Clinical trial results:
A Phase III Observer-Blind, Randomized, Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Immunogenicity of Two Trivalent Subunit Inactivated Influenza Vaccines (Agrippal and Fluvirin) in Healthy Children Aged 3 to 8 years, in Healthy Children/Adolescents Aged 9 to 17 Years And in Healthy Adults Aged 18 to 64 Years

Summary

EudraCT number	2014-004757-14
Trial protocol	Outside EU/EEA
Global end of trial date	20 December 2007
Results information	
Result version number	v2 (current)
This version publication date	28 July 2016
First version publication date	04 February 2015
Version creation reason	• Correction of full data set Required for the re-QC because of EudraCT system glitch as possible updates to results are required. Moreover, the study is now transferred to another primary user.

Trial information

Trial identification	
Sponsor protocol code	V71P5
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00464672
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Vaccines and Diagnostics S.r.l.
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines , RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines , RegistryContactVaccinesUS@novartis.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	06 March 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate immunogenicity, measured by seroprotection (percentage of subjects achieving a hemagglutination inhibition [HI] titer ≥40) and by percentage of subjects achieving seroconversion (defined as negative pre-vaccination serum [HI<10]/post-vaccination HI titer ≥40) or significant increase (defined as at least a 4-fold increase in titer from non-negative prevaccination serum [HI≥10]), of one injection of Agrippal, administered to healthy adults aged 18 to 64 years according to the CBER Guidance for Industry issued in May 2007.

To evaluate safety and tolerability of one injection of either Agrippal or Fluvirin, administered to adults aged 18 to 64 years and Children/adolescents aged 9 to 17 years and two injections of either Agrippal or Fluvirin, administered 4 weeks apart to healthy children aged 3 to 8 years.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practices (GCPs) and the applicable regulatory requirement(s) for the country in which the trial was conducted, GCP according to International Conference on Harmonisation (ICH) guidelines, and applicable Standard Operating Procedures (SOPs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1893
Worldwide total number of subjects	1893
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)	824
Adolescents (12-17 years)	376
Adults (18-64 years)	691
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 2 study centers in Argentina.

Pre-assignment

Screening details:

All enrolled subjects were included in the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Influenza Virus Vaccine (18 to 64 Years)

Arm description:

One injection of the investigational influenza virus vaccine was administered intramuscularly.

Arm type	Experimental
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One 0.5 mL IM injection, in the deltoid muscle, preferably of the non-dominant arm.

Arm title	Comparator Influenza Vaccine (18 to 64 Years)

Arm description:

One injection of the comparator influenza vaccine was administered intramuscularly.

Arm type	Active comparator
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived, Fluvirin platform)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One 0.5 mL IM injection, in the deltoid muscle, preferably of the non-dominant arm.

Arm title	Influenza Virus Vaccine (9 to 17 Years)

Arm description:

One injection of the investigational influenza virus vaccine was administered intramuscularly.

Arm type	Experimental

Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One 0.5 mL IM injection, in the deltoid muscle, preferably of the non-dominant arm.

Arm title	Comparator Influenza Vaccine (9 to 17 Years)

Arm description:

One injection of the comparator influenza vaccine was administered intramuscularly

Arm type	Active comparator
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived, Fluvirin platform)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One 0.5 mL IM injection, in the deltoid muscle, preferably of the non-dominant arm.

Arm title	Influenza Virus Vaccine (3 to 8 Years)

Arm description:

Two injections of the investigational influenza virus vaccine were administered intramuscularly.

Arm type	Experimental
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Two 0.5 mL intramuscular (IM) injections administered 4 weeks apart, in the deltoid muscle, preferably of the non-dominant arm.

Arm title	Comparator Influenza Vaccine (3 to 8 Years)

Arm description:

Two injections of the comparator influenza vaccine were administered intramuscularly.

Arm type	Active comparator
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, egg-derived, Fluvirin platform)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Two 0.5 mL intramuscular (IM) injections administered 4 weeks apart, in the deltoid muscle, preferably of the non-dominant arm.

Number of subjects in period 1	Influenza Virus Vaccine (18 to 64 Years)	Comparator Influenza Vaccine (18 to 64 Years)	Influenza Virus Vaccine (9 to 17 Years)
Started	460	232	400
Completed	435	222	400
Not completed	25	10	0
Consent withdrawn by subject	-	-	-
Lost to follow-up	25	10	-

Number of subjects in period 1	Comparator Influenza Vaccine (9 to 17 Years)	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (3 to 8 Years)
Started	200	402	199
Completed	199	392	195
Not completed	1	10	4
Consent withdrawn by subject	1	9	4
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Influenza Virus Vaccine (18 to 64 Years)
Reporting group description:	
One injection of the investigational influenza virus vaccine was administered intramuscularly.	
Reporting group title	Comparator Influenza Vaccine (18 to 64 Years)
Reporting group description:	
One injection of the comparator influenza vaccine was administered intramuscularly.	
Reporting group title	Influenza Virus Vaccine (9 to 17 Years)
Reporting group description:	
One injection of the investigational influenza virus vaccine was administered intramuscularly.	
Reporting group title	Comparator Influenza Vaccine (9 to 17 Years)
Reporting group description:	
One injection of the comparator influenza vaccine was administered intramuscularly	
Reporting group title	Influenza Virus Vaccine (3 to 8 Years)
Reporting group description:	
Two injections of the investigational influenza virus vaccine were administered intramuscularly.	
Reporting group title	Comparator Influenza Vaccine (3 to 8 Years)
Reporting group description:	
Two injections of the comparator influenza vaccine were administered intramuscularly.	

Reporting group values	Influenza Virus Vaccine (18 to 64 Years)	Comparator Influenza Vaccine (18 to 64 Years)	Influenza Virus Vaccine (9 to 17 Years)
Number of subjects	460	232	400
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)	0	0	149
Adolescents (12-17 years)	0	0	251
Adults (18-64 years)	458	232	0
From 65-84 years	2	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	38.8	37.8	12.7
standard deviation	± 12.4	± 12.6	± 2.6
Gender categorical Units: Subjects			
Female	293	130	222
Male	167	102	178

Reporting group values	Comparator Influenza Vaccine (9 to 17 Years)	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (3 to 8 Years)

Number of subjects	200	402	199
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)	74	402	199
Adolescents (12-17 years)	125	0	0
Adults (18-64 years)	1	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	12.8	5.5	5.4
standard deviation	± 2.6	± 1.7	± 1.7
Gender categorical Units: Subjects			
Female	109	172	98
Male	91	230	101

Reporting group values	Total		
Number of subjects	1893		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	824		
Adolescents (12-17 years)	376		
Adults (18-64 years)	691		
From 65-84 years	2		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	1024		
Male	869		

End points

End points reporting groups

Reporting group title	Influenza Virus Vaccine (18 to 64 Years)
Reporting group description:	
One injection of the investigational influenza virus vaccine was administered intramuscularly.	
Reporting group title	Comparator Influenza Vaccine (18 to 64 Years)
Reporting group description:	
One injection of the comparator influenza vaccine was administered intramuscularly.	
Reporting group title	Influenza Virus Vaccine (9 to 17 Years)
Reporting group description:	
One injection of the investigational influenza virus vaccine was administered intramuscularly.	
Reporting group title	Comparator Influenza Vaccine (9 to 17 Years)
Reporting group description:	
One injection of the comparator influenza vaccine was administered intramuscularly	
Reporting group title	Influenza Virus Vaccine (3 to 8 Years)
Reporting group description:	
Two injections of the investigational influenza virus vaccine were administered intramuscularly.	
Reporting group title	Comparator Influenza Vaccine (3 to 8 Years)
Reporting group description:	
Two injections of the comparator influenza vaccine were administered intramuscularly.	
Subject analysis set title	Agrippal-Enrolled Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who had data in the DEMOG panel.	
Subject analysis set title	Fluvirin-Enrolled Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who had data in the DEMOG panel.	
Subject analysis set title	Agrippal - MITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects in the enrolled population who received a study vaccination, and provided at least one evaluable serum sample.	
Subject analysis set title	Fluvirin - MITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects in the enrolled population who received a study vaccination, and provided at least one evaluable serum sample.	
Subject analysis set title	Agrippal - Per-Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the Full Analysis Set/MITT population who received all the relevant doses of vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol deviation	
Subject analysis set title	Fluvirin - Per-Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the Full Analysis Set/MITT population who received all the relevant doses of vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol deviation.	
Subject analysis set title	Agrippal - Safety Population

Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed population who provided post-baseline safety data.

Subject analysis set title	Fluvirin - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed population who provided post-baseline safety data.

Primary: Percentage of Subjects With Seroprotection, in Healthy Adults 18 to 64 Years of Age

End point title	Percentage of Subjects With Seroprotection, in Healthy Adults 18 to 64 Years of Age[1][2]

End point description:

To evaluate immunogenicity, measured by seroprotection (percentage of subjects achieving a hemagglutination inhibition [HI] titer ≥40) after one injection of the investigational influenza virus vaccine, administered to healthy adults 18 to 64 years of age. The CBER Guidance states that the lower bound of the two-sided 95% CI for the percentage of subjects achieving seroprotection meet or exceed 70%.

End point type	Primary

End point timeframe:

21 days after 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: There were no statistical analysis done.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (18 to 64 Years)	Comparator Influenza Vaccine (18 to 64 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	424	219		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Strain A/H1N1	93 (90 to 95)	99 (97 to 100)		
Strain A/H3N2	96 (94 to 98)	100 (98 to 100)		
Strain B	91 (87 to 93)	86 (81 to 91)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Achieving a Seroconversion Rate, in Adults 18 to 64 Years of Age

End point title	Percentage of Subjects Achieving a Seroconversion Rate, in Adults 18 to 64 Years of Age[3][4]

End point description:

Seroconversion rate is defined as percentage of subjects achieving seroconversion (defined as negative pre-vaccination serum [HI<10]/ post-vaccination HI titer ≥40) or significant increase defined as at least a 4-fold increase). According to the CBER Guidance, the lower bound of the two-sided 95% CI for the

percentage of subjects achieving seroconversion/significant increase meets or exceeds 40%.

End point type	Primary

End point timeframe:

21 days after 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: There were no statistical analysis done.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (18 to 64 Years)	Comparator Influenza Vaccine (18 to 64 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	424	219		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Strain A/H1N1	74 (69 to 78)	86 (81 to 90)		
Strain A/H3N2	72 (68 to 76)	89 (84 to 92)		
Strain B	77 (72 to 81)	74 (68 to 80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Local and Systemic Symptoms in Adults 18 to 64 Years of Age

End point title	Number of Subjects Reporting Solicited Local and Systemic Symptoms in Adults 18 to 64 Years of Age[5]

End point description:

Solicited local and systemic reactions were assessed after vaccination in adults 18 to 64 years of age.

End point type	Secondary

End point timeframe:

7 days after vaccination

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (18 to 64 Years)	Comparator Influenza Vaccine (18 to 64 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	232[6]		
Units: Number of Subjects				
Any local reaction	161	89		
Erythema	27	12		
Induration	38	24		
Swelling	29	15		

Ecchymosis	24	15		
Pain	117	70		
Any Systemic Reaction	147	84		
Chills	21	17		
Malaise	55	27		
Myalgia	66	37		
Arthralgia	30	14		
Headache	108	42		
Sweating	24	11		
Fatigue	46	24		
Fever	10	6		

Notes:

[6] - Actual number of subjects analysed are 233 as one subject was mistakenly enrolled in this age strata

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroprotection, in Healthy Children/Adolescents 9 to 17 Years of Age

End point title	Percentage of Subjects With Seroprotection, in Healthy Children/Adolescents 9 to 17 Years of Age[7]

End point description:

To descriptively evaluate immunogenicity, measured by seroprotection rate (percentage of subjects achieving a hemagglutination inhibition [HI] titer ≥40) after one injection of investigational influenza virus vaccine, administered to healthy children/adolescents 9 to 17 years of age.

End point type	Secondary

End point timeframe:

21 days after vaccination

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (9 to 17 Years)	Comparator Influenza Vaccine (9 to 17 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	192		
Units: Percentages of subjects				
number (confidence interval 95%)				
Strain A/H1N1	99 (97 to 100)	98 (96 to 100)		
Strain A/H3N2	100 (99 to 100)	100 (98 to 100)		
Strain B	93 (90 to 95)	89 (84 to 93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Seroconversion Rate, in Healthy Children/Adolescents 9 to 17 Years of Age

End point title	Percentage of Subjects Achieving Seroconversion Rate, in Healthy Children/Adolescents 9 to 17 Years of Age[8]

End point description:

Seroconversion rate is defined as percentage of subjects achieving seroconversion (defined as negative pre-vaccination serum [HI<10]/ post-vaccination HI titer ≥40) or significant increase (defined as at least a 4-fold increase) after one injection of the investigational influenza virus vaccine, administered to healthy children/adolescents 9 to 17 years of age.

End point type	Secondary

End point timeframe:

21 days after vaccination

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (9 to 17 Years)	Comparator Influenza Vaccine (9 to 17 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	192		
Units: Percentage of subjects				
number (confidence interval 95%)				
Strain A/H1N1	92 (88 to 94)	91 (86 to 94)		
Strain A/H3N2	67 (62 to 72)	92 (87 to 95)		
Strain B	81 (76 to 84)	73 (67 to 80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs), in Healthy Children/Adolescents 9 to 17 Years of Age

End point title	Geometric Mean Titers (GMTs), in Healthy Children/Adolescents 9 to 17 Years of Age[9]

End point description:

To evaluate immunogenicity measured by GMTs after one injection of investigational influenza virus vaccine, administered to healthy children/adolescents 9 to 17 years of age.

End point type	Secondary

End point timeframe:

21 days after vaccination

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (9 to 17 Years)	Comparator Influenza Vaccine (9 to 17 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	192		
Units: Titers				
geometric mean (confidence interval 95%)				
Strain A/H1N1	960 (857 to 1076)	1246 (1058 to 1467)		
Strain A/H3N2	493 (453 to 536)	1463 (1296 to 1651)		
Strain B	144 (127 to 163)	114 (95 to 136)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Local and Systemic Symptoms in Children/Adolescents 9 to 17 Years of Age

End point title	Number of Subjects Reporting Solicited Local and Systemic Symptoms in Children/Adolescents 9 to 17 Years of Age[10]

End point description:

Solicited local and systemic reactions were assessed after vaccination in children/adolescents 9 to 17 years of age.

End point type	Secondary

End point timeframe:

7 days after vaccination

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (9 to 17 Years)	Comparator Influenza Vaccine (9 to 17 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	199		
Units: Number of Subjects				
Any local reaction	134	62		
Erythema	7	3		
Induration	28	13		
Swelling	28	14		
Ecchymosis	9	1		
Pain	117	58		
Any Systemic reaction	91	49		
Chills	18	11		
Malaise	18	8		
Myalgia	35	25		
Arthralgia	11	5		

Headache	52	22		
Sweating	4	3		
Fatigue	25	9		
Fever	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Seroprotection, in Healthy Children 3 to 8 years Age

End point title	Percentage of Subjects With Seroprotection, in Healthy Children 3 to 8 years Age[11]

End point description:

To descriptively evaluate immunogenicity, measured by seroprotection rate (percentage of subjects achieving a hemagglutination inhibition [HI] titer ≥40) after two injections of the investigational influenza virus vaccine, in healthy children 3 to 8 years of age.

End point type	Secondary

End point timeframe:

50 days after vaccination

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (3 to 8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	149		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Strain A/H1N1	97 (94 to 99)	99 (95 to 100)		
Strain A/H3N2	100 (99 to 100)	99 (96 to 100)		
Strain B	85 (80 to 89)	81 (73 to 87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Seroconversion Rate, in Healthy Children 3 to 8 Years of Age

End point title	Percentage of Subjects Achieving Seroconversion Rate, in Healthy Children 3 to 8 Years of Age[12]

End point description:

Seroconversion rate is defined as percentage of subjects achieving seroconversion (defined as negative pre-vaccination serum [HI<10]/ post-vaccination HI titer ≥40) or significant increase (defined as at least a 4-fold increase) after two injections of the investigational influenza virus vaccine, in healthy

children 3 to 8 years of age.

End point type	Secondary

End point timeframe:

50 days after vaccination

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (3 to 8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	149		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Strain A/H1N1	95 (91 to 97)	97 (92 to 99)		
Strain A/H3N2	86 (82 to 90)	95 (90 to 98)		
Strain B	83 (78 to 87)	79 (72 to 85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs), in Healthy Children 3 to 8 Years of Age

End point title	Geometric Mean Titers (GMTs), in Healthy Children 3 to 8 Years of Age[13]

End point description:

To evaluate immunogenicity measured by GMTs after two injections of the investigational influenza virus vaccine, in healthy children 3 to 8 years of age.

End point type	Secondary

End point timeframe:

50 days after vaccination

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (3 to 8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	149		
Units: Titers				
geometric mean (confidence interval 95%)				
Strain A/H1N1	625 (532 to 734)	716 (570 to 898)		
Strain A/H3N2	710 (637 to 792)	1472 (1263 to 1715)		

Strain B	157 (133 to 185)	126 (100 to 158)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Local and Systemic Symptoms after 1st vaccination in Children 3 to 8 Years of Age

End point title	Number of Subjects Reporting Solicited Local and Systemic Symptoms after 1st vaccination in Children 3 to 8 Years of Age[14]

End point description:

Solicited local and systemic reactions were assessed after 1st injection in children 3 to 8 years of age.

End point type	Secondary

End point timeframe:

7 days after 1st Vaccination

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (3 to 8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	199		
Units: Number of Subjects				
Any Local Reaction	92	56		
Erythema	9	5		
Induration	11	10		
Swelling	22	16		
Ecchymosis	18	9		
Pain	68	40		
Any Systemic Reaction	66	38		
Chills	10	8		
Malaise	21	12		
Myalgia	19	9		
Arthralgia	5	2		
Headache	28	18		
Sweating	5	3		
Fatigue	18	9		
Fever	12	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Local and Systemic Symptoms after 2nd vaccination in Children 3 to 8 Years of Age

End point title	Number of Subjects Reporting Solicited Local and Systemic Symptoms after 2nd vaccination in Children 3 to 8 Years of Age[15]

End point description:

Solicited local and systemic reactions were assessed after 2nd vaccination in children 3 to 8 years of age.

End point type	Secondary

End point timeframe:

7 days after 2nd Vaccination

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (3 to 8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	197		
Units: Number of Subjects				
Any Local Reaction	66	39		
Erythema	3	3		
Induration	13	8		
Swelling	13	8		
Ecchymosis	10	5		
Pain	57	35		
Any Systemic Reaction	41	21		
Chills	8	5		
Malaise	19	7		
Myalgia	19	10		
Arthralgia	5	1		
Headache	15	11		
Sweating	3	1		
Fatigue	10	4		
Fever	10	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs), in Healthy adults 18 to 64 Years of Age

End point title	Geometric Mean Titers (GMTs), in Healthy adults 18 to 64 Years of Age[16]

End point description:

Immunogenicity measured by GMTs after one injection of the investigational influenza virus vaccine, in healthy adults 18 to 64 years of age.

End point type	Secondary

End point timeframe:

21 days after vaccination

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There were no statistical analysis done.

End point values	Influenza Virus Vaccine (18 to 64 Years)	Comparator Influenza Vaccine (18 to 64 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	424	219		
Units: Titers				
geometric mean (confidence interval 95%)				
Strain A/H1N1	244 (214 to 278)	512 (426 to 615)		
Strain A/H3N2	219 (196 to 245)	485 (415 to 567)		
Strain B	126 (113 to 140)	104 (90 to 122)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited adverse events were collected from 21 days after the last vaccination (up to day 53) to study termination (up to day 216). All serious adverse events were collected throughout the entire study period (up to day 216).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Influenza Virus Vaccine (9 to 17 Years)

Reporting group description:

One injection of the investigational influenza virus vaccine was administered intramuscularly.

Reporting group title	Comparator Influenza Vaccine (18 to 64 Years)

Reporting group description:

One injection of the comparator influenza vaccine was administered intramuscularly.

Reporting group title	Influenza Virus Vaccine (18 to 64 Years)

Reporting group description:

One injection of the investigational influenza virus vaccine was administered intramuscularly.

Reporting group title	Comparator Influenza Vaccine (3 to 8 Years)

Reporting group description:

Two injections of the comparator influenza vaccine were administered intramuscularly.

Reporting group title	Influenza Virus Vaccine (3 to 8 Years)

Reporting group description:

Two injections of the investigational influenza virus vaccine were administered intramuscularly.

Reporting group title	Comparator Influenza Vaccine (9 to 17 Years)

Reporting group description:

One injection of the comparator influenza vaccine was administered intramuscularly.

Serious adverse events	Influenza Virus Vaccine (9 to 17 Years)	Comparator Influenza Vaccine (18 to 64 Years)	Influenza Virus Vaccine (18 to 64 Years)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 400 (1.00%)	2 / 233 (0.86%)	6 / 460 (1.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
OVARIAN EPITHELIAL CANCER			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	1 / 460 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

EYE INJURY			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
PRESYNCOPE			
subjects affected / exposed	0 / 400 (0.00%)	1 / 233 (0.43%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	1 / 460 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
VISUAL ACUITY REDUCED TRANSIENTLY			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	1 / 460 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
CHRONIC GASTRITIS			
subjects affected / exposed	0 / 400 (0.00%)	1 / 233 (0.43%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	1 / 400 (0.25%)	0 / 233 (0.00%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ASTHMATIC CRISIS			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

RENAL COLIC			
subjects affected / exposed	1 / 400 (0.25%)	0 / 233 (0.00%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	2 / 400 (0.50%)	0 / 233 (0.00%)	1 / 460 (0.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	1 / 460 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSENTERY			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	1 / 460 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENCEPHALITIS			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 400 (0.00%)	0 / 233 (0.00%)	0 / 460 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Comparator Influenza Vaccine (3 to 8 Years)	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (9 to 17 Years)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 199 (1.51%)	3 / 402 (0.75%)	0 / 199 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
OVARIAN EPITHELIAL CANCER			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
EYE INJURY			
subjects affected / exposed	0 / 199 (0.00%)	1 / 402 (0.25%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
PRESYNCOPE			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
ABORTION SPONTANEOUS			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
VISUAL ACUITY REDUCED TRANSIENTLY			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
CHRONIC GASTRITIS			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			

subjects affected / exposed	1 / 199 (0.50%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ASTHMATIC CRISIS			
subjects affected / exposed	0 / 199 (0.00%)	1 / 402 (0.25%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
RENAL COLIC			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSENTERY			
subjects affected / exposed	0 / 199 (0.00%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENCEPHALITIS			
subjects affected / exposed	1 / 199 (0.50%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 199 (0.50%)	0 / 402 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

URINARY TRACT INFECTION			
subjects affected / exposed	0 / 199 (0.00%)	1 / 402 (0.25%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Influenza Virus Vaccine (9 to 17 Years)	Comparator Influenza Vaccine (18 to 64 Years)	Influenza Virus Vaccine (18 to 64 Years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 400 (41.75%)	128 / 233 (54.94%)	235 / 460 (51.09%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	52 / 400 (13.00%)	45 / 233 (19.31%)	111 / 460 (24.13%)
occurrences (all)	56	54	133
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	18 / 400 (4.50%)	18 / 233 (7.73%)	22 / 460 (4.78%)
occurrences (all)	24	20	25
FATIGUE			
subjects affected / exposed	25 / 400 (6.25%)	24 / 233 (10.30%)	47 / 460 (10.22%)
occurrences (all)	25	26	51
INJECTION SITE ERYTHEMA			
subjects affected / exposed	7 / 400 (1.75%)	12 / 233 (5.15%)	27 / 460 (5.87%)
occurrences (all)	7	12	27
INJECTION SITE HAEMORRHAGE			
subjects affected / exposed	9 / 400 (2.25%)	15 / 233 (6.44%)	25 / 460 (5.43%)
occurrences (all)	9	15	25
INJECTION SITE INDURATION			
subjects affected / exposed	28 / 400 (7.00%)	24 / 233 (10.30%)	38 / 460 (8.26%)
occurrences (all)	28	24	38
INJECTION SITE PAIN			
subjects affected / exposed	117 / 400 (29.25%)	70 / 233 (30.04%)	117 / 460 (25.43%)
occurrences (all)	120	70	121
INJECTION SITE SWELLING			

subjects affected / exposed	28 / 400 (7.00%)	15 / 233 (6.44%)	29 / 460 (6.30%)
occurrences (all)	28	15	29
MALAISE			
subjects affected / exposed	18 / 400 (4.50%)	28 / 233 (12.02%)	56 / 460 (12.17%)
occurrences (all)	18	29	61
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS			
subjects affected / exposed	4 / 400 (1.00%)	11 / 233 (4.72%)	24 / 460 (5.22%)
occurrences (all)	4	14	26
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	11 / 400 (2.75%)	15 / 233 (6.44%)	32 / 460 (6.96%)
occurrences (all)	11	16	38
MYALAGIA			
subjects affected / exposed	35 / 400 (8.75%)	38 / 233 (16.31%)	66 / 460 (14.35%)
occurrences (all)	36	39	74

Non-serious adverse events	Comparator Influenza Vaccine (3 to 8 Years)	Influenza Virus Vaccine (3 to 8 Years)	Comparator Influenza Vaccine (9 to 17 Years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 199 (45.73%)	153 / 402 (38.06%)	80 / 199 (40.20%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	26 / 199 (13.07%)	41 / 402 (10.20%)	23 / 199 (11.56%)
occurrences (all)	30	46	29
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	12 / 199 (6.03%)	18 / 402 (4.48%)	11 / 199 (5.53%)
occurrences (all)	14	19	11
FATIGUE			
subjects affected / exposed	12 / 199 (6.03%)	26 / 402 (6.47%)	9 / 199 (4.52%)
occurrences (all)	14	28	9
INJECTION SITE ERYTHEMA			
subjects affected / exposed	7 / 199 (3.52%)	12 / 402 (2.99%)	3 / 199 (1.51%)
occurrences (all)	8	12	3
INJECTION SITE HAEMORRHAGE			

subjects affected / exposed	13 / 199 (6.53%)	26 / 402 (6.47%)	1 / 199 (0.50%)
occurrences (all)	14	28	1
INJECTION SITE INDURATION			
subjects affected / exposed	16 / 199 (8.04%)	23 / 402 (5.72%)	13 / 199 (6.53%)
occurrences (all)	18	24	13
INJECTION SITE PAIN			
subjects affected / exposed	59 / 199 (29.65%)	97 / 402 (24.13%)	58 / 199 (29.15%)
occurrences (all)	75	129	58
INJECTION SITE SWELLING			
subjects affected / exposed	20 / 199 (10.05%)	34 / 402 (8.46%)	14 / 199 (7.04%)
occurrences (all)	24	37	14
MALAISE			
subjects affected / exposed	19 / 199 (9.55%)	37 / 402 (9.20%)	8 / 199 (4.02%)
occurrences (all)	19	41	8
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS			
subjects affected / exposed	4 / 199 (2.01%)	8 / 402 (1.99%)	3 / 199 (1.51%)
occurrences (all)	4	8	3
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	3 / 199 (1.51%)	10 / 402 (2.49%)	5 / 199 (2.51%)
occurrences (all)	3	12	5
MYALAGIA			
subjects affected / exposed	17 / 199 (8.54%)	34 / 402 (8.46%)	25 / 199 (12.56%)
occurrences (all)	19	41	26

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2007	To include children / adolescents aged 9 to 17 and adults aged 18 to 64 years to the originally proposed study population.
26 June 2007	The primary immunogenicity objective, which previously included all 3 age strata and was amended to refer to the adults aged 18 to 64 only. The secondary objective was also amended to refer to adults aged 18 to 64 years for one injection of Fluvirin, children/adolescents aged 9 to 17 years for one injection of either Agrippal or Fluvirin and children aged 3 to 8 years for two injections of either Agrippal or Fluvirin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

NA

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22691101