Clinical trial results:
One-, Three-, Five- and Ten-Year Data on the Long-Term Immunogenicity of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) in Adolescents 11–14 Years of Age

Summary

EudraCT number	2015-005844-32
Trial protocol	Outside EU/EEA
Global end of trial date	20 February 2009

Results information

Result version number	v1 (current)
This version publication date	16 April 2016
First version publication date	16 April 2016

Trial information

Trial identification

Sponsor protocol code	Td9805-LT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur Limited
Sponsor organisation address	1755 Steeles Ave. West, Toronto, Canada, M2R 3T4
Public contact	Director, Clinical Development, Sanofi Pasteur Limited, 1 416-667-2273, Miggi.Tomovici@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur Limited, 1 416-667-2273, Miggi.Tomovici@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	20 February 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the antibody levels for tetanus, diphtheria and pertussis at 1 year, 3 years, 5 years and 10 years after vaccination with Tdap Vaccine.

Protection of trial subjects:

Subjects were vaccinated in a previous study, Td9805. No vaccination was administered as part of this long-term immunogenicity follow-up study.

Background therapy:

In Td9805, subjects were randomized to receive either Tdap followed by Hepatitis B vaccine one month later (Group 1) or Tdap and Hepatitis B vaccines concomitantly (Group 2). For the long-term immunogenicity studies, subjects in both groups were recalled for serology at 1, 3, 5, and 10 years post-vaccination.

Evidence for comparator:

Not applicable

Actual start date of recruitment	17 November 1999
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: 267
Worldwide total number of subjects	267
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)	193
Adolescents (12-17 years)	74
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study subjects were enrolled from 17 November 1999 to 20 February 2009 at 1 clinic center in Canada.

Pre-assignment

Screening details:

A total of 267 subjects who met all inclusion and none of the exclusion criteria were enrolled in the long-term immunogenicity study.

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; Tdap/Hepatitis

Arm description:

Subjects received Tdap at month 0 and Hepatitis B at months 1, 2, and 7.

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 at Month 0.

Investigational medicinal product name	Hepatitis B Vaccine (Recombivax HB®)
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 each at Months 1, 7, and 7.

Arm title	Group 2; Tdap and Hepatitis

Arm description:

Subjects received Tdap and Hepatitis B at Month 0 and Hepatitis B at Months 1 and 6.

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 at Month 0.

Investigational medicinal product name	Hepatitis B Vaccine (Recombivax HB®)
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 at Month 0 concurrent with Tdap and 1 injection each at Months 1 and 6.

Number of subjects in period 1	Group 1; Tdap/Hepatitis	Group 2; Tdap and Hepatitis
Started	135	132
Completed	74	76
Not completed	61	56
Lost to follow-up	61	56

Baseline characteristics

Reporting groups	
Reporting group title	Group 1; Tdap/Hepatitis
Reporting group description:	
Subjects received Tdap at month 0 and Hepatitis B at months 1, 2, and 7.	
Reporting group title	Group 2; Tdap and Hepatitis
Reporting group description:	
Subjects received Tdap and Hepatitis B at Month 0 and Hepatitis B at Months 1 and 6.	

Reporting group values	Group 1; Tdap/Hepatitis	Group 2; Tdap and Hepatitis	Total
Number of subjects	135	132	267
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)	93	100	193
Adolescents (12-17 years)	42	32	74
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	11.39	11.32	
standard deviation	± 0.23	± 0.23	-
Gender categorical Units: Subjects			
Female	62	61	123
Male	73	71	144

End points

End points reporting groups

Reporting group title	Group 1; Tdap/Hepatitis
Reporting group description:	
Subjects received Tdap at month 0 and Hepatitis B at months 1, 2, and 7.	
Reporting group title	Group 2; Tdap and Hepatitis
Reporting group description:	
Subjects received Tdap and Hepatitis B at Month 0 and Hepatitis B at Months 1 and 6.	

Primary: Percentage of Subjects with Seroprotection to Tetanus and Diphtheria Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point title	Percentage of Subjects with Seroprotection to Tetanus and Diphtheria Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently[1]

End point description:

Anti-Diphtheria antibody responses were measured using a micrometabolic inhibition test. Anti-Tetanus antibody responses were measured using an enzyme-linked immunosorbent assay (ELISA). Seroprotection was defined as post-vaccination antibody titers ≥ 0.01 IU/mL for Diphtheria and ≥ 0.01 EU/mL for Tetanus.

End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and 1 month and 1, 3, 5, and 10 years 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 vaccine groups from the primary series for the long term follow-up period.

End point values	Group 1; Tdap/Hepatitis	Group 2; Tdap and Hepatitis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of subjects				
number (not applicable)				
Diphtheria; Pre-vaccination	100	100		
Diphtheria; 1 month Post-vaccination	100	100		
Diphtheria; 1 year Post-vaccination	100	100		
Diphtheria; 3 years Post-vaccination	100	100		
Diphtheria; 5 years Post-vaccination	100	100		
Diphtheria; 10 years Post-vaccination	100	98.7		
Tetanus; Pre-vaccination	100	98.5		
Tetanus; 1 month Post-vaccination	100	100		
Tetanus; 1 year Post-vaccination	100	100		
Tetanus; 3 years Post-vaccination	100	100		
Tetanus; 5 years Post-vaccination	100	100		
Tetanus; 10 years Post-vaccination	100	100		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects with Seroprotection to Tetanus and Diphtheria Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point title	Percentage of Subjects with Seroprotection to Tetanus and Diphtheria Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point description:

Anti-Diphtheria antibody responses were measured using a micrometabolic inhibition test. Anti-Tetanus antibody responses were measured using an enzyme-linked immunosorbent assay (ELISA). Seroprotection was defined as post-vaccination antibody titers ≥ 0.1 IU/mL for Diphtheria and ≥ 0.1 EU/mL for Tetanus.

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and 1 month and 1, 3, 5, and 10 years post-vaccination

End point values	Group 1; Tdap/Hepatitis	Group 2; Tdap and Hepatitis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of subjects				
number (not applicable)				
Diphtheria; Pre-vaccination	85.9	79.5		
Diphtheria; 1 month Post-vaccination	100	100		
Diphtheria; 1 year Post-vaccination	100	97.4		
Diphtheria; 3 years Post-vaccination	100	97.4		
Diphtheria; 5 years Post-vaccination	76.7	74		
Diphtheria; 10 years Post-vaccination	73	60		
Tetanus; Pre-vaccination	100	97.7		
Tetanus; 1 month Post-vaccination	100	100		
Tetanus; 1 year Post-vaccination	100	100		
Tetanus; 3 years Post-vaccination	100	100		
Tetanus; 5 years Post-vaccination	100	100		
Tetanus; 10 years Post-vaccination	98.6	100		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Geometric Mean Titers of Antibodies for Diphtheria and Tetanus Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point title	Summary of Geometric Mean Titers of Antibodies for Diphtheria and Tetanus Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point description:

Anti-Diphtheria antibody responses were measured using a micrometabolic inhibition test. Anti-Tetanus antibody responses were measured using an enzyme-linked immunosorbent assay (ELISA).

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and 1 month and 1, 3, 5, and 10 years post-vaccination

End point values	Group 1; Tdap/Hepatitis	Group 2; Tdap and Hepatitis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Diphtheria; Pre-vaccination	0.38 (0.31 to 0.46)	0.3 (0.24 to 0.38)		
Diphtheria; 1 month Post-vaccination	8.13 (7.01 to 9.43)	6.65 (5.53 to 8)		
Diphtheria; 1 year Post-vaccination	0.97 (0.82 to 1.16)	1.01 (0.82 to 1.24)		
Diphtheria; 3 years Post-vaccination	0.84 (0.7 to 1.02)	0.75 (0.59 to 0.96)		
Diphtheria; 5 years Post-vaccination	0.2 (0.17 to 0.24)	0.18 (0.14 to 0.23)		
Diphtheria; 10 years Post-vaccination	0.22 (0.17 to 0.29)	0.19 (0.14 to 0.27)		
Tetanus; Pre-vaccination	1.19 (1.05 to 1.35)	0.9 (0.76 to 1.06)		
Tetanus; 1 month Post-vaccination	28.52 (24.9 to 32.67)	25.18 (22.04 to 28.77)		
Tetanus; 1 year Post-vaccination	4.88 (3.99 to 5.98)	5.82 (5.02 to 6.75)		
Tetanus; 3 years Post-vaccination	2.48 (2.13 to 2.89)	2.89 (2.56 to 3.27)		
Tetanus; 5 years Post-vaccination	2.69 (2.23 to 3.24)	2.69 (2.29 to 3.17)		
Tetanus; 10 years Post-vaccination	1.14 (0.9 to 1.45)	1.28 (1.06 to 1.54)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Geometric Mean Titers of Antibodies for Pertussis Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point title	Summary of Geometric Mean Titers of Antibodies for Pertussis Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point description:

Anti-Pertussis (Pertussis toxoid, Filamentous hemagglutinin, Fimbriae types 2 and 3, and Pertactin) antibody responses were measured using an indirect enzyme-linked immunosorbent assay (ELISA).

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and 1 month and 1, 3, 5, and 10 years post-vaccination

End point values	Group 1; Tdap/Hepatitis	Group 2; Tdap and Hepatitis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Pertussis toxoid; Pre-vaccination	11.79 (9.29 to 14.95)	10.49 (8.4 to 13.09)		
Pertussis toxoid; 1 month Post-vaccination	163.6 (136.19 to 196.52)	143.47 (119.12 to 172.8)		
Pertussis toxoid; 1 year Post-vaccination	54.79 (42.65 to 70.4)	48.85 (37.54 to 63.56)		
Pertussis toxoid; 3 years Post-vaccination	34.69 (25.78 to 46.68)	38.45 (27.54 to 53.68)		
Pertussis toxoid; 5 years Post-vaccination	29.36 (22.23 to 38.78)	27.07 (20.87 to 35.1)		
Pertussis toxoid; 10 years Post-vaccination	13.76 (9.15 to 20.7)	11.19 (7.95 to 15.77)		
Filamentous hemagglutinin; Pre-vaccination	32.07 (26.2 to 39.24)	34.03 (28.2 to 41.06)		
Filamentous hemagglutinin;1 month Post-vaccination	425.81 (362.52 to 500.15)	369.06 (315.69 to 431.44)		
Filamentous hemagglutinin; 1 year Post-vaccination	118.59 (94.26 to 149.21)	96.28 (77.9 to 119)		
Filamentous hemagglutinin;3 years Post-vaccination	84.18 (67.83 to 104.47)	77.18 (61.63 to 96.65)		
Filamentous hemagglutinin;5 years Post-vaccination	69.96 (56.97 to 85.9)	59.51 (49.87 to 71.02)		
Filamentous hemagglutinin;10 year Post-vaccination	41.91 (32.58 to 53.91)	38.96 (31.09 to 48.81)		
Pertactin; Pre-vaccination	8.7 (6.88 to 11)	8.02 (6.34 to 10.15)		
Pertactin; 1 month Post-vaccination	272.94 (218.43 to 341.06)	298.73 (242.89 to 367.41)		

Pertactin; 1 year Post-vaccination	75.29 (55.49 to 102.17)	76.59 (57.4 to 102.2)		
Pertactin; 3 years Post-vaccination	53.75 (40.18 to 71.91)	55.06 (42.28 to 71.7)		
Pertactin; 5 years Post-vaccination	42.73 (33.38 to 54.71)	49.26 (38.91 to 62.38)		
Pertactin; 10 years Post-vaccination	27.68 (21.02 to 36.43)	25.29 (19.31 to 33.12)		
Fimbriae; Pre-vaccination	45.58 (36.92 to 56.27)	45.39 (36.74 to 56.07)		
Fimbriae; 1 month Post-vaccination	998.38 (834.57 to 1194.3)	1124 (939.24 to 1345.1)		
Fimbriae; 1 year Post-vaccination	325.31 (259.6 to 407.65)	324.38 (251.33 to 418.67)		
Fimbriae; 3 years Post-vaccination	179.93 (144.63 to 223.84)	184.24 (146.04 to 232.42)		
Fimbriae; 5 years Post-vaccination	157.84 (128.35 to 194.11)	157.74 (126.65 to 196.46)		
Fimbriae; 10 years Post-vaccination	120.28 (95.98 to 150.72)	112.76 (88.19 to 144.18)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects with Seropostivity to Pertussis Antigens Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point title	Percentage of Subjects with Seropostivity to Pertussis Antigens Following Vaccination with Either Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (Tdap) Vaccine or Tdap and Hepatitis B Vaccines Given Concurrently

End point description:

Anti-Pertussis (Pertussis toxoid, Filamentous hemagglutinin, Fimbriae types 2 and 3, and Pertactin) antibody responses were measured using an indirect enzyme-linked immunosorbent assay (ELISA). Seropositivity rates, defined as the percentage of subjects with ≥ 1, 2, and 4 times the lower limit of quantitation (LLOQ) for the pertussis antigens, was 5 EU/mL for Pertussis toxoid, 3 EU/mL for Filamentous hemagglutinin and Pertactin, 17 EU/mL for Fimbriae types 2 and 3 for 1 month and 1, 3, and 5 years; 4 EU/mL for Pertussis toxoid, Fimbriae types 2 and 3, and Pertactin, and 3 EU/mL for Filamentous hemagglutinin for the 10 years.

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and 1 month and 1, 3, 5, and 10 years post-vaccination

End point values	Group 1; Tdap/Hepatitis	Group 2; Tdap and Hepatitis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	132		
Units: Percentage of subjects				
number (not applicable)				
Pertussis toxoid; Pre-vaccination	68.1	68.2		
Pertussis toxoid; 1 month Post-vaccination	99.3	99.2		
Pertussis toxoid; 1 year Post-vaccination	97.4	97.4		
Pertussis toxoid; 3 years Post-vaccination	92	93.5		
Pertussis toxoid; 5 years Post-vaccination	94.2	92.4		
Pertussis toxoid; 10 years Post-vaccination	70.6	69		
Filamentous hemagglutinin; Pre-vaccination	94.8	97.7		
Filamentous hemagglutinin;1 month Post-vaccination	100	100		
Filamentous hemagglutinin; 1 year Post-vaccination	98.7	100		
Filamentous hemagglutinin;3 years Post-vaccination	98.9	98.7		
Filamentous hemagglutinin;5 years Post-vaccination	100	100		
Filamentous hemagglutinin;10 year Post-vaccination	100	100		
Pertactin; Pre-vaccination	76.3	75		
Pertactin; 1 month Post-vaccination	100	100		
Pertactin; 1 year Post-vaccination	97.4	98.7		
Pertactin; 3 years Post-vaccination	96.6	98.7		
Pertactin; 5 years Post-vaccination	98.8	98.7		
Pertactin; 10 years Post-vaccination	95.9	93.4		
Fimbriae; Pre-vaccination	77.8	75.8		
Fimbriae; 1 month Post-vaccination	100	100		
Fimbriae; 1 year Post-vaccination	100	100		
Fimbriae; 3 years Post-vaccination	97.7	98.7		
Fimbriae; 5 years Post-vaccination	97.7	98.7		
Fimbriae; 10 years Post-vaccination	100	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

This was a long-term immunogenicity follow-up study of patients that participated in a previous study, Td9805. No vaccines were administered in this study and adverse event data were also not collected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: This was a long-term immunogenicity follow-up study of patients that participated in a previous study, Td9805. No vaccines were administered in this study and adverse event data were also not collected.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2001	Details regarding the planned long-term follow-up serology studies were included which also involved the collection of additional blood samples at 1, 3, 5, and 10 years post-vaccination.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported