



## Clinical trial results:

### A Phase III, Observer-blind, Randomized, Controlled, Multicenter Study to Evaluate the Safety of a Trivalent Subunit Influenza Vaccine Produced either in Mammalian Cell Culture or in Embryonated Chicken Eggs (Fluvirin®), in Healthy Children and Adolescents 4 to 17 Years of Age.

#### Summary

EudraCT number	2012-001223-13
Trial protocol	Outside EU/EEA
Global end of trial date	13 June 2014

#### Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	17 March 2015
Version creation reason	<ul style="list-style-type: none"><li>• 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.</li></ul>

#### Trial information

##### Trial identification

Sponsor protocol code	V58_31
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01857206
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics
Sponsor organisation address	Via Fiorentina, 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	29 August 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 June 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate safety and tolerability of one or two doses (administered 4 weeks apart) of mammalian cell culture-derived influenza vaccine (TIVc) and Fluvirin (TIVf) in children and adolescents  $\geq 4$  to  $\leq 17$  years of age.

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, Novartis Vaccine and Diagnostics codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 May 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 322
Country: Number of subjects enrolled	United States: 314
Country: Number of subjects enrolled	New Zealand: 99
Country: Number of subjects enrolled	Philippines: 680
Country: Number of subjects enrolled	Thailand: 640
Worldwide total number of subjects	2055
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)	1451
Adolescents (12-17 years)	604
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at a total of 34 centers in 5 countries. 18 sites in the US, 6 sites in Australia, 2 sites in New Zealand, 5 sites in the Philippines and 3 sites in Thailand.

### 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, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	TIVc

Arm description:

Subjects  $\geq 4$  to  $\leq 17$  years of age received one or two doses of mammalian cell-culture-derived trivalent influenza vaccine based on their previous vaccination status.

Arm type	Experimental
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, mammalian cell culture-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:

Subjects  $\geq 4$  to  $\leq 8$  years previously vaccinated and all subjects  $\geq 9$  to  $\leq 17$ : one dose of 0.5mL TIVc. Subjects  $\geq 4$  to  $\leq 8$  years not previously vaccinated: two doses of 0.5mL TIVc.

<b>Arm title</b>	TIVf
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Arm description:

Subjects  $\geq 4$  to  $\leq 17$  years of age received one or two doses of egg-derived trivalent influenza vaccine based on their previous vaccination status.

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 pen
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects  $\geq 4$  to  $\leq 8$  years previously vaccinated and all subjects  $\geq 9$  to  $\leq 17$ : one dose of 0.5mL TIVf. Subjects  $\geq 4$  to  $\leq 8$  years not previously vaccinated: two doses of 0.5mL TIVf.

<b>Number of subjects in period 1</b>	TIVc	TIVf
Started	1372	683
Completed	1359	673
Not completed	13	10
Consent withdrawn by subject	1	-
Unclassified	3	3
Lost to follow-up	9	6
Administrative reason	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	TIVc
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Reporting group description:

Subjects  $\geq 4$  to  $\leq 17$  years of age received one or two doses of mammalian cell-culture-derived trivalent influenza vaccine based on their previous vaccination status.

Reporting group title	TIVf
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Reporting group description:

Subjects  $\geq 4$  to  $\leq 17$  years of age received one or two doses of egg-derived trivalent influenza vaccine based on their previous vaccination status.

Reporting group values	TIVc	TIVf	Total
Number of subjects	1372	683	2055
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	9.1 $\pm 3.8$	9.3 $\pm 3.9$	-
Gender categorical Units: Subjects			
Female	703	349	1052
Male	669	334	1003

## End points

### End points reporting groups

Reporting group title	TIVc
Reporting group description: Subjects $\geq 4$ to $\leq 17$ years of age received one or two doses of mammalian cell-culture-derived trivalent influenza vaccine based on their previous vaccination status.	
Reporting group title	TIVf
Reporting group description: Subjects $\geq 4$ to $\leq 17$ years of age received one or two doses of egg-derived trivalent influenza vaccine based on their previous vaccination status.	
Subject analysis set title	TIVc ( $\geq 4$ to $\leq 8$ years)- Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects in the exposed set who have either postvaccination safety data or solicited safety data.	
Subject analysis set title	TIVf ( $\geq 4$ to $\leq 8$ years)- Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects in the exposed set who have either postvaccination safety data or solicited safety data.	
Subject analysis set title	TIVc ( $\geq 9$ to $\leq 17$ years)- Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects in the exposed set who have either postvaccination safety data or solicited safety data.	
Subject analysis set title	TIVc ( $\geq 9$ to $\leq 17$ years)- Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects in the exposed set who have either postvaccination safety data or solicited safety data.	

### **Primary: 1. Number Of Subjects Reporting Solicited Local and Systemic Adverse Events and Other Indicators Of Reactogenicity After Any Vaccination.**

End point title	1. Number Of Subjects Reporting Solicited Local and Systemic Adverse Events and Other Indicators Of Reactogenicity After Any Vaccination. <sup>[1]</sup>
End point description: Safety was assessed as the number of subjects who reported solicited local and systemic adverse events and other indicators of reactogenicity following vaccination with either mammalian cell culture-derived or egg-derived trivalent influenza vaccination in subjects aged $\geq 4$ To $\leq 17$ Years.  Analysis was done on the solicited safety dataset, i.e., the subjects in the exposed population who provided postvaccination solicited safety data.	
End point type	Primary
End point timeframe: Day 1 to Day 7 after any 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: Evaluation of the safety endpoints was of descriptive nature without prespecified criteria.

End point values	TIVc ( $\geq 4$ to $\leq 8$ years)- Safety Set	TIVf ( $\geq 4$ to $\leq 8$ years)- Safety Set	TIVc ( $\geq 9$ to $\leq 17$ years)- Safety Set	TIVc ( $\geq 9$ to $\leq 17$ years)- Safety Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	688	341	341	682
Units: Subjects				
Any Local	422	202	160	370
Injection site Induration (AE)	109	43	33	46
Injection site Swelling (AE)	87	37	26	36
Injection site Erythema (AE)	148	57	37	72
Injection site Ecchymosis (AE)	68	30	11	27
Injection site Pain (AE)	384	186	142	356
Any Systemic	252	110	113	267
Chills (AE)	47	17	7	39
Nausea (AE)	57	26	16	45
Myalgia (AE)	113	41	44	126
Arthralgia (AE)	39	16	14	54
Headache (AE)	105	42	57	128
Fatigue (AE)	92	34	56	109
Loss of appetite (AE)	68	25	12	50
Malaise(AE)	112	43	46	99
Sweating (AE)	39	20	23	52
Fever ( $\geq 38^{\circ}\text{C}$ ) (AE)	48	30	5	12
$\geq 40^{\circ}\text{C}$ (AE)	3	0	0	0
Prevention of pain and (or) fever (Indicator)	61	29	10	24
Treatment of pain and (or) fever (Indicator)	90	40	18	39

## Statistical analyses

No statistical analyses for this end point

### Primary: 2. Number Of Subjects Reporting Unsolicited Adverse Events After Any Vaccination.

End point title	2. Number Of Subjects Reporting Unsolicited Adverse Events After Any Vaccination. <sup>[2]</sup>
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End point description:

Safety was assessed as the number of subjects who reported unsolicited adverse events following vaccination with either mammalian cell culture-derived or egg-derived trivalent influenza vaccination in subjects aged  $\geq 4$  To  $\leq 17$  Years.

Analysis was done on the unsolicited safety dataset, i.e. the subjects in the exposed population who provided postvaccination unsolicited safety data.

End point type	Primary
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End point timeframe:

Day 1 to Day 49 for subjects aged  $\geq 4$  To  $\leq 8$  years not previously vaccinated. Day 1 to Day 28 for subjects aged  $\geq 4$  To  $\leq 8$  years previously vaccinated and all subjects aged  $\geq 9$  To  $\leq 17$  years.

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: Evaluation of the safety endpoints was of descriptive nature without prespecified criteria.

End point values	TIVc ( $\geq 4$ to $\leq 8$ years)- Safety Set	TIVf ( $\geq 4$ to $\leq 8$ years)- Safety Set	TIVc ( $\geq 9$ to $\leq 17$ years)- Safety Set	TIVc ( $\geq 9$ to $\leq 17$ years)- Safety Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	688	341	341	682
Units: Subjects				
Any AE	277	139	88	158
At least possibly related AEs	50	26	22	32

## Statistical analyses

No statistical analyses for this end point

### Primary: 3. Number Of Subjects Reporting Unsolicited Serious Adverse Events After Any Vaccination.

End point title	3. Number Of Subjects Reporting Unsolicited Serious Adverse Events After Any Vaccination. <sup>[3]</sup>
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End point description:

Safety was assessed as the number of subjects who reported serious adverse events (SAEs), medically attended AEs and new onset of chronic diseases (NOCD) in subjects aged  $\geq 4$  To  $\leq 17$  Years.

Analysis was done on the unsolicited safety dataset, i.e. the subjects in the exposed population who provided postvaccination unsolicited safety data.

End point type	Primary
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End point timeframe:

Day 1 to Day 183 for previously vaccinated subjects and Day 1 to Day 213 for not-previously vaccinated subjects

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: Evaluation of the safety endpoints was of descriptive nature without prespecified criteria.

End point values	TIVc ( $\geq 4$ to $\leq 8$ years)- Safety Set	TIVf ( $\geq 4$ to $\leq 8$ years)- Safety Set	TIVc ( $\geq 9$ to $\leq 17$ years)- Safety Set	TIVc ( $\geq 9$ to $\leq 17$ years)- Safety Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	688	341	341	682
Units: Subjects				
SAE	17	7	9	7
At least possibly related SAEs	0	0	0	0
AE leading to withdrawal	0	0	0	0
Medically attended AE	284	139	105	172
NOCD	5	4	1	3
Death	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

6 months or 7 months based on the previous vaccination status of the subjects.  
Of a total of 2055 subjects and 2050 subjects were included in unolicted safety set.

Adverse event reporting additional description:

Subjects aged  $\geq 4$  to  $\leq 8$  years not previously vaccinated, AEs collected from day 1 to 7 and day 29 to 35; SAEs, medically attended AEs and NOCD till day 213. Subjects aged  $\geq 4$  to  $\leq 8$  years previously vaccinated and subjects aged  $\geq 9$  to  $\leq 17$  Years, AEs were collected from day 1 to 7; SAEs, medically attended AEs and NOCD were collected till day 183.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	TIVc
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Reporting group description:

Subjects  $\geq 4$  to  $\leq 17$  years of age received one or two doses of mammalian cell-culture-derived trivalent influenza vaccine based on their previous vaccination status.

Reporting group title	TIVf
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Reporting group description:

Subjects  $\geq 4$  to  $\leq 17$  years of age received one or two doses of egg-derived trivalent influenza vaccine based on their previous vaccination status.

<b>Serious adverse events</b>	TIVc	TIVf	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 1370 (1.75%)	16 / 682 (2.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	3 / 1370 (0.22%)	3 / 682 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal scratch			
subjects affected / exposed	1 / 1370 (0.07%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			

subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ligament rupture</b>			
subjects affected / exposed	0 / 1370 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Head injury</b>			
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Multiple injuries</b>			
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Radius fracture</b>			
subjects affected / exposed	1 / 1370 (0.07%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nervous system disorders</b>			
<b>Cerebellar ataxia</b>			
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Visual field defect</b>			
subjects affected / exposed	0 / 1370 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pregnancy, puerperium and perinatal conditions</b>			
<b>Abortion spontaneous</b>			
subjects affected / exposed	0 / 1370 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexal torsion			
subjects affected / exposed	0 / 1370 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 1370 (0.00%)	1 / 682 (0.15%)	
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 / 1370 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	2 / 1370 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	1 / 1370 (0.07%)	1 / 682 (0.15%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dengue fever		
subjects affected / exposed	3 / 1370 (0.22%)	3 / 682 (0.44%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	2 / 1370 (0.15%)	1 / 682 (0.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nasopharyngitis		
subjects affected / exposed	0 / 1370 (0.00%)	1 / 682 (0.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pharyngitis		
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pharyngotonsillitis		
subjects affected / exposed	0 / 1370 (0.00%)	1 / 682 (0.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory syncytial virus infection		
subjects affected / exposed	0 / 1370 (0.00%)	1 / 682 (0.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sinusitis bacterial		

subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 1370 (0.07%)	0 / 682 (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: 5 %

<b>Non-serious adverse events</b>	TIVc	TIVf	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1019 / 1370 (74.38%)	482 / 682 (70.67%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	245 / 1370 (17.88%)	106 / 682 (15.54%)	
occurrences (all)	310	125	
General disorders and administration site conditions			
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	87 / 1370 (6.35%)	26 / 682 (3.81%)	
occurrences (all)	95	28	
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	204 / 1370 (14.89%)	92 / 682 (13.49%)	
occurrences (all)	247	111	
Injection site erythema			
alternative assessment type: Systematic			

subjects affected / exposed	249 / 1370 (18.18%)	111 / 682 (16.28%)	
occurrences (all)	295	134	
Injection site haemorrhage			
subjects affected / exposed	96 / 1370 (7.01%)	41 / 682 (6.01%)	
occurrences (all)	110	51	
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	162 / 1370 (11.82%)	78 / 682 (11.44%)	
occurrences (all)	185	85	
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	818 / 1370 (59.71%)	370 / 682 (54.25%)	
occurrences (all)	979	456	
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	136 / 1370 (9.93%)	72 / 682 (10.56%)	
occurrences (all)	157	83	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	211 / 1370 (15.40%)	89 / 682 (13.05%)	
occurrences (all)	260	109	
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	80 / 1370 (5.84%)	51 / 682 (7.48%)	
occurrences (all)	92	60	
Gastrointestinal disorders			
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	106 / 1370 (7.74%)	44 / 682 (6.45%)	
occurrences (all)	121	49	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	91 / 1370 (6.64%)	43 / 682 (6.30%)	
occurrences (all)	100	55	

<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>98 / 1370 (7.15%)</p> <p>109</p>	<p>31 / 682 (4.55%)</p> <p>35</p>	
<p>Myalgia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>245 / 1370 (17.88%)</p> <p>275</p>	<p>86 / 682 (12.61%)</p> <p>95</p>	
<p>Infections and infestations</p> <p>Upper respiratory tract infection</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>191 / 1370 (13.94%)</p> <p>229</p>	<p>86 / 682 (12.61%)</p> <p>104</p>	
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>119 / 1370 (8.69%)</p> <p>144</p>	<p>37 / 682 (5.43%)</p> <p>39</p>	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2012	Included comprehensive revision of the protocol in accordance with the memo provided by CBER, following the revised "Safety Data Collection process" as agreed with CBER.
14 March 2013	Included comprehensive revision of the protocol, including language to allow extension in northern hemisphere, improve clarity on the definition of previously vaccinated status, allow reminder and safety calls to be performed as a clinic visit, correct reflection of diary card, further specification in exclusion criteria, further specification of the physical examination requirements and a number of other corrections; impacting study conduct and/or analyses, and EC/IRB approval was obtained prior to FSFV.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported