1 dose of Adacel® vaccine on Day 0 (Visit 1).	
Reporting group title	Subjects 11 to <12 Years of Age
Reporting group description:	
Subjects received 1 dose of Adacel® vaccine on Day 0 (Visit 1).	

Serious adverse events	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 650 (0.00%)	1 / 649 (0.15%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 650 (0.00%)	1 / 649 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Subjects 10 to <11 Years of Age	Subjects 11 to <12 Years of Age	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	521 / 650 (80.15%)	522 / 649 (80.43%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	213 / 650 (32.77%)	243 / 649 (37.44%)	
occurrences (all)	213	243	

General disorders and administration site conditions			
Injection-site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed	254 / 650 (39.08%)	248 / 649 (38.21%)	
occurrences (all)	254	248	
Injection-site Pain			
alternative assessment type: Systematic			
subjects affected / exposed	521 / 650 (80.15%)	522 / 649 (80.43%)	
occurrences (all)	521	522	
Injection-site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	227 / 650 (34.92%)	216 / 649 (33.28%)	
occurrences (all)	227	216	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	169 / 650 (26.00%)	189 / 649 (29.12%)	
occurrences (all)	169	189	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	316 / 650 (48.62%)	364 / 649 (56.09%)	
occurrences (all)	316	364	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2011	The planned trial period was revised; booster responses (tetanus and diphtheria) were updated as primary objectives; non-inferiority analysis of booster response rates was added as a primary endpoint; booster response rates (tetanus and diphtheria) were updated to primary endpoints; primary hypothesis was revised; planned sample size and schedule of procedures were amended to include a time window for post-vaccination and recording of safety data, respectively; exclusion criteria were modified; and statistical and assessment methods were revised.
11 March 2011	Exclusion criterion was modified to improve clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported