Clinical trial results:
Safety and Immunogenicity of Tdap Vaccine Compared to DTaP vaccine as Fifth Dose Booster in Children 4 to 6 Years of Age

Summary

EudraCT number	2015-003500-23
Trial protocol	Outside EU/EEA
Global end of trial date	16 October 2009

Results information

Result version number	v1 (current)
This version publication date	19 February 2016
First version publication date	19 February 2016

Trial information

Trial identification

Sponsor protocol code	Td517

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00467519
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	Medical Team Leader, Scientific and Medical Affairs Department, Sanofi Pasteur Inc., 1 570-957-5433, vitali.pool@sanofipasteur.com
Scientific contact	Medical Team Leader, Scientific and Medical Affairs Department, Sanofi Pasteur Inc., 1 570-957-5433, vitali.pool@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	16 December 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 October 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To compare the immune responses of Tdap to DTaP vaccine when each is administered as a 5th dose to DAPTACEL- or Pentacel-primed subjects and given concurrently, but in a separate arm from poliomyelitis, measles, mumps, rubella (MMR) and varicella vaccines to children aged 4 to 6 years, as measured by seroprotection rates (≥ 0.1 IU/mL), serothreshold rates (≥ 1.0 IU/mL) and booster response rates for diphtheria and tetanus.

2) To compare immune responses of Tdap to DTaP vaccine when administered as a 5th dose to DAPTACEL- or Pentacel-primed subjects and given concurrently, but in a separate arm from poliomyelitis, measles, mumps, rubella (MMR) and varicella vaccines to children aged 4 to 6 years, as measured by booster response rates and GMTs for pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN] and fimbriae types 2 and 3 [FIM]).

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	13 April 2007
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: 18
Country: Number of subjects enrolled	United States: 1024
Worldwide total number of subjects	1042
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)	1042
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:

Subjects were enrolled from 13 April 2007 to 16 October 2009 in 42 clinical centers in the United States and 1 clinical center in Canada.

Pre-assignment

Screening details:

A total of 1042 subjects who met the inclusion and exclusion criteria were enrolled and vaccinated.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

The subject, Investigator, study site and sponsor personnel were blinded to the vaccine administered, except for an unblinded study nurse who administered the vaccines and the site monitors. To maintain the blind, the unblinded nurse did not participate in the collection of safety data. The randomization code was generated by the Sponsor and was kept in a secured filed at the Sponsor's site. The Investigator and health authorities could request code breaking for an SAE, if required, by protocol.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tdap Vaccine Group

Arm description:

Subjects 4 to 6 years of age who had previously received 4 doses of Pentacel or DAPTACEL received a booster dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap).

Arm type	Experimental
Investigational medicinal product name	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap)
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.

Investigational medicinal product name	Poliovirus Vaccine Inactivated (IPV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

0.5 mL, intramuscular or subcutaneous, 1 injection on Day 0.

Investigational medicinal product name	Measles, Mumps and Rubella Virus Vaccine Live (MMR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, administered as either 1 injection alone in combination with varicella vaccine

Investigational medicinal product name	Varicella Virus Vaccine Live (Varicella vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, administered as either 1 injection alone or in combination with MMR vaccine.

Arm title	DTaP Vaccine Group

Arm description:

Subjects 4 to 6 years of age who had previously received 4 doses of Pentacel or DAPTACEL received a booster dose of diphtheria, tetanus and acellular pertussis vaccine (DTaP).

Arm type	Active comparator
Investigational medicinal product name	Diphtheria, Tetanus, and Acellular Pertussis Vaccine (DTaP)
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.

Investigational medicinal product name	Poliovirus Vaccine Inactivated (IPV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

0.5 mL, intramuscular or subcutaneous, 1 injection on Day 0.

Investigational medicinal product name	Measles, Mumps and Rubella Virus Vaccine Live (MMR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, administered as either 1 injection alone in combination with varicella vaccine

Investigational medicinal product name	Varicella Virus Vaccine Live (Varicella vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous, administered as either 1 injection alone or in combination with MMR vaccine.

Number of subjects in period 1	Tdap Vaccine Group	DTaP Vaccine Group
Started	531	511
Completed	517	488
Not completed	14	23
Consent withdrawn by subject	4	10
Lost to follow-up	2	9

Protocol deviation	8	4

Baseline characteristics

Reporting groups	
Reporting group title	Tdap Vaccine Group
Reporting group description:	
Subjects 4 to 6 years of age who had previously received 4 doses of Pentacel or DAPTACEL received a booster dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap).	
Reporting group title	DTaP Vaccine Group
Reporting group description:	
Subjects 4 to 6 years of age who had previously received 4 doses of Pentacel or DAPTACEL received a booster dose of diphtheria, tetanus and acellular pertussis vaccine (DTaP).	

Reporting group values	Tdap Vaccine Group	DTaP Vaccine Group	Total
Number of subjects	531	511	1042
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)	531	511	1042
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	4.45	4.42	
standard deviation	± 0.48	± 0.47	-
Gender categorical			
Units: Subjects			
Female	275	244	519
Male	256	267	523

End points

End points reporting groups

Reporting group title	Tdap Vaccine Group
Reporting group description:	
Subjects 4 to 6 years of age who had previously received 4 doses of Pentacel or DAPTACEL received a booster dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap).	
Reporting group title	DTaP Vaccine Group
Reporting group description:	
Subjects 4 to 6 years of age who had previously received 4 doses of Pentacel or DAPTACEL received a booster dose of diphtheria, tetanus and acellular pertussis vaccine (DTaP).	

Primary: Percentage of Subjects Who Achieved Seroprotection at Baseline and 30 Days Post-vaccination for Diphtheria and Tetanus at ≥ 0.1 IU/mL Level

End point title	Percentage of Subjects Who Achieved Seroprotection at Baseline and 30 Days Post-vaccination for Diphtheria and Tetanus at ≥ 0.1 IU/mL Level[1]
End point description:	
Seroprotection rate of level ≥ 0.1 IU/mL was defined as antibody concentrations ≥ 0.1 IU/mL. Diphtheria titers were determined by toxin neutralization assay; tetanus titers were determined by enzyme-linked immunosorbent assay (ELISA).	
End point type	Primary
End point timeframe:	
Pre-dose and 30 days 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	Tdap Vaccine Group	DTaP Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	426		
Units: Percentage of subjects				
number (not applicable)				
Diphtheria (IU/mL); Pre-dose	65	69		
Diphtheria (IU/mL); Post-dose	100	100		
Tetanus (IU/mL); Pre-dose	81	85		
Tetanus (IU/mL); Post-dose	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Who Achieved Serothreshold at Baseline and 30 Days Post-vaccination for Diphtheria and Tetanus at Level ≥ 1.0 IU/mL

End point title	Percentage of Subjects Who Achieved Serothreshold at Baseline and 30 Days Post-vaccination for Diphtheria and

	Tetanus at Level ≥ 1.0 IU/mL[2]

End point description:

Serothreshold rate at level ≥ 1.0 IU/mL was defined as antibody concentrations ≥ 1.0 IU/mL. Diphtheria titers were determined by toxin neutralization assay; tetanus titers were determined by enzyme-linked immunosorbent assay (ELISA).

End point type	Primary

End point timeframe:

Pre-dose and 30 days 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	Tdap Vaccine Group	DTaP Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	426		
Units: Percentage of subjects				
number (not applicable)				
Diphtheria (IU/mL); Pre-dose	4	7		
Diphtheria (IU/mL); Post-dose	99	100		
Tetanus (IU/mL); Pre-dose	11	12		
Tetanus (IU/mL); Post-dose	97	98		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Who Demonstrated Booster Response at 30 Days Post-vaccination for Pertussis

End point title	Percentage of Subjects Who Demonstrated Booster Response at 30 Days Post-vaccination for Pertussis[3]

End point description:

Booster response was defined as post-titer ≥ 0.4 IU/mL and pre-titer < 0.1 IU/mL, or Post-/Pre-titer ≥ 4 increase and pre-titer ≥ 0.1 IU/mL but < 2 IU/mL, or Post-/Pre-titer ≥ 2 increase and pre-titer ≥ 2 IU/mL.

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

End point type	Primary

End point timeframe:

30 days post-vaccination

Notes:

[3] - 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	Tdap Vaccine Group	DTaP Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	423		
Units: Percentage of subjects				
number (not applicable)				
Pertussis Toxoid (EU/mL)	88	94		
Filamentous hemagglutinin (EU/mL)	92	89		
Pertactin (EU/mL)	92	95		
Fimbriae types 2 and 3 (EU/mL)	95	94		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Who Demonstrated Booster Response at 30 Days Post-vaccination for Diphtheria and Tetanus

End point title	Percentage of Subjects Who Demonstrated Booster Response at 30 Days Post-vaccination for Diphtheria and Tetanus[4]

End point description:

Booster response was defined as post-titer ≥ 0.4 IU/mL and pre-titer < 0.1 IU/mL, or Post-/Pre-titer ≥ 4 increase and pre-titer ≥ 0.1 IU/mL but < 2 IU/mL, or Post-/Pre-titer ≥ 2 increase and pre-titer ≥ 2 IU/mL.

Post-vaccination titers for diphtheria was determined by neutralization assay; tetanus titers were determined by enzyme-linked immunosorbent assay (ELISA).

End point type	Primary

End point timeframe:

30 days post-vaccination

Notes:

[4] - 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	Tdap Vaccine Group	DTaP Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	426		
Units: Percentage of subjects				
number (not applicable)				
Diphtheria (IU/mL)	99	99		
Tetanus (IU/mL)	98	97		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) at Baseline and 30 Days Post-vaccination for Pertussis

End point title	Geometric Mean Titers (GMTs) at Baseline and 30 Days Post-vaccination for Pertussis[5]

End point description:

Pre- and post-vaccination GMTs and their 95% confidence intervals for pertussis toxoid (PT), pertussis filamentous hemagglutinin (FHA), pertussis pertactin (PRN), and pertussis fimbriae types 2 and 3 (FIM) were determined by enzyme-linked immunosorbent assay (ELISA).

End point type	Primary

End point timeframe:

Pre-dose and 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	Tdap Vaccine Group	DTaP Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	426		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Pertussis toxoid; Pre-dose	4.58 (4.16 to 5.05)	4.98 (4.49 to 5.51)		
Pertussis toxoid; Post-dose	53.1 (49.3 to 57.2)	86.4 (79.9 to 93.5)		
Filamentous hemagglutinin; Pre-dose	7.56 (6.64 to 8.61)	7.6 (6.59 to 8.76)		
Filamentous hemagglutinin; Post-dose	102 (93.1 to 111)	86.5 (78.3 to 95.5)		
Pertactin; Pre-dose	9.31 (8.4 to 10.3)	11.1 (10 to 12.4)		
Pertactin; Post-dose	121 (109 to 134)	173 (155 to 193)		
Fimbriae types 2 and 3; Pre-dose	23.8 (21 to 27)	24.4 (21.4 to 27.7)		
Fimbriae types 2 and 3; Post-dose	425 (387 to 467)	388 (354 to 425)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects Reporting at Least 1 Solicited Injection Site or Solicited Systemic Reaction Post-vaccination

End point title	Number of Subjects Reporting at Least 1 Solicited Injection Site or Solicited Systemic Reaction Post-vaccination

End point description:

Solicited injection site reactions: Pain, Erythema/Redness, Swelling, and Increased limb circumference (both arms). 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/Redness and Swelling, > 50 mm; Limb circumference, > 40 mm increase over pre-vaccination measurement. Grade 3 systemic reactions: Fever, >39.5°C (> 103.1°F); Headache, Malaise, and Myalgia, Prevents daily activities.

End point type	Other pre-specified

End point timeframe:
Days 0 to 7 post-vaccination

End point values	Tdap Vaccine Group	DTaP Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	531	511		
Units: Number of subjects				
number (not applicable)				
Any Solicited Injection Site Reaction	455	451		
Any Pain	318	334		
Grade 3 Pain	1	4		
Any Erythema	140	201		
Grade 3 Erythema	17	65		
Any Swelling	100	144		
Grade 3 Swelling	8	23		
Any Increased Left Limb Circumference	309	353		
Grade 3 Left Limb Circumference	1	5		
Any Increased Right Limb Circumference	241	244		
Grade 3 Right Limb Circumference	1	0		
Any Solicited Systemic Reaction	256	260		
Any Fever	25	26		
Grade 3 Fever	1	1		
Any Headache	60	74		
Grade 3 Headache	3	4		
Any Malaise	143	150		
Grade 3 Malaise	5	7		
Any Myalgia	185	196		
Grade 3 Myalgia	3	8		

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	11

Reporting groups

Reporting group title	Tdap Vaccine Group

Reporting group description:

Subjects 4 to 6 years of age who had previously received 4 doses of Pentacel or DAPTACEL received a booster dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap).

Reporting group title	DTaP Vaccine Group

Reporting group description:

Subjects 4 to 6 years of age who had previously received 4 doses of Pentacel or DAPTACEL received a booster dose of diphtheria, tetanus and acellular pertussis vaccine (DTaP).

Serious adverse events	Tdap Vaccine Group	DTaP Vaccine Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 531 (0.75%)	5 / 511 (0.98%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 531 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 531 (0.00%)	1 / 511 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 531 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	1 / 531 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 531 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 531 (0.19%)	0 / 511 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 531 (0.19%)	3 / 511 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tdap Vaccine Group	DTaP Vaccine Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	318 / 531 (59.89%)	353 / 511 (69.08%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed[1]	60 / 529 (11.34%)	74 / 495 (14.95%)	
occurrences (all)	60	74	
General disorders and administration site conditions			
Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed[2]	140 / 529 (26.47%)	201 / 494 (40.69%)	
occurrences (all)	140	201	
Fever			
alternative assessment type: Systematic			

subjects affected / exposed[3]	25 / 527 (4.74%)	26 / 493 (5.27%)	
occurrences (all)	25	26	
Increased left limb circumference			
alternative assessment type: Systematic			
subjects affected / exposed[4]	309 / 527 (58.63%)	353 / 494 (71.46%)	
occurrences (all)	309	353	
Increased right limb circumference			
alternative assessment type: Systematic			
subjects affected / exposed[5]	241 / 527 (45.73%)	244 / 494 (49.39%)	
occurrences (all)	241	244	
Injection site Bruising			
subjects affected / exposed	28 / 531 (5.27%)	40 / 511 (7.83%)	
occurrences (all)	31	42	
Injection site Induration			
subjects affected / exposed	20 / 531 (3.77%)	28 / 511 (5.48%)	
occurrences (all)	21	30	
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed[6]	318 / 529 (60.11%)	334 / 495 (67.47%)	
occurrences (all)	318	334	
Injection site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[7]	100 / 529 (18.90%)	144 / 493 (29.21%)	
occurrences (all)	100	144	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	48 / 531 (9.04%)	29 / 511 (5.68%)	
occurrences (all)	49	31	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed[8]	185 / 529 (34.97%)	196 / 495 (39.60%)	
occurrences (all)	185	196	

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 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 7 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 7 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 7 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 7 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 7 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 7 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.

[8] - 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 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
26 October 2007	Study design rationale, inclusion criteria, randomization, and power calculations were updated; a Canadian site was added; 7 year long-term immunogenicity assessment was removed; new product batch numbers were added, archiving procedures were updated, indications for the investigational product were revised; and clarification was made on site practices, blinding/unblinding procedures, and storage conditions.
24 February 2009	Primary objectives and sample size were revised; vaccine dosing and indications were updated; study period was extended; references to 3-year follow up were removed; non-inferiority margins were updated; and storage and shipment conditions were further clarified.
19 May 2009	Changes were made regarding interim analysis of data, antibody assessment, evaluation of immune responses, and collection of blood samples; consent form was also updated with postmarketing information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported