



## Clinical trial results:

### **Safety and Immunogenicity of Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (ADACEL™) Vaccine Compared to Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine (QUADRACEL™) as Fifth Dose in Children 4-6 Years of Age**

#### **Summary**

EudraCT number	2015-005589-43
Trial protocol	Outside EU/EEA
Global end of trial date	

#### **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	Td508
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##### **Additional study identifiers**

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

Notes:

##### **Sponsors**

Sponsor organisation name	Aventis Pasteur Limited
Sponsor organisation address	1755 Steeles Ave. West, Toronto, Canada, M2R 3T4
Public contact	Director, Clinical Development, Aventis Pasteur Limited, 1 416-667-2273, miggi.tomovici@sanofipasteur.com
Scientific contact	Director, Clinical Development, Aventis 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	Interim
Date of interim/final analysis	03 February 2004
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2003
Global end of trial reached?	No

Notes:

## General information about the trial

Main objective of the trial:

1. To compare the immunogenicity of the tetanus and lower dose diphtheria toxoids of ADACEL™ with QUADRACEL™ when given as a fifth dose.
2. To compare the redness, swelling, pain, and fever rates after the ADACEL™ dose with the rates of these adverse events observed after the QUADRACEL™ dose when given as a fifth dose.

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 enrolled in this study were due for their fifth dose and had completed the primary series and fourth dose that consisted of four previous administrations of the pentavalent vaccine, PENTACEL®.

Evidence for comparator:

Not applicable

Actual start date of recruitment	12 August 2002
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 590
Worldwide total number of subjects	590
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)	590
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:

The study subjects were enrolled from 12 August 2002 to 11 January 2003 at 8 clinic centers in Canada.

### Pre-assignment

Screening details:

A total of 593 subjects were enrolled and randomized in the study, 590 were vaccinated and reported.

### 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:

This modified double-blind study used a single unblinded vaccine administrator and blinded safety assessors. The Investigator and study/sponsor personnel were blind to the vaccines. The study vaccination nurse was responsible for administration of the vaccine and keeping the treatment randomization cards. Blinded or unblinded staff could collect blood samples. In the event of an emergency, i.e., serious adverse event, the code could be broken by the Investigator according to protocol.

### Arms

Are arms mutually exclusive?	Yes
Arm title	ADACEL®

Arm description:

Subjects received one dose of investigational vaccine ADACEL® on Day 0. Subjects randomized to the ADACEL® group were also offered an optional one dose of Inactivated Poliomyelitis Vaccine (mIPV) vaccine 4-6 weeks after vaccination. Mumps, measles, and rubella (MMR) administration was optional on Day 35 (Visit 2) if needed to satisfy provincial vaccination requirements.

Arm type	Experimental
Investigational medicinal product name	ADACEL® (TdcP Vaccine - Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis Vaccine)
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 dose on Day 0.

Investigational medicinal product name	mIPV (Inactivated Poliomyelitis Vaccine, diploid cell origin - MRC-5 cell culture)
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 dose on Day 35 (Visit 2).

Investigational medicinal product name	MMR®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

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**Dosage and administration details:**

0.5 mL, subcutaneous, 1 optional dose on Day 35 (Visit 2).

<b>Arm title</b>	QUADRACEL®
Arm description: Subjects received one dose of the control vaccine (QUADRACEL®) on Day 0. Mumps, measles, and rubella (MMR) administration was optional on Day 35 (Visit 2) if needed to satisfy provincial vaccination requirements.	
Arm type	Active comparator
Investigational medicinal product name	QUADRACEL® (HCPDT-mIPV: Component Pertussis Vaccine and Diphtheria and Tetanus Toxoids Adsorbed Combined with Inactivated Poliomyelitis Vaccine)
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 dose on Day 0.

<b>Number of subjects in period 1</b>	ADACEL®	QUADRACEL®
Started	298	292
Completed	297	291
Not completed	1	1
Consent withdrawn by subject	1	-
Protocol deviation	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	ADACEL®
Reporting group description:	
Subjects received one dose of investigational vaccine ADACEL® on Day 0. Subjects randomized to the ADACEL® group were also offered an optional one dose of Inactivated Poliomyelitis Vaccine (mIPV) vaccine 4-6 weeks after vaccination. Mumps, measles, and rubella (MMR) administration was optional on Day 35 (Visit 2) if needed to satisfy provincial vaccination requirements.	
Reporting group title	QUADRACEL®
Reporting group description:	
Subjects received one dose of the control vaccine (QUADRACEL®) on Day 0. Mumps, measles, and rubella (MMR) administration was optional on Day 35 (Visit 2) if needed to satisfy provincial vaccination requirements.	

Reporting group values	ADACEL®	QUADRACEL®	Total
Number of subjects	298	292	590
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)	298	292	590
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	4.6	4.6	
standard deviation	± 0.4	± 0.33	-
Gender categorical			
Units: Subjects			
Female	154	148	302
Male	144	144	288

## End points

### End points reporting groups

Reporting group title	ADACEL®
Reporting group description: Subjects received one dose of investigational vaccine ADACEL® on Day 0. Subjects randomized to the ADACEL® group were also offered an optional one dose of Inactivated Poliomyelitis Vaccine (mIPV) vaccine 4-6 weeks after vaccination. Mumps, measles, and rubella (MMR) administration was optional on Day 35 (Visit 2) if needed to satisfy provincial vaccination requirements.	
Reporting group title	QUADRACEL®
Reporting group description: Subjects received one dose of the control vaccine (QUADRACEL®) on Day 0. Mumps, measles, and rubella (MMR) administration was optional on Day 35 (Visit 2) if needed to satisfy provincial vaccination requirements.	

### Primary: Percentage of Subjects with Seroprotection to Tetanus and Diphtheria Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age

End point title	Percentage of Subjects with Seroprotection to Tetanus and Diphtheria Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
End point description: Anti-Diphtheria antibody responses were measured using a microneutralization assay. Anti-Tetanus immunoglobulin G antibody titers were determined by an enzyme-linked immunosorbent assay (ELISA). Seroprotection for diphtheria and tetanus antibody levels $\geq 0.1$ IU/mL.	
End point type	Primary
End point timeframe: Day 0 (pre-vaccination) and Day 35 post-vaccination	

End point values	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	254		
Units: Percentage of subjects				
number (not applicable)				
Anti-Diphtheria; Pre-vaccination	86	87.4		
Anti-Diphtheria; Post-vaccination	100	100		
Anti-Tetanus; Pre-vaccination	95.5	96.4		
Anti-Tetanus; Post-vaccination	100	100		

### Statistical analyses

Statistical analysis title	Proportion Difference; Anti-Diphtheria Post-dose
Statistical analysis description: Analysis of the proportion difference in diphtheria seroprotection rates (post-vaccination) between subjects in each group.	
Comparison groups	ADACEL® v QUADRACEL®

Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	Proportion difference
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[1] - Proportion difference was calculated by subtracting the percentage of seroprotected subjects (i.e., achieved titers  $\geq 0.1$  IU/mL) in the QUADRACEL group minus the percentage of subjects seroprotected (i.e., achieved titers  $\geq 0.1$  IU/mL) in the ADACEL group.

<b>Statistical analysis title</b>	Proportion Difference; Anti-Diphtheria Post-dose
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Statistical analysis description:

Analysis of the proportion difference in diphtheria seroprotection rates (post-vaccination) between subjects in each group.

Comparison groups	ADACEL® v QUADRACEL®
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
Parameter estimate	Proportion difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[2] - Proportion difference was calculated by subtracting the percentage of seroprotected subjects (i.e., achieved titers  $\geq 0.1$  IU/mL) in the QUADRACEL group minus the percentage of subjects seroprotected (i.e., achieved titers  $\geq 0.1$  IU/mL) in the ADACEL group.

<b>Statistical analysis title</b>	Proportion Difference; Anti-Tetanus Post-dose
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Statistical analysis description:

Analysis of the proportion difference in tetanus seroprotection rates (post-vaccination) between subjects in each group.

Comparison groups	ADACEL® v QUADRACEL®
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
Parameter estimate	Proportion difference
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[3] - Proportion difference was calculated by subtracting the percentage of seroprotected subjects (i.e., achieved titers  $\geq 0.1$  IU/mL) in the QUADRACEL group minus the percentage of subjects seroprotected (i.e., achieved titers  $\geq 0.1$  IU/mL) in the ADACEL group.



<b>Statistical analysis title</b>	Proportion Difference; Anti-Tetanus Post-dose
Statistical analysis description:	
Analysis of the proportion difference in tetanus seroprotection rates (pre-vaccination) between subjects in each group.	
Comparison groups	ADACEL® v QUADRACEL®
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
Parameter estimate	Proportion difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[4] - Proportion difference was calculated by subtracting the percentage of seroprotected subjects (i.e., achieved titers  $\geq 0.1$  IU/mL) in the QUADRACEL group minus the percentage of subjects seroprotected (i.e., achieved titers  $\geq 0.1$  IU/mL) in the ADACEL group.

### **Primary: Summary of Safety Profile Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose in Children 4-6 Years of Age**

End point title	Summary of Safety Profile Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose in Children 4-6 Years of Age
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End point description:

Solicited reactions: Erythema, Swelling, Pain, Fever ( $\geq 38.0^{\circ}\text{C}$ ).

End point type	Primary
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End point timeframe:

Day 0 up to Day 35 (4-6 weeks) post-vaccination

<b>End point values</b>	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Number of subjects				
number (not applicable)				
Immediate reactions (Within 30 minutes)	7	7		
Any Solicited local reaction (Days 0-14)	181	239		
Any Solicited systemic reaction (Days 0-14)	161	184		
Erythema; Days 0-14	103	150		
Swelling; Days 0-14	72	98		
Pain; Days 0-14	118	195		
Fever ( $\geq 38.0^{\circ}\text{C}$ ); Days 0-14	26	49		
Erythema; Days 0-3	102	148		
Swelling; Days 0-3	71	98		
Pain; Days 0-3	114	195		
Fever ( $\geq 38.0^{\circ}\text{C}$ ); Days 0-3	8	23		
Unsolicited adverse events; Day 0 - Weeks 4 to 6	127	115		

Serious adverse events; Day 0 - Weeks 4 to 6	1	0		
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## Statistical analyses

<b>Statistical analysis title</b>	Comparison of Erythema Reaction Rates
Statistical analysis description:	
Difference (%) in Erythema reaction rates at Day 0 to 3 between ADACEL® and QUADRACEL® groups	
Comparison groups	ADACEL® v QUADRACEL®
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[5]</sup>
Parameter estimate	Mean difference (final values)
Point estimate	-16.81
Confidence interval	
level	90 %
sides	2-sided
lower limit	-23.42
upper limit	-10.19

Notes:

[5] - Difference (%) in Erythema reaction rates at Day 0 to 3 between ADACEL® and QUADRACEL® groups.

Erythema reactions in the ADACEL® group is non-inferior to the QUADRACEL® group if the upper limit of the two-sided 90% confidence interval (CI) of the difference between the 2 groups is less than 10%.

<b>Statistical analysis title</b>	Comparison of Swelling Reaction Rates
Statistical analysis description:	
Difference (%) in Swelling reaction rates at Day 0 to 3 between ADACEL® and QUADRACEL® groups	
Comparison groups	ADACEL® v QUADRACEL®
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[6]</sup>
Parameter estimate	Mean difference (final values)
Point estimate	-9.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.08
upper limit	-3.86

Notes:

[6] - Difference (%) in Swelling reaction rates at Day 0 to 3 between ADACEL® and QUADRACEL® groups.

Swelling reactions in the ADACEL® group is non-inferior to the QUADRACEL® group if the upper limit of the two-sided 90% confidence interval (CI) of the difference between the 2 groups is less than 10%.

<b>Statistical analysis title</b>	Comparison of Pain Reaction Rates
Statistical analysis description:	
Difference (%) in Pain reaction rates at Day 0 to 3 between ADACEL® and QUADRACEL® groups	
Comparison groups	ADACEL® v QUADRACEL®

Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[7]</sup>
Parameter estimate	Mean difference (final values)
Point estimate	-27.64
Confidence interval	
level	90 %
sides	2-sided
lower limit	-35.47
upper limit	-22.51

Notes:

[7] - Difference (%) in Pain reaction rates at Day 0 to 3 between ADACEL® and QUADRACEL® groups. Pain reactions in the ADACEL® group is non-inferior to the QUADRACEL® group if the upper limit of the two-sided 90% confidence interval (CI) of the difference between the 2 groups is less than 10%.

<b>Statistical analysis title</b>	Comparison of Fever Reaction Rates
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Statistical analysis description:

Difference (%) in Fever reaction rates at Day 0 to 3 between ADACEL® and QUADRACEL® groups

Comparison groups	ADACEL® v QUADRACEL®
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[8]</sup>
Parameter estimate	Mean difference (final values)
Point estimate	-5.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.28
upper limit	-2.22

Notes:

[8] - Difference (%) in Fever reaction rates at Day 0 to 3 between ADACEL® and QUADRACEL® groups. Fever reactions in the ADACEL® group is non-inferior to the QUADRACEL® group if the upper limit of the two-sided 90% confidence interval (CI) of the difference between the 2 groups is less than 10%.

### **Secondary: Percentage of Subjects with Four-fold Antibody Response Rate to Tetanus and Diphtheria Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age**

End point title	Percentage of Subjects with Four-fold Antibody Response Rate to Tetanus and Diphtheria Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
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End point description:

Anti-Diphtheria antibody responses were measured by a microneutralization assay. Anti-Tetanus immunoglobulin G antibody titers were determined by an enzyme-linked immunosorbent assay (ELISA).

End point type	Secondary
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End point timeframe:

Day 35 post-vaccination

End point values	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	254		
Units: Percentage of subjects				
number (not applicable)				
Anti-Diphtheria	89.8	93.7		
Anti-Tetanus	94.3	93.7		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of Geometric Mean of Anti-Tetanus and Anti-Diphtheria Titers Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age

End point title	Summary of Geometric Mean of Anti-Tetanus and Anti-Diphtheria Titers Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
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End point description:

Anti-Diphtheria antibody responses were measured by a microneutralization assay. Anti-Tetanus immunoglobulin G antibody titers were determined by an enzyme-linked immunosorbent assay (ELISA).

End point type	Secondary
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End point timeframe:

Day 0 (pre-vaccination) and Day 35 post-vaccination

End point values	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	254		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Diphtheria; Pre-vaccination	0.48 (0.4 to 0.57)	0.49 (0.4 to 0.59)		
Anti-Diphtheria; Post-vaccination	6.1 (5.42 to 6.86)	13.58 (11.5 to 16.04)		
Anti-Tetanus; Pre-vaccination	0.52 (0.46 to 0.59)	0.57 (0.51 to 0.64)		
Anti-Tetanus; Post-vaccination	7.2 (6.67 to 7.77)	6.65 (6.1 to 7.25)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of Geometric Mean of Anti-Pertussis Titers Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age

End point title	Summary of Geometric Mean of Anti-Pertussis Titers Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
End point description: Pertussis Anti-Pertactin, Anti-Pertussis Toxoid, Anti-Filamentous hemagglutinin, and Anti-Fimbriae Types 2 and 3 antibody titers were determined by an enzyme-linked immunosorbent assay (ELISA).	
End point type	Secondary
End point timeframe: Day 0 (pre-vaccination) and Day 35 post-vaccination	

End point values	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	254		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Anti-Pertussis Toxoid; Pre-vaccination	19.86 (17.48 to 22.56)	19.3 (16.86 to 22.1)		
Anti-Pertussis Toxoid; Post-vaccination	297.14 (269.32 to 327.83)	331.33 (298.98 to 367.17)		
Anti-Filamentous hemagglutinin; Pre-vaccination	15.1 (13.04 to 17.5)	15.37 (13.26 to 17.82)		
Anti-Filamentous hemagglutinin; Post-vaccination	198.04 (179.57 to 218.41)	258.14 (235.48 to 282.99)		
Anti-Fimbriae Types 2 and 3; Pre-vaccination	52.3 (45.41 to 60.23)	52.59 (45.86 to 60.3)		
Anti-Fimbriae Types 2 and 3; Post-vaccination	1177.19 (1048.75 to 1321.36)	737.62 (658.56 to 826.16)		
Anti-Pertactin; Pre-vaccination	16.25 (14.34 to 18.43)	16.32 (14.36 to 18.55)		
Anti-Pertactin; Post-vaccination	303.76 (270.53 to 341.08)	243.12 (214.9 to 275.05)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Four-fold Antibody Response Rate to Pertussis Antigens Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age

End point title	Percentage of Subjects with Four-fold Antibody Response Rate to Pertussis Antigens Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
End point description: Pertussis Anti-Pertactin, Anti-Pertussis Toxoid, Anti-Filamentous hemagglutinin, and Anti-Fimbriae Types 2 and 3 antibody titers were determined by an enzyme-linked immunosorbent assay (ELISA).	
End point type	Secondary

End point timeframe:  
Day 35 post-vaccination

End point values	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	254		
Units: Percentage of subjects				
number (not applicable)				
Anti-Pertussis Toxoid	91.9	96.8		
Anti-Filamentous hemagglutinin	88.1	92.8		
Anti-Fimbriae Types 2 and 3	94.6	87.6		
Anti-Pertactin	94.3	92		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Solicited Local Reactions by Maximum Intensity and Time Period Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age

End point title	Percentage of Subjects With Solicited Local Reactions by Maximum Intensity and Time Period Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
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End point description:

Solicited local reactions: Erythema, Swelling, Pain, and Underarm lymph node swelling.

Mild Solicited local reactions: Erythema and Swelling, < 10 mm; Pain and Underarm lymph node swelling, Noticeable but did not interfere with activities, easily tolerated.

Moderate Solicited local reactions: Erythema and Swelling, 10-34 mm, Pain and Underarm lymph node swelling, Interfered with activities but did not require medical care or absenteeism.

Severe Solicited local reactions: Erythema and Swelling, ≥ 35 mm; Pain and Underarm lymph node swelling, Incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.

End point type	Secondary
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End point timeframe:

Days 0-3, 4-14, and 0-14 post-vaccination, late onset (max. intensity on Days 4-14 by those who reported no events during Days 0-3), and re-occurrence (onset of events within Days 0-3 that were reported to have stopped and re-occurred prior to Day 14)

End point values	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage of subjects				
number (not applicable)				
Any Erythema; Days 0-3	34.23	51.03		
Any Erythema; Days 4-14	8.39	11.03		
Any Erythema; Days 0-14	34.56	51.72		

Any Erythema; Late Onset	0.34	0.69		
Any Erythema; Re-occurrence	3.02	1.03		
Mild Erythema; Days 0-3	15.1	13.1		
Mild Erythema; Days 4-14	4.7	4.83		
Mild Erythema; Days 0-14	15.1	13.79		
Mild Erythema; Late Onset	0	0.69		
Mild Erythema; Re-occurrence	1.68	0.34		
Moderate Erythema; Days 0-3	7.38	9.31		
Moderate Erythema; Days 4-14	2.68	1.72		
Moderate Erythema; Days 0-14	7.72	8.97		
Moderate Erythema; Late Onset	0.34	0		
Moderate Erythema; Re-occurrence	0.34	0.34		
Severe Erythema; Days 0-3	11.74	28.62		
Severe Erythema; Days 4-14	1.01	4.48		
Severe Erythema; Days 0-14	11.74	28.97		
Severe Erythema; Late Onset	0	0		
Severe Erythema; Re-occurrence	1.01	0.34		
Any Swelling; Days 0-3	23.83	33.79		
Any Swelling; Days 4-14	7.05	9.66		
Any Swelling; Days 0-14	24.16	33.79		
Any Swelling; Late Onset	0.34	0.34		
Any Swelling; Re-occurrence	1.34	1.38		
Mild Swelling; Days 0-3	9.06	7.93		
Mild Swelling; Days 4-14	3.69	3.45		
Mild Swelling; Days 0-14	9.4	7.93		
Mild Swelling; Late Onset	0.34	0		
Mild Swelling; Re-occurrence	0.67	0.34		
Moderate Swelling; Days 0-3	4.7	8.28		
Moderate Swelling; Days 4-14	2.01	3.45		
Moderate Swelling; Days 0-14	4.7	8.62		
Moderate Swelling; Late Onset	0	0.34		
Moderate Swelling; Re-occurrence	0.67	0.34		
Severe Swelling; Days 0-3	10.07	17.24		
Severe Swelling; Days 4-14	1.34	2.76		
Severe Swelling; Days 0-14	10.07	17.24		
Severe Swelling; Late Onset	0	0		
Severe Swelling; Re-occurrence	0	0.34		
Any Pain; Days 0-3	38.26	67.24		
Any Pain; Days 4-14	4.36	4.83		
Any Pain; Days 0-14	39.6	67.24		
Any Pain; Late Onset	1.34	0		
Any Pain; Re-occurrence	1.01	3.79		
Mild Pain; Days 0-3	33.89	51.38		
Mild Pain; Days 4-14	4.36	4.83		
Mild Pain; Days 0-14	35.23	51.38		
Mild Pain; Late Onset	1.34	0		
Mild Pain; Re-occurrence	1.01	3.79		
Moderate Pain; Days 0-3	4.03	14.83		
Moderate Pain; Days 4-14	0	0		
Moderate Pain; Days 0-14	4.03	14.83		
Moderate Pain; Late Onset	0	0		
Moderate Pain; Re-occurrence	0	0		

Severe Pain; Days 0-3	0.34	1.03		
Severe Pain; Days 4-14	0	0		
Severe Pain; Days 0-14	0.34	1.03		
Severe Pain; Late Onset	0	0		
Severe Pain; Re-occurrence	0	0		
Any Underarm lymph node swelling; Days 0-3	4.36	6.9		
Any Underarm lymph node swelling; Days 4-14	2.68	4.14		
Any Underarm lymph node swelling; Days 0-14	5.37	8.28		
Any Underarm lymph node swelling; Late Onset	1.01	1.38		
Any Underarm lymph node swelling; Re- occurrence	0.67	1.03		
Mild Underarm lymph node swelling; Days 0-3	4.03	6.55		
Mild Underarm lymph node swelling; Days 4-14	2.35	3.45		
Mild Underarm lymph node swelling; Days 0-14	4.7	7.24		
Mild Underarm lymph node swelling; Late Onset	0.67	1.38		
Mild Underarm lymph node swelling; Re- occurrence	0.67	0.69		
Moderate Underarm lymph node swelling; Days 0-3	0.34	0.34		
Moderate Underarm lymph node swelling; Days 4-14	0.34	0.69		
Moderate Underarm lymph node swelling; Days 0-14	0.67	1.03		
Moderate Underarm lymph node swelling; Late Onset	0.34	0		
Moderate Underarm lymph node swelling; Reoccurrence	0	0.34		
Severe Underarm lymph node swelling; Days 0-3	0	0		
Severe Underarm lymph node swelling; Days 4-14	0	0		
Severe Underarm lymph node swelling; Days 0-14	0	0		
Severe Underarm lymph node swelling; Late Onset	0	0		
Severe Underarm lymph node swelling; Re-occurrence	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Change in Limb Circumference by Time Period Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age

End point title	Percentage of Subjects With Change in Limb Circumference by Time Period Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
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End point description:

At baseline, limb circumference was measured over the site the vaccine was administered. Limb circumference was measured and recorded by the parent every day for the 14 days following vaccination. Arm swelling was defined as the increase in measurement on Days 0-14 as compared to the baseline taken pre-vaccination. The percentage of subjects with an increase from baseline (0-0.99 cm, 1.00-1.99 cm, 2.00-2.99 cm, and  $\geq 3$  cm) are reported.

End point type	Secondary
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End point timeframe:

Days 0-3, 4-14, and 0-14 post-vaccination, late onset (max. intensity on Days 4-14 by those who reported no events during Days 0-3), and re-occurrence (onset of events within Days 0-3 that were reported to have stopped and re-occurred prior to Day 14)

End point values	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	282		
Units: Percentage of subjects				
number (not applicable)				
Increase from baseline (0-0.99 cm); Days 0-3	31.62	28.72		
Increase from baseline (0-0.99 cm); Days 4-14	30.58	27.4		
Increase from baseline (0-0.99 cm); Days 0-14	37.11	36.88		
Increase from baseline (0-0.99 cm); Late onset	7.56	8.19		
Increase from baseline (0-0.99 cm); Re-occurrence	17.18	11.35		
Increase from baseline (1.00-1.99 cm); Days 0-3	5.84	5.67		
Increase from baseline (1.00-1.99 cm); Days 4-14	4.81	2.85		
Increase from baseline (1.00-1.99 cm); Days 0-14	8.25	5.67		
Increase from baseline (1.00-1.99 cm); Late onset	0.69	0		
Increase from baseline(1.00-1.99 cm);Re-occurrence	1.03	0.71		
Increase from baseline (2.00-2.99 cm); Days 0-3	0.69	1.06		
Increase from baseline (2.00-2.99 cm); Days 4-14	0.69	0		
Increase from baseline (2.00-2.99 cm); Days 0-14	1.03	1.06		
Increase from baseline (2.00-2.99 cm); Late onset	0	0		
Increase from baseline(2.00-2.99 cm);Re-occurrence	0	0		
Increase from baseline ( $\geq 3$ cm); Days 0-3	0	0.35		
Increase from baseline ( $\geq 3$ cm); Days 4-14	0	0		
Increase from baseline ( $\geq 3$ cm); Days 0-14	0	0.35		
Increase from baseline ( $\geq 3$ cm); Late onset	0	0		
Increase from baseline ( $\geq 3$ cm); Re-occurrence	0	0		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Solicited Systemic Reactions by Maximum Intensity and Time Period Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age

End point title	Percentage of Subjects With Solicited Systemic Reactions by Maximum Intensity and Time Period Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
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End point description:

Solicited systemic reactions: Fever, Chills, Headache, Generalized body ache and/or muscle weakness, Tiredness and/or decreased energy, Nausea, Vomiting, Diarrhea, Sore and/or swollen joints, and Anorexia.

Grade 3 Solicited systemic reactions: Fever,  $\geq 39.5^{\circ}\text{C}$ ; Chills, Headache, Generalized body ache and/or muscle weakness, Tiredness and/or decreased energy, Nausea, Vomiting, Diarrhea, Sore and/or swollen joints, Incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism. Anorexia, Skipped 3 or more meals.

End point type	Secondary
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End point timeframe:

Days 0-3 and Days 0-14 post-vaccination

End point values	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage of subjects				
number (not applicable)				
No Fever; Days 0-3	97.32	92.07		
No Fever; Days 0-14	92.95	89.66		
Mild Fever; Days 0-3	2.01	5.17		
Mild Fever; Days 0-14	3.69	5.52		
Moderate Fever; Days 0-3	0.34	1.72		
Moderate Fever; Days 0-14	2.01	3.45		
Severe Fever; Days 0-3	0.34	0.69		
Severe Fever; Days 0-14	1.34	0.69		
No Chills; Days 0-3	96.97	93.45		
No Chills; Days 0-14	92.95	90		
Mild Chills; Days 0-3	2.02	5.52		
Mild Chills; Days 0-14	5.37	7.93		
Moderate Chills; Days 0-3	1.01	1.03		
Moderate Chills; Days 0-14	1.68	1.72		
Severe Chills; Days 0-3	0	0		
Severe Chills; Days 0-14	0	0.34		

No Headache; Days 0-3	90.91	88.28		
No Headache; Days 0-14	83.56	83.1		
Mild Headache; Days 0-3	8.08	11.03		
Mild Headache; Days 0-14	13.09	14.83		
Moderate Headache; Days 0-3	1.01	0.69		
Moderate Headache; Days 0-14	3.36	1.38		
Severe Headache; Days 0-3	0	0		
Severe Headache; Days 0-14	0	0.69		
No body ache/muscle weakness; Days 0-3	96.97	95.17		
No body ache/muscle weakness; Days 0-14	93.62	91.72		
Mild body ache/muscle weakness; Days 0-3	3.03	3.79		
Mild body ache/muscle weakness; Days 0-14	5.03	5.52		
Moderate body ache/muscle weakness; Days 0-3	0	1.03		
Moderate body ache/muscle weakness; Days 0-14	1.34	2.07		
Severe body ache/muscle weakness; Days 0-3	0	0		
Severe body ache/muscle weakness; Days 0-14	0	0.69		
No Tiredness; Days 0-3	78.79	69.66		
No Tiredness; Days 0-14	68.46	63.45		
Mild Tiredness; Days 0-3	18.18	22.76		
Mild Tiredness; Days 0-14	23.49	25.86		
Moderate Tiredness; Days 0-3	2.69	5.86		
Moderate Tiredness; Days 0-14	7.72	7.59		
Severe Tiredness; Days 0-3	0.34	1.72		
Severe Tiredness; Days 0-14	0.34	3.1		
No Nausea; Days 0-3	97.98	96.21		
No Nausea; Days 0-14	90.6	90		
Mild Nausea; Days 0-3	2.02	2.07		
Mild Nausea; Days 0-14	5.7	5.17		
Moderate Nausea; Days 0-3	0	1.72		
Moderate Nausea; Days 0-14	3.69	4.48		
Severe Nausea; Days 0-3	0	0		
Severe Nausea; Days 0-14	0	0.34		
No Vomiting; Days 0-3	98.99	97.24		
No Vomiting; Days 0-14	91.95	90		
Mild Vomiting; Days 0-3	0.34	0.69		
Mild Vomiting; Days 0-14	3.69	3.1		
Moderate Vomiting; Days 0-3	0.67	2.07		
Moderate Vomiting; Days 0-14	3.02	6.9		
Severe Vomiting; Days 0-3	0	0		
Severe Vomiting; Days 0-14	1.34	0		
No Diarrhea; Days 0-3	94.95	95.86		
No Diarrhea; Days 0-14	85.57	90.34		
Mild Diarrhea; Days 0-3	5.05	4.14		
Mild Diarrhea; Days 0-14	12.08	8.97		
Moderate Diarrhea; Days 0-3	0	0		
Moderate Diarrhea; Days 0-14	1.68	0		

Severe Diarrhea; Days 0-3	0	0		
Severe Diarrhea; Days 0-14	0.67	0.69		
No Sore and/or swollen joints; Days 0-3	96.97	95.86		
No Sore and/or swollen joints; Days 0-14	95.97	95.52		
Mild Sore and/or swollen joints; Days 0-3	2.69	3.79		
Mild Sore and/or swollen joints; Days 0-14	3.02	3.79		
Moderate Sore and/or swollen joints; Days 0-3	0.34	0.34		
Moderate Sore and/or swollen joints; Days 0-14	1.01	0.69		
Severe Sore and/or swollen joints; Days 0-3	0	0		
Severe Sore and/or swollen joints; Days 0-14	0	0		
No Anorexia; Days 0-3	89.23	86.55		
No Anorexia; Days 0-14	78.52	77.93		
Mild Anorexia; Days 0-3	10.1	10.34		
Mild Anorexia; Days 0-14	16.11	15.86		
Moderate Anorexia; Days 0-3	0.67	2.41		
Moderate Anorexia; Days 0-14	4.7	4.14		
Severe Anorexia; Days 0-3	0	0.69		
Severe Anorexia; Days 0-14	0.67	2.07		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Rash by Maximum Intensity and Time Period Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age

End point title	Percentage of Subjects With Rash by Maximum Intensity and Time Period Following Vaccination with Either ADACEL® or QUADRACEL® as Fifth Dose at 4-6 Years of Age
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End point description:

Rash was defined as the presence of welts (large, red, swollen patches). A "rash" reaction was intended to capture subjects with an allergic reaction to the vaccine that was manifested by rash (excluding other obvious causes of rash, i.e., diaper rash or poison ivy).

End point type	Secondary
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End point timeframe:

Days 0-3, 4-14, and 0-14 post-vaccination, late onset (max. intensity on Days 4-14 by those reporting no events during Days 0-3), and re-occurrence (onset of events within Days 0-3 that stopped and re-occurred prior to Day 14).

<b>End point values</b>	ADACEL®	QUADRACEL®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage of subjects				
number (not applicable)				
No Rash; Days 0-3	95.29	92.07		
No Rash; Days 4-14	94.3	91.38		
No Rash; Days 0-14	91.61	85.86		
No Rash; Late Onset	96.31	93.79		
No Rash; Re-occurrence	99.66	98.62		
Any Rash; Days 0-3	4.71	7.93		
Any Rash; Days 4-14	5.7	8.62		
Any Rash; Days 0-14	8.39	14.14		
Any Rash; Late Onset	3.69	6.21		
Any Rash; Re-occurrence	0.34	1.38		

## 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 35 post-vaccination

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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### Reporting groups

Reporting group title	ADACEL®
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Reporting group description:

Subjects received one dose of investigational vaccine ADACEL® on Day 0. Subjects randomized to the ADACEL® group also received one dose of Inactivated Poliomyelitis Vaccine (mIPV) vaccine 4-6 weeks after vaccination. Mumps, measles, and rubella (MMR) administration was optional on Day 35 (Visit 2) if needed to satisfy provincial vaccination requirements.

Reporting group title	QUADRACEL®
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Reporting group description:

Subjects received one dose of the control vaccine (QUADRACEL®) on Day 0.

Serious adverse events	ADACEL®	QUADRACEL®	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 298 (0.34%)	0 / 292 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Phimosis			
subjects affected / exposed	1 / 298 (0.34%)	0 / 292 (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: 1 %

Non-serious adverse events	ADACEL®	QUADRACEL®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 298 (39.60%)	195 / 292 (66.78%)	
General disorders and administration site conditions			
Injection site Bruising			
subjects affected / exposed	6 / 298 (2.01%)	4 / 292 (1.37%)	
occurrences (all)	6	4	

Injection site Erythema subjects affected / exposed occurrences (all)	3 / 298 (1.01%) 3	4 / 292 (1.37%) 4	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	10 / 298 (3.36%) 11	4 / 292 (1.37%) 4	
Gastrointestinal disorders Abdominal pain nos subjects affected / exposed occurrences (all)	6 / 298 (2.01%) 6	1 / 292 (0.34%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Nasal congestion subjects affected / exposed occurrences (all)  Rhinorrhoea subjects affected / exposed occurrences (all)  Asthma nos subjects affected / exposed occurrences (all)  Pharyngitis subjects affected / exposed occurrences (all)	20 / 298 (6.71%) 22  9 / 298 (3.02%) 11  7 / 298 (2.35%) 7  5 / 298 (1.68%) 5  4 / 298 (1.34%) 4	25 / 292 (8.56%) 26  4 / 292 (1.37%) 4  6 / 292 (2.05%) 6  2 / 292 (0.68%) 2  3 / 292 (1.03%) 3	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)  Ear infection nos subjects affected / exposed occurrences (all)  Otitis media nos	44 / 298 (14.77%) 45  9 / 298 (3.02%) 9	32 / 292 (10.96%) 33  8 / 292 (2.74%) 8	

subjects affected / exposed	3 / 298 (1.01%)	6 / 292 (2.05%)	
occurrences (all)	3	6	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2002	Deleted statement regarding the anonymous testing of serum samples after the completion of the study and procedures for long-term storage and further testing of serum samples were clarified.
28 August 2002	Randomization and vaccination procedures were modified to include procedures to maintain the modified double-blind study design; blinding and code-breaking procedures were clarified; exclusion criteria and statistical analyses were updated; procedures for collecting and reporting safety events on the diary card were clarified; and procedures for handling the vaccines and collection of blood samples were updated. Clarifications of the parent's responsibility to report past vaccinations/pertussis diagnosis as well as severe reactions that may occur following vaccinations were provided.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported