



## Clinical trial results:

**A Phase III, double-blind, randomized, multicenter study to assess safety and immunogenicity of GlaxoSmithKline Biologicals' Quadrivalent Split Virion Influenza Vaccine (GSK2321138A) manufactured with a new process, in adults aged 18 to 49 years and in children aged 6 months to 17 years.**

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## Summary

EudraCT number	2014-000955-10
Trial protocol	DE ES CZ
Global end of trial date	18 April 2015

## Results information

Result version number	v1
This version publication date	20 April 2016
First version publication date	20 April 2016

## Trial information

### Trial identification

Sponsor protocol code	201251
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02207413
WHO universal trial number (UTN)	-

Notes:

## Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupport@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupport@gsk.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	18 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To describe the safety of 1 dose of FLU D-QIV vaccine produced by the IP and 1 dose of FLU D-QIV vaccine produced by the LP in terms of solicited (7 days after vaccination), unsolicited adverse events (AEs) 21 days after vaccination in subjects aged 18-49 years and Oculorespiratory Syndrome (ORS) over 3 days post vaccination in 18-49 & 3-17 years of age
- To demonstrate the immunogenic non-inferiority of FLU D-QIV IP as compared to FLU D-QIV LP in terms of haemagglutination inhibition (HI) geometric mean titer (GMT) ratio at 28 days after completion of the vaccination series in subjects aged 3-17 years.
- To demonstrate the immunogenic non-inferiority of FLU D-QIV IP as compared to FLU D-QIV LP in terms of HI GMT ratio at 28 days after completion of the vaccination series in subjects aged 6-35 months.
- To demonstrate there is no significant increase of fever  $\geq 38^{\circ}\text{C}$  after any dose with FLU D-QIV IP compared to FLU D-QIV LP during the 7 days post-vaccination in subjects aged 6-35 months

Protection of trial subjects:

All subjects were supervised for 30 min after vaccination/product administration with appropriate medical treatment readily available. Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products. Subjects were followed-up for 31 days after the last vaccination/product administration.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 177
Country: Number of subjects enrolled	Spain: 455
Country: Number of subjects enrolled	Czech Republic: 174
Country: Number of subjects enrolled	France: 226
Country: Number of subjects enrolled	Germany: 537
Country: Number of subjects enrolled	United States: 138
Country: Number of subjects enrolled	Bangladesh: 179
Worldwide total number of subjects	1886
EEA total number of subjects	1569

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	623
Children (2-11 years)	849
Adolescents (12-17 years)	287
Adults (18-64 years)	127
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Primed subjects: Received 2 doses of seasonal influenza vaccine separated by at least one month during the last season or had received at least 1 dose prior to last season. Unprimed subjects: Did not receive any seasonal influenza vaccine in the past or received only 1 dose for the first time in the last influenza season.

### Pre-assignment

Screening details:

For 5 subjects, study vaccine dose not administered at all but subject number was allocated. Some data has been analysed in sub-groups by age: 3-4 years, 5-17 years, 6 months to <5 years.

### Period 1

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

Blinding implementation details:

By double-blind, it was meant that during the course of the study, the subject, subject's parent(s)/LAR(s), investigator and sponsor staff who were involved in the treatment or clinical evaluation of the subjects and review/analysis of data were unaware of the treatment assignments. The laboratory in charge of the laboratory testing was blinded to the treatment, and codes were used to link the subject and study to each sample.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Influsplit Tetra_IP Adult Group

Arm description:

Subjects in the Influsplit Tetra\_IP group aged between 18 to 49 years received 1 dose of Influsplit Tetra™ vaccine produced by investigational process (IP) at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm.

Arm type	Experimental
Investigational medicinal product name	Influsplit Tetra™ vaccine produced by investigational process (IP)
Investigational medicinal product code	
Other name	Fluarix Tetra™, Fluarix Quadrivalent® (GSK2321138A)
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Influsplit Tetra™ vaccine using a new manufacturing process administered intramuscularly (IM) in the deltoid region of non-dominant arm (Dose 1) in Adults Group and in non-dominant deltoid or left anterolateral thigh (Dose 1) and dominant deltoid or right anterolateral (Dose 2 – unprimed subjects) in 6-35m and 3-17y Groups.

<b>Arm title</b>	Influsplit Tetra_LP Adult Group
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Arm description:

Subjects in the Influsplit Tetra\_LP aged between 18 to 49 years received 1 dose of Influsplit Tetra™ vaccine produced by currently licensed process (LP) at Day 0. Influsplit Tetra™ vaccine produced by currently LP was administered intramuscularly in the deltoid region of left or non-dominant arm.

Arm type	Active comparator
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Investigational medicinal product name	Influsplit Tetra™ vaccine produced by licensed process (LP)
Investigational medicinal product code	
Other name	Fluarix Tetra™, Fluarix Quadrivalent® (GSK2321138A)
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

Influsplit Tetra™ vaccine using a licensed manufacturing process administered IM in the deltoid region of non-dominant arm (Dose 1) in Adults Group and in non-dominant deltoid or left anterolateral thigh (Dose 1) and dominant deltoid or right anterolateral (Dose 2 – unprimed subjects) in 6-35m and 3-17y Groups.

<b>Arm title</b>	Influsplit Tetra_IP 3-17y Group
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**Arm description:**

Subjects in the Influsplit Tetra\_IP group aged between 3 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by IP at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Arm type	Experimental
Investigational medicinal product name	Influsplit Tetra™ vaccine produced by investigational process (IP)
Investigational medicinal product code	
Other name	Fluarix Tetra™, Fluarix Quadrivalent® (GSK2321138A)
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

Influsplit Tetra™ vaccine using a new manufacturing process administered intramuscularly (IM) in the deltoid region of non-dominant arm (Dose 1) in Adults Group and in non-dominant deltoid or left anterolateral thigh (Dose 1) and dominant deltoid or right anterolateral (Dose 2 – unprimed subjects) in 6-35m and 3-17y Groups.

<b>Arm title</b>	Influsplit Tetra_LP 3-17y Group
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**Arm description:**

Subjects in the Influsplit Tetra\_LP group aged between 3 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by LP at Day 0. Influsplit Tetra™ vaccine produced by LP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Arm type	Active comparator
Investigational medicinal product name	Influsplit Tetra™ vaccine produced by licensed process (LP)
Investigational medicinal product code	
Other name	Fluarix Tetra™, Fluarix Quadrivalent® (GSK2321138A)
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

Influsplit Tetra™ vaccine using a licensed manufacturing process administered IM in the deltoid region of non-dominant arm (Dose 1) in Adults Group and in non-dominant deltoid or left anterolateral thigh (Dose 1) and dominant deltoid or right anterolateral (Dose 2 – unprimed subjects) in 6-35m and 3-17y Groups.

<b>Arm title</b>	Influsplit Tetra_IP 6-35m Group
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**Arm description:**

Subjects in the Influsplit Tetra\_IP group aged between 6 months to 35 months received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Influsplit Tetra™ vaccine produced by IP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects ≥ 12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects ≥ 12 months of age (Day 28).

Arm type	Experimental
Investigational medicinal product name	Influsplit Tetra™ vaccine produced by investigational process (IP)
Investigational medicinal product code	
Other name	Fluarix Tetra™, Fluarix Quadrivalent® (GSK2321138A)
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

Influsplit Tetra™ vaccine using a new manufacturing process administered intramuscularly (IM) in the deltoid region of non-dominant arm (Dose 1) in Adults Group and in non-dominant deltoid or left anterolateral thigh (Dose 1) and dominant deltoid or right anterolateral (Dose 2 – unprimed subjects) in 6-35m and 3-17y Groups.

<b>Arm title</b>	Influsplit Tetra_LP 6-35m Group
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**Arm description:**

Subjects in the Influsplit Tetra\_LP group aged between 6 months to 35 months received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Influsplit Tetra™ vaccine produced by LP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects ≥ 12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects ≥ 12 months of age (Day 28).

Arm type	Active comparator
Investigational medicinal product name	Influsplit Tetra™ vaccine produced by licensed process (LP)
Investigational medicinal product code	
Other name	Fluarix Tetra™, Fluarix Quadrivalent® (GSK2321138A)
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

Influsplit Tetra™ vaccine using a licensed manufacturing process administered IM in the deltoid region of non-dominant arm (Dose 1) in Adults Group and in non-dominant deltoid or left anterolateral thigh (Dose 1) and dominant deltoid or right anterolateral (Dose 2 – unprimed subjects) in 6-35m and 3-17y Groups.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group	Influsplit Tetra_IP 3-17y Group
Started	60	60	410
Completed	59	60	410
Not completed	1	0	0
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	-	-
Migrated/moved from study area	-	-	-
Lost to follow-up	-	-	-

<b>Number of subjects in period 1<sup>[1]</sup></b>	Influsplit Tetra_LP 3-17y Group	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group
Started	411	466	474
Completed	410	459	461
Not completed	1	7	13
Consent withdrawn by subject	-	3	7
Adverse event, non-fatal	-	2	1

Migrated/moved from study area	-	1	-
Lost to follow-up	1	1	5

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: For 5 subjects, study vaccine dose not administered at all but subject number was allocated.

## Baseline characteristics

### Reporting groups

Reporting group title	Influsplit Tetra_IP Adult Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 18 to 49 years received 1 dose of Influsplit Tetra™ vaccine produced by investigational process (IP) at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm.

Reporting group title	Influsplit Tetra_LP Adult Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP aged between 18 to 49 years received 1 dose of Influsplit Tetra™ vaccine produced by currently licensed process (LP) at Day 0. Influsplit Tetra™ vaccine produced by currently LP was administered intramuscularly in the deltoid region of left or non-dominant arm.

Reporting group title	Influsplit Tetra_IP 3-17y Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 3 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by IP at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Reporting group title	Influsplit Tetra_LP 3-17y Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP group aged between 3 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by LP at Day 0. Influsplit Tetra™ vaccine produced by LP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Reporting group title	Influsplit Tetra_IP 6-35m Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 6 months to 35 months received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Influsplit Tetra™ vaccine produced by IP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects ≥ 12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects ≥ 12 months of age (Day 28).

Reporting group title	Influsplit Tetra_LP 6-35m Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP group aged between 6 months to 35 months received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Influsplit Tetra™ vaccine produced by LP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects ≥ 12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects ≥ 12 months of age (Day 28).

Reporting group values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group	Influsplit Tetra_IP 3-17y Group
Number of subjects	60	60	410
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			



Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median standard deviation	29.8 ± 8.7	31.2 ± 9.3	9.4 ± 4.2
Gender categorical Units: Subjects			
Female Male	41 19	35 25	196 214
Age Continuous Units: Months median standard deviation	0 ± 0	0 ± 0	0 ± 0

<b>Reporting group values</b>	Influsplit Tetra_LP 3-17y Group	Influsplit Tetra_IP 6- 35m Group	Influsplit Tetra_LP 6-35m Group
Number of subjects	411	466	474
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median standard deviation	9.4 ± 4.2	0 ± 0	0 ± 0
Gender categorical Units: Subjects			
Female Male	187 224	223 243	209 265
Age Continuous Units: Months median standard deviation	0 ± 0	19.7 ± 8	19.9 ± 8.3

<b>Reporting group values</b>	Total		
Number of subjects	1881		

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)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
median			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	891		
Male	990		
Age Continuous			
Units: Months			
median			
standard deviation	-		

## End points

### End points reporting groups

Reporting group title	Influsplit Tetra_IP Adult Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 18 to 49 years received 1 dose of Influsplit Tetra™ vaccine produced by investigational process (IP) at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm.

Reporting group title	Influsplit Tetra_LP Adult Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP aged between 18 to 49 years received 1 dose of Influsplit Tetra™ vaccine produced by currently licensed process (LP) at Day 0. Influsplit Tetra™ vaccine produced by currently LP was administered intramuscularly in the deltoid region of left or non-dominant arm.

Reporting group title	Influsplit Tetra_IP 3-17y Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 3 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by IP at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Reporting group title	Influsplit Tetra_LP 3-17y Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP group aged between 3 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by LP at Day 0. Influsplit Tetra™ vaccine produced by LP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Reporting group title	Influsplit Tetra_IP 6-35m Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 6 months to 35 months received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Influsplit Tetra™ vaccine produced by IP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects  $\geq$  12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects  $\geq$  12 months of age (Day 28).

Reporting group title	Influsplit Tetra_LP 6-35m Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP group aged between 6 months to 35 months received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Influsplit Tetra™ vaccine produced by LP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects  $\geq$  12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects  $\geq$  12 months of age (Day 28).

Subject analysis set title	Influsplit Tetra_IP 3-4y Group
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects in the Influsplit Tetra\_IP group aged between 3 to 4 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Subject analysis set title	Influsplit Tetra_LP 3-4y Group
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects in the Influsplit Tetra\_LP group aged between 3 to 4 years received 1 dose (primed subjects)

at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Influsplit Tetra™ vaccine produced by LP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Subject analysis set title	Influsplit Tetra_IP 5-17y Group
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects in the Influsplit Tetra\_IP group aged between 5 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by IP at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Subject analysis set title	Influsplit Tetra_LP 5-17y Group
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects in the Influsplit Tetra\_LP group aged between 5 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by LP at Day 0. Influsplit Tetra™ vaccine produced by LP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Subject analysis set title	Influsplit Tetra_IP 6m-<5y Group
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects in the Influsplit Tetra\_IP group aged between 6 months to <5 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Influsplit Tetra™ vaccine produced by IP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects ≥ 12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects ≥ 12 months of age (Day 28).

Subject analysis set title	Influsplit Tetra_LP 6m-<5y Group
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects in the Influsplit Tetra\_LP group aged between 6 months to <5 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Influsplit Tetra™ vaccine produced by LP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects ≥ 12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects ≥ 12 months of age (Day 28).

### **Primary: Number of subjects aged 18-49 years reporting solicited local adverse events (AEs).**

End point title	Number of subjects aged 18-49 years reporting solicited local adverse events (AEs). <sup>[1][2]</sup>
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End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of the specified solicited local symptom regardless of its intensity. Grade 3 pain = significant pain at rest and pain that prevented normal everyday activities. Grade 3 redness and swelling = greater than 100 millimeters (mm) i.e. >100mm.

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	59		
Units: Subjects				
Any Pain	41	32		
Grade 3 Pain	1	0		
Any Redness	1	1		
Grade 3 Redness	0	0		
Any Swelling	2	4		
Grade 3 Swelling	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects aged 18-49 years reporting any, grade 3 and related solicited general symptoms.

End point title	Number of subjects aged 18-49 years reporting any, grade 3 and related solicited general symptoms. <sup>[3]</sup> <sup>[4]</sup>
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End point description:

Solicited general symptoms assessed were fatigue, gastrointestinal symptoms, headache, Joint Pain, myalgia, shivering and fever. Gastrointestinal symptoms included nausea, vomiting, diarrhoea and/or abdominal pain. Any was defined as any solicited general symptom reported irrespective of intensity and relationship to vaccination. Grade 3 was defined as symptoms that prevented normal activities. Related was defined as symptoms assessed by the investigator to have a causal relationship to vaccination. Any fever was defined as subjects with a documented temperature of greater than or equal to ( $\geq$ ) 38°C/100.4°F by any route and all subjects reporting temperature less than ( $<$ ) 38°C but with missing values (MC) for at least one day during the solicited period. Grade 3 fever was defined as temperature  $\geq$  39.0°C.

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	59		
Units: Subjects				
Any Fatigue	32	20		

Grade 3 Fatigue	0	0		
Related Fatigue	28	20		
Any Gastrointestinal symptoms	6	6		
Grade 3 Gastrointestinal symptoms	0	0		
Related Gastrointestinal symptoms	4	4		
Any Headache	30	16		
Grade 3 Headache	1	1		
Related Headache	26	14		
Any Joint Pain	8	5		
Grade 3 Joint Pain	0	0		
Related Joint Pain	8	5		
Any Myalgia	21	13		
Grade 3 Myalgia	1	0		
Related Myalgia	20	13		
Any Shivering	9	7		
Grade 3 Shivering	1	0		
Related Shivering	8	6		
Any Fever	2	2		
Fever ( $\geq 38.0^{\circ}\text{C}$ )	2	1		
Grade 3 Fever	0	0		
Related Fever	2	2		
$\geq 38.0^{\circ}\text{C}$ Related Fever	2	1		

## Statistical analyses

No statistical analyses for this end point

### Primary: Duration of solicited local and general AEs in subjects aged 18-49 years.

End point title	Duration of solicited local and general AEs in subjects aged 18-49 years. <sup>[5][6]</sup>
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End point description:

Duration was defined as number of days with any grade of local and general symptoms.

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[6] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	32		
Units: Days				
median (full range (min-max))				

Fatigue [N=32,20]	2 (1 to 7)	2 (1 to 4)		
Gastrointestinal symptoms [N=6,6]	1.5 (1 to 4)	1 (1 to 3)		
Headache [N=30,16]	1 (1 to 6)	1.5 (1 to 5)		
Joint Pain [N=8,5]	1 (1 to 4)	3 (1 to 4)		
Myalgia [N=21,13]	2 (1 to 7)	2 (1 to 4)		
Pain [N=41,32]	2 (1 to 3)	2 (1 to 7)		
Redness [N=1,1]	2 (2 to 2)	1 (1 to 1)		
Shivering [N=9,7]	2 (1 to 4)	3 (1 to 5)		
Swelling [N=2,4]	1.5 (1 to 2)	2.5 (2 to 4)		
Fever [N=2,2]	1 (1 to 1)	1.5 (1 to 2)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects aged 18-49 years reporting solicited Oculorespiratory Syndrome (ORS) like symptoms.

End point title	Number of subjects aged 18-49 years reporting solicited Oculorespiratory Syndrome (ORS) like symptoms. <sup>[7][8]</sup>
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End point description:

Oculorespiratory syndrome (ORS) was defined as the occurrence within 24 hours after vaccination of one or more of the following newly onset symptoms: bilateral red eyes, cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, sore throat, facial swelling. Any was defined as any ORS symptom regardless of intensity grade or relationship to vaccination. Grade 3 ORS was defined as ORS symptoms that prevented normal activities. Related ORS was defined as ORS symptom(s) assessed by the investigator as causally related to the vaccination.

End point type	Primary
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End point timeframe:

During the 3-day (Days 0-2) post-vaccination period

Notes:

[7] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	59		
Units: Subjects				
Any Chest Tightness	0	0		
Grade 3 Chest Tightness	0	0		
Related Chest Tightness	0	0		
Any Cough	3	2		
Grade 3 Cough	0	0		
Related Cough	3	1		
Any Difficulty Breathing	0	0		
Grade 3 Difficulty Breathing	0	0		
Related Difficulty Breathing	0	0		

Any Hoarseness	1	1		
Grade 3 Hoarseness	0	0		
Related Hoarseness	1	1		
Any Red Eyes	1	1		
Grade 3 Red Eyes	0	0		
Related Red Eyes	1	0		
Any Sore Throat	4	2		
Grade 3 Sore Throat	0	0		
Related Sore Throat	3	1		
Any Swallowing Difficulty	3	1		
Grade 3 Swallowing Difficulty	0	0		
Related Swallowing Difficulty	2	0		
Any Swelling of the face	0	0		
Grade 3 Swelling of the face	0	0		
Related Swelling of the face	0	0		
Any Wheezing	0	0		
Grade 3 Wheezing	0	0		
Related Wheezing	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects aged 18-49 years reporting the occurrence of medically attended events (MAEs).

End point title	Number of subjects aged 18-49 years reporting the occurrence of medically attended events (MAEs). <sup>[9]</sup> <sup>[10]</sup>
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End point description:

MAEs were defined as adverse events with medically-attended visits that were not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Any was defined as any occurrence of MAE(s). Grade 3 was defined as MAE that prevented normal activities. Related was defined as MAE assessed by the investigator to be causally related to the study vaccination.

End point type	Primary
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End point timeframe:

During the entire study period (approximately 21 days following vaccination)

Notes:

[9] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: Subjects				
Any MAE(s)	9	8		



Grade 3 MAE(s)	3	1		
Related MAE(s)	0	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects aged 3-17 years reporting solicited local adverse events (AEs).

End point title	Number of subjects aged 3-17 years reporting solicited local adverse events (AEs). <sup>[11][12]</sup>
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End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of the specified solicited local symptom regardless of its intensity. Grade 3 pain = Cried when limb was moved/spontaneously painful. Grade 3 redness and swelling = greater than 50 millimeters (mm) i.e. >50mm.

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[11] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	410		
Units: Subjects				
Any Pain, Dose 1 [N=410,410]	243	253		
Grade 3 Pain, Dose 1 [N=410,410]	14	20		
Any Redness, Dose 1 [N=410,410]	118	119		
Grade 3 Redness, Dose 1 [N=410,410]	8	7		
Any Swelling, Dose 1 [N=410,410]	102	100		
Grade 3 Swelling, Dose 1 [N=410,410]	7	7		
Any Pain, Dose 2 [N=103,99]	36	39		
Grade 3 Pain, Dose 2 [N=103,99]	0	2		
Any Redness, Dose 2 [N=103,99]	25	21		
Grade 3 Redness, Dose 2 [N=103,99]	0	0		
Any Swelling, Dose 2 [N=103,99]	16	17		
Grade 3 Swelling, Dose 2 [N=103,99]	1	0		
Any Pain, Across Doses [N=410,410]	252	264		
Grade 3 Pain, Across Doses [N=410,410]	14	21		
Any Redness, Across Doses [N=410,410]	129	128		

Grade 3 Redness, Across Doses [N=410,410]	8	7		
Any Swelling, Across Doses [N=410,410]	109	110		
Grade 3 Swelling, Across Doses [N=410,410]	8	7		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects aged 3-4 years reporting any, grade 3 and related solicited general symptoms.

End point title	Number of subjects aged 3-4 years reporting any, grade 3 and related solicited general symptoms. <sup>[13]</sup>
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End point description:

Solicited general symptoms assessed were drowsiness, irritability/fussiness, loss of appetite and fever. Any was defined as any solicited general symptom reported irrespective of intensity and relationship to vaccination. Related was defined as symptoms assessed by the investigator to have a causal relationship to vaccination. Grade 3 irritability/fussiness was defined as crying that could not be comforted/prevented normal activity. Grade 3 loss of appetite was defined as not eating at all. Grade 3 drowsiness was defined as drowsiness that prevented normal activity. Any fever was defined as subjects with a documented temperature of greater than or equal to ( $\geq$ ) 38°C/100.4°F by any route and all subjects reporting temperature less than ( $<$ ) 38°C but with missing values (MC) for at least one day during the solicited period. Grade 3 fever was defined as temperature greater than ( $>$ ) 39.0°C.

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[13] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

End point values	Influsplit Tetra_IP 3-4y Group	Influsplit Tetra_LP 3-4y Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	72		
Units: Subjects				
Any Drowsiness, Dose 1 [N=70,72]	14	7		
Grade 3 Drowsiness, Dose 1 [N=70,72]	0	1		
Related Drowsiness, Dose 1 [N=70,72]	10	4		
Any Irritability, Dose 1 [N=70,72]	9	12		
Grade 3 Irritability, Dose 1 [N=70,72]	1	1		
Related Irritability, Dose 1 [N=70,72]	6	8		
Any Loss of appetite, Dose 1 [N=70,72]	9	14		
Grade 3 Loss of appetite, Dose 1 [N=70,72]	2	1		
Related Loss of appetite, Dose 1 [N=70,72]	6	6		
Any Fever, Dose 1 [N=70,72]	5	7		
Fever ( $\geq$ 38.0°C), Dose 1 [N=70,72]	4	7		
Grade 3 Fever, Dose 1 [N=70,72]	1	3		
Related Fever, Dose 1 [N=70,72]	1	5		

≥38.0°C Related Fever, Dose 1 [N=70,72]	1	5		
Any Drowsiness, Dose 2 [N=40,41]	5	6		
Grade 3 Drowsiness, Dose 2 [N=40,41]	0	1		
Related Drowsiness, Dose 2 [N=40,41]	3	4		
Any Irritability, Dose 2 [N=40,41]	2	8		
Grade 3 Irritability, Dose 2 [N=40,41]	0	0		
Related Irritability, Dose 2 [N=40,41]	2	6		
Any Loss of appetite, Dose 2 [N=40,41]	4	6		
Grade 3 Loss of appetite, Dose 2 [N=40,41]	0	0		
Related Loss of appetite, Dose 2 [N=40,41]	2	3		
Any Fever, Dose 2 [N=40,41]	0	4		
Fever (≥38.0°C), Dose 2 [N=40,41]	0	3		
Grade 3 Fever, Dose 2 [N=40,41]	0	0		
Related Fever, Dose 2 [N=40,41]	0	2		
≥38.0°C Related Fever, Dose 2 [N=40,41]	0	1		
Any Drowsiness, Across Doses [N=70,72]	16	11		
Grade 3 Drowsiness, Across Doses [N=70,72]	0	2		
Related Drowsiness, Across Doses [N=70,72]	10	8		
Any Irritability, Across Doses [N=70,72]	10	16		
Grade 3 Irritability ,Across Doses [N=70,72]	1	1		
Related Irritability, Across Doses [N=70,72]	7	11		
Any Loss of appetite,Across Doses [N=70,72]	13	16		
Grade 3 Loss of appetite, Across Doses [N=70,72]	2	1		
Related Loss of appetite, Across Doses [N=70,72]	8	8		
Any Fever, Across Doses [N=70,72]	5	10		
Fever (≥38.0°C), Across Doses [N=70,72]	4	9		
Grade 3 Fever, Across Doses [N=70,72]	1	3		
Related Fever, Across Doses [N=70,72]	1	6		
≥38.0°C Related Fever, Across Doses [N=70,72]	1	5		

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects aged 5-17 years reporting any, grade 3 and related solicited general symptoms.

End point title	Number of subjects aged 5-17 years reporting any, grade 3 and related solicited general symptoms. <sup>[14]</sup>
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End point description:

Solicited general symptoms assessed were fatigue, gastrointestinal symptoms, headache, joint pain, myalgia, shivering and fever (Fever = temperature above 38.0 degrees Celsius (°C)). Gastrointestinal

symptoms included nausea, vomiting, diarrhoea and/or abdominal pain. Any = any solicited general symptom reported irrespective of intensity and relationship to vaccination. Related = symptoms considered by the investigator to have a causal relationship to vaccination. Grade 3 symptoms = symptoms that prevented normal activity. Any fever = all subjects with a documented temperature of  $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$  by any route and all subjects reporting temperature  $< 38^{\circ}\text{C}$  but with missing values (MC) for at least one day during the solicited period. Grade 3 fever = temperature above  $39.0^{\circ}\text{C}$ .

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[14] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

End point values	Influsplit Tetra_IP 5-17y Group	Influsplit Tetra_LP 5-17y Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	340	338		
Units: Subjects				
Any Fatigue, Dose 1 [N=340,338]	94	99		
Grade 3 Fatigue, Dose 1 [N=340,338]	8	13		
Related Fatigue, Dose 1 [N=340,338]	65	70		
Any Gastrointestinal, Dose 1 [N=340,338]	35	32		
Grade 3 Gastrointestinal, Dose 1 [N=340,338]	2	1		
Related Gastrointestinal, Dose 1 [N=340,338]	18	16		
Any Headache, Dose 1 [N=340,338]	82	76		
Grade 3 Headache, Dose 1 [N=340,338]	3	9		
Related Headache, Dose 1 [N=340,338]	46	50		
Any Joint Pain, Dose 1 [N=340,338]	34	38		
Grade 3 Joint Pain, Dose 1 [N=340,338]	3	2		
Related Joint Pain, Dose 1 [N=340,338]	25	29		
Any Myalgia, Dose 1 [N=340,338]	70	84		
Grade 3 Myalgia, Dose 1 [N=340,338]	3	5		
Related Myalgia, Dose 1 [N=340,338]	55	72		
Any Shivering, Dose 1 [N=340,338]	20	29		
Grade 3 Shivering, Dose 1 [N=340,338]	0	3		
Related Shivering, Dose 1 [N=340,338]	16	20		
Any Fever, Dose 1 [N=340,338]	12	9		
Fever ( $\geq 38.0^{\circ}\text{C}$ ), Dose 1 [N=340,338]	11	8		
Grade 3 Fever, Dose 1 [N=340,338]	0	0		
Related Fever, Dose 1 [N=340,338]	10	7		
$\geq 38.0^{\circ}\text{C}$ Related Fever, Dose 1 [N=340,338]	9	6		
Any Fatigue, Dose 2 [N=63,58]	8	4		
Grade 3 Fatigue, Dose 2 [N=63,58]	0	0		
Related Fatigue, Dose 2 [N=63,58]	4	4		
Any Gastrointestinal, Dose 2 [N=63,58]	3	1		
Grade 3 Gastrointestinal, Dose 2 [N=63,58]	0	0		
Related Gastrointestinal, Dose 2 [N=63,58]	0	0		
Any Headache, Dose 2 [N=63,58]	2	7		

Grade 3 Headache, Dose 2 [N=63,58]	0	0		
Related Headache, Dose 2 [N=63,58]	2	4		
Any Joint Pain, Dose 2 [N=63,58]	2	4		
Grade 3 Joint Pain, Dose 2 [N=63,58]	1	0		
Related Joint Pain, Dose 2 [N=63,58]	1	3		
Any Myalgia, Dose 2 [N=63,58]	3	9		
Grade 3 Myalgia, Dose 2 [N=63,58]	1	0		
Related Myalgia, Dose 2 [N=63,58]	2	7		
Any Shivering, Dose 2 [N=63,58]	2	2		
Grade 3 Shivering, Dose 2 [N=63,58]	0	0		
Related Shivering, Dose 2 [N=63,58]	0	1		
Any Fever, Dose 2 [N=63,58]	3	0		
Fever ( $\geq 38.0^{\circ}\text{C}$ ), Dose 2 [N=63,58]	2	0		
Grade 3 Fever, Dose 2 [N=63,58]	1	0		
Related Fever, Dose 2 [N=63,58]	2	0		
$\geq 38.0^{\circ}\text{C}$ Related Fever, Dose 2 [N=63,58]	1	0		
Any Fatigue, Across Doses [N=340,338]	97	101		
Grade 3 Fatigue, Across Doses [N=340,338]	8	13		
Related Fatigue, Across Doses [N=340,338]	66	72		
Any Gastrointestinal, Across Doses [N=340,338]	38	32		
Grade 3 Gastrointestinal, Across Doses [N=340,338]	2	1		
Related Gastrointestinal, Across Doses [N=340,338]	18	16		
Any Headache, Across Doses [N=340,338]	83	80		
Grade 3 Headache, Across Doses [N=340,338]	3	9		
Related Headache, Across Doses [N=340,338]	48	53		
Any Joint Pain, Across Doses [N=340,338]	35	42		
Grade 3 Joint Pain, Across Doses [N=340,338]	4	2		
Related Joint Pain, Across Doses [N=340,338]	25	32		
Any Myalgia, Across Doses [N=340,338]	71	88		
Grade 3 Myalgia, Across Doses [N=340,338]	4	5		
Related Myalgia, Across Doses [N=340,338]	56	76		
Any Shivering, Across Doses [N=340,338]	21	31		
Grade 3 Shivering, Across Doses [N=340,338]	0	3		
Related Shivering, Across Doses [N=340,338]	16	21		
Any Fever, Across Doses [N=340,338]	14	9		
Fever ( $\geq 38.0^{\circ}\text{C}$ ), Across Doses [N=340,338]	12	8		
Grade 3 Fever, Across Doses [N=340,338]	1	0		
Related Fever, Across Doses [N=340,338]	12	7		

≥38.0°C Related Fever, Across Doses [N=340,338]	10	6		
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## Statistical analyses

No statistical analyses for this end point

### Primary: Duration of solicited local AEs in subjects aged 3-17 years.

End point title	Duration of solicited local AEs in subjects aged 3-17
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End point description:

Duration was defined as number of days with any grade of local symptoms.

"9999" as results when about the Influsplit Tetra\_LP 3-17y Group are placeholder values for confidence interval results being not applicable/missing.

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[15] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	253		
Units: Days				
median (full range (min-max))				
Pain, Dose 1 [N=243,253]	2 (1 to 7)	2 (1 to 7)		
Pain, Dose 2 [N=36,39]	1 (1 to 5)	2 (1 to 3)		
Redness, Dose 1 [N=18,19]	2 (1 to 6)	1 (1 to 4)		
Redness, Dose 2 [N=2,2]	1 (1 to 1)	1.5 (1 to 2)		
Swelling, Dose 1 [N=22,29]	2 (1 to 6)	2 (1 to 5)		
Swelling, Dose 2 [N=3,NA]	4 (4 to 5)	9999 (9999 to 9999)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Duration of solicited general AEs in subjects aged 3-4 years.

End point title	Duration of solicited general AEs in subjects aged 3-4 years. <sup>[17]</sup>
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End point description:

Duration was defined as number of days with any grade of general symptoms.

"9999" as results when about the Influsplit Tetra\_LP 3-4y Group are placeholder values for confidence interval results being not applicable/missing.

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[17] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

End point values	Influsplit Tetra_IP 3-4y Group	Influsplit Tetra_LP 3-4y Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	14		
Units: Days				
median (full range (min-max))				
Drowsiness, Dose 1 [N=14,7]	1 (1 to 6)	1 (1 to 7)		
Drowsiness, Dose 2 [N=5,6]	1 (1 to 2)	2 (1 to 5)		
Irritability, Dose 1 [N=9,12]	2 (1 to 2)	1 (1 to 4)		
Irritability, Dose 2 [N=2,8]	1 (1 to 1)	1 (1 to 7)		
Loss of appetite, Dose 1 [N=9,14]	3 (1 to 7)	2 (1 to 7)		
Loss of appetite, Dose 2 [N=4,6]	1 (1 to 2)	4 (1 to 7)		
Fever, Dose 1 [N=5,7]	2 (1 to 5)	1 (1 to 5)		
Fever, Dose 2 [N=NA,4]	9999 (9999 to 9999)	1.5 (1 to 3)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Duration of solicited general AEs in subjects aged 5-17 years.

End point title	Duration of solicited general AEs in subjects aged 5-17
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End point description:

Duration was defined as number of days with any grade of general symptoms.

"9999" as results when about the Influsplit Tetra\_LP 5-17y Group are placeholder values for confidence interval results being not applicable/missing.

End point type	Primary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[18] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

End point values	Influsplit Tetra_IP 5-17y Group	Influsplit Tetra_LP 5-17y Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	99		
Units: Days				
median (full range (min-max))				
Fatigue, Dose 1 [N=94,99]	2 (1 to 7)	2 (1 to 6)		
Fatigue, Dose 2 [N=8,4]	1 (1 to 3)	1.5 (1 to 3)		
Gastrointestinal symptoms, Dose 1 [N=35,32]	1 (1 to 6)	1 (1 to 5)		
Gastrointestinal symptoms, Dose 2 [N=3,1]	2 (1 to 2)	1 (1 to 1)		
Headache, Dose 1 [N=82,76]	1 (1 to 7)	2 (1 to 6)		
Headache, Dose 2 [N=2,7]	2.5 (2 to 3)	2 (1 to 3)		
Joint Pain, Dose 1 [N=34,38]	2 (1 to 7)	1 (1 to 5)		
Joint Pain, Dose 2 [N=2,4]	1 (1 to 1)	1 (1 to 1)		
Myalgia, Dose 1 [N=70,84]	2 (1 to 5)	1 (1 to 5)		
Myalgia, Dose 2 [N=3,9]	1 (1 to 2)	1 (1 to 3)		
Shivering, Dose 1 [N=20,29]	1 (1 to 6)	1 (1 to 5)		
Shivering, Dose 2 [N=2,2]	1 (1 to 1)	1 (1 to 1)		
Fever, Dose 1 [N=12,9]	1 (1 to 2)	1 (1 to 6)		
Fever, Dose 2 [N=3,NA]	2 (1 to 2)	9999 (9999 to 9999)		

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects aged 3-17 years reporting solicited oculorespiratory syndrome (ORS) like symptoms.

End point title	Number of subjects aged 3-17 years reporting solicited oculorespiratory syndrome (ORS) like symptoms. <sup>[19][20]</sup>
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End point description:

Oculorespiratory syndrome (ORS) was defined as the occurrence within 24 hours after vaccination of one or more of the following newly onset symptoms: bilateral red eyes, cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, sore throat, facial swelling. Any = occurrence of any ORS symptom regardless of intensity grade or relationship to vaccination. Grade 3 = ORS symptoms that prevented normal activities. Related = ORS symptom assessed by the investigator as causally related to the vaccination.

End point type	Primary
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End point timeframe:

During the 3-day (Days 0-2) post-vaccination period

Notes:

[19] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[20] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study



End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	410		
Units: Subjects				
Any Chest Tightness, Dose 1 [N=410,410]	2	6		
Grade 3 Chest Tightness, Dose 1 [N=410,410]	0	0		
Related Chest Tightness, Dose 1 [N=410,410]	0	3		
Any Cough, Dose 1 [N=410,410]	35	31		
Grade 3 Cough, Dose 1 [N=410,410]	2	1		
Related Cough, Dose 1 [N=410,410]	12	10		
Any Difficulty Breathing, Dose 1 [N=410,410]	5	11		
Grade 3 Difficulty Breathing, Dose 1 [N=410,410]	0	0		
Related Difficulty Breathing, Dose 1 [N=410,410]	2	7		
Any Hoarseness, Dose 1 [N=410,410]	10	12		
Grade 3 Hoarseness, Dose 1 [N=410,410]	0	0		
Related Hoarseness, Dose 1 [N=410,410]	2	6		
Any Red Eyes, Dose 1 [N=410,410]	14	12		
Grade 3 Red Eyes, Dose 1 [N=410,410]	0	0		
Related Red Eyes, Dose 1 [N=410,410]	6	9		
Any Sore throat, Dose 1 [N=410,410]	14	18		
Grade 3 Sore throat, Dose 1 [N=410,410]	1	0		
Related Sore throat, Dose 1 [N=410,410]	2	9		
Any Swallowing Difficulty, Dose 1 [N=410,410]	5	6		
Grade 3 Swallowing Difficulty, Dose 1 [N=410,410]	0	0		
Related Swallowing Difficulty, Dose 1 [N=410,410]	1	3		
Any Swelling of the face, Dose 1 [N=410,410]	3	2		
Grade 3 Swelling of the face, Dose 1 [N=410,410]	0	0		
Related Swelling of the face, Dose 1 [N=410,410]	3	2		
Any Wheezing, Dose 1 [N=410,410]	1	5		
Grade 3 Wheezing, Dose 1 [N=410,410]	0	0		
Related Wheezing, Dose 1 [N=410,410]	1	4		
Any Chest Tightness, Dose 2 [N=103,99]	0	0		
Grade 3 Chest Tightness, Dose 2 [N=103,99]	0	0		
Related Chest Tightness, Dose 2 [N=103,99]	0	0		
Any Cough, Dose 2 [N=103,99]	6	13		
Grade 3 Cough, Dose 2 [N=103,99]	0	2		
Related Cough, Dose 2 [N=103,99]	1	1		

Any Difficulty Breathing, Dose 2 [N=103,99]	0	2		
Grade 3 Difficulty Breathing, Dose 2 [N=103,99]	0	0		
Related Difficulty Breathing, Dose 2 [N=103,99]	0	0		
Any Hoarseness, Dose 2 [N=103,99]	2	3		
Grade 3 Hoarseness, Dose 2 [N=103,99]	0	0		
Related Hoarseness, Dose 2 [N=103,99]	1	0		
Any Red Eyes, Dose 2 [N=103,99]	0	1		
Grade 3 Red Eyes, Dose 2 [N=103,99]	0	1		
Related Red Eyes, Dose 2 [N=103,99]	0	1		
Any Sore Throat, Dose 2 [N=103,99]	2	3		
Grade 3 Sore Throat, Dose 2 [N=103,99]	0	1		
Related Sore Throat, Dose 2 [N=103,99]	0	0		
Any Swallowing Difficulty, Dose 2 [N=103,99]	2	1		
Grade 3 Swallowing Difficulty, Dose 2 [N=103,99]	0	1		
Related Swallowing Difficulty, Dose 2 [N=103,99]	1	0		
Any Swelling of the face, Dose 2 [N=103,99]	0	1		
Grade 3 Swelling of the face, Dose 2 [N=103,99]	0	0		
Related Swelling of the face, Dose 2 [N=103,99]	0	0		
Any Wheezing, Dose 2 [N=103,99]	0	2		
Grade 3 Wheezing, Dose 2 [N=103,99]	0	0		
Related Wheezing, Dose 2 [N=103,99]	0	0		
Any Chest Tightness, Across Doses [N=410,410]	2	6		
Grade 3 Chest Tightness, Across Doses [N=410,410]	0	0		
Related Chest Tightness, Across Doses [N=410,410]	0	3		
Any Cough, Across Doses [N=410,410]	39	39		
Grade 3 Cough, Across Doses [N=410,410]	2	3		
Related Cough, Across Doses [N=410,410]	13	11		
Any Difficulty Breathing, Across Doses [N=410,410]	5	13		
Grade3 DifficultyBreathing,Across Doses[N=410,410]	0	0		
Related DifficultyBreathing,AcrossDoses[N=410,	2	7		
Any Hoarseness, Across Doses [N=410,410]	11	15		
Grade 3 Hoarseness, Across Doses [N=410,410]	0	0		
Related Hoarseness, Across Doses [N=410,410]	3	6		
Any Red Eyes, Across Doses [N=410,410]	14	13		
Grade 3 Red Eyes, Across Doses [N=410,410]	0	1		

Related Red Eyes, Across Doses [N=410,410]	6	10		
Any Sore Throat, Across Doses [N=410,410]	15	21		
Grade 3 Sore Throat, Across Doses [N=410,410]	1	1		
Related Sore Throat, Across Doses [N=410,410]	2	9		
Any Swallowing Difficulty, Across Doses[N=410,410]	6	7		
Grade3 SwallowingDifficulty,AcrossDoses[N=41	0	1		
Related SwallowingDifficulty,AcrossDoses[N=41	2	3		
Any Swelling of the face,Across Doses [N=410,410]	3	3		
Grade3 Swelling of the face,AcrossDoses[N=410,410]	0	0		
Related Swelling of the face,AcrossDoses[N=410,410]	3	2		
Any Wheezing, Across Doses [N=410,410]	1	7		
Grade 3 Wheezing, Across Doses [N=410,410]	0	0		
Related Wheezing, Across Doses [N=410,410]	1	4		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects aged 3-17 years reporting the occurrence of all Medically Attended Events (MAEs).

End point title	Number of subjects aged 3-17 years reporting the occurrence of all Medically Attended Events (MAEs). <sup>[21][22]</sup>
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End point description:

MAEs were defined as adverse events with medically-attended visits that were not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Any was defined as any occurrence of MAE(s). Grade 3 was a MAE that prevented normal activities. Related was defined as a MAE assessed by the investigator to be causally related to the study vaccination.

End point type	Primary
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End point timeframe:

During the entire study period (approximately 28 days (primed subjects) and 56 days (unprimed subjects) following vaccination

Notes:

[21] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[22] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	411		
Units: Subjects				
Any MAE(s)	59	52		
Grade 3 MAE(s)	7	6		
Related MAE(s)	2	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects aged 18-49 years reporting any, grade 3 and related unsolicited adverse events (AEs)

End point title	Number of subjects aged 18-49 years reporting any, grade 3 and related unsolicited adverse events (AEs) <sup>[23]</sup> <sup>[24]</sup>
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End point description:

An unsolicited AE was defined as an untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as occurrence of any unsolicited symptom regardless of intensity grade or relation to vaccination.

End point type	Primary
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End point timeframe:

During the 21-day (Days 0-20) follow-up period after vaccination

Notes:

[23] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[24] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: Subjects				
Any Unsolicited AEs	14	14		
Grade 3 Unsolicited AEs	3	2		
Related Unsolicited AEs	2	1		

## Statistical analyses

No statistical analyses for this end point

**Primary: Number of subjects aged 3-17 years reporting any, grade 3 and related unsolicited adverse events (AEs).**

End point title	Number of subjects aged 3-17 years reporting any, grade 3 and related unsolicited adverse events (AEs). <sup>[25][26]</sup>
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## End point description:

An unsolicited AE was defined as an untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as occurrence of any unsolicited symptom regardless of intensity grade or relation to vaccination.

End point type	Primary
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## End point timeframe:

During the 28-day (Days 0-27) follow-up period after vaccination

## Notes:

[25] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[26] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	411		
Units: Subjects				
Any Unsolicited AEs	83	86		
Grade 3 Unsolicited AEs	12	8		
Related Unsolicited AEs	10	7		

**Statistical analyses**

No statistical analyses for this end point

**Primary: Number of subjects aged 6-35 months reporting fever  $\geq 38^{\circ}\text{C}$  across doses.**

End point title	Number of subjects aged 6-35 months reporting fever $\geq 38^{\circ}\text{C}$ across doses. <sup>[27][28]</sup>
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## End point description:

Any fever = all subjects with a documented temperature of  $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$  by any route and all subjects reporting temperature  $< 38^{\circ}\text{C}$  but with missing values (MC) for at least one day during the solicited period.

End point type	Primary
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## End point timeframe:

During 7 days (Days 0-6) post-vaccination

## Notes:

[27] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[28] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered

End point values	Influsplit Tetra_IP 6- 35m Group	Influsplit Tetra_LP 6- 35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	470		
Units: Subjects				
Any Fever	76	70		
Fever ( $\geq 38^{\circ}\text{C}$ )	72	69		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects aged 18-49 years, reporting any and related serious adverse events (SAEs)

End point title	Number of subjects aged 18-49 years, reporting any and related serious adverse events (SAEs) <sup>[29]</sup> <sup>[30]</sup>
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End point description:

A serious adverse event was defined as any untoward medical occurrence that: resulted in death, was life threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

End point type	Primary
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End point timeframe:

During the entire study period (approximately 21 days)

Notes:

[29] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[30] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: Subjects				
Any SAEs	1	1		
Related SAEs	0	0		

## Statistical analyses

**Primary: Number of subjects aged 3-17 years, reporting any and related serious adverse events (SAEs)**

End point title	Number of subjects aged 3-17 years, reporting any and related serious adverse events (SAEs) <sup>[31][32]</sup>
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## End point description:

A serious adverse event was defined as any untoward medical occurrence that: resulted in death, was life threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

End point type	Primary
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## End point timeframe:

During the entire study period [approximately 28 days (primed subjects) and 56 days (unprimed subjects)]

## Notes:

[31] - 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: The scope of this primary endpoint was descriptive, no statistical analyses were conducted.

[32] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	411		
Units: Subjects				
Any SAEs	1	0		
Related SAEs	0	0		

**Statistical analyses**

No statistical analyses for this end point

**Primary: Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 3-17 years by calculating serum antihaemagglutination (HA) antibody titers against the 4 vaccine strains.**

End point title	Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 3-17 years by calculating serum antihaemagglutination (HA) antibody titers against the 4 vaccine strains. <sup>[33]</sup>
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## End point description:

HI antibody titres were expressed as adjusted geometric mean titers (GMTs) and adjusted GMT ratios. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), FluA/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Primary
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## End point timeframe:

At Day 28 post last vaccination

Notes:

[33] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	402		
Units: Adjusted GMT				
number (not applicable)				
H1N1	707.3	684.9		
H3N2	160.6	168.8		
Yamagata	496	509.4		
Victoria	240.8	250.4		

## Statistical analyses

Statistical analysis title	Non-inferiority of (HI) antibodies
Statistical analysis description:	
The adjusted GMT of HI antibodies for H1N1 strain at post-vaccination of each vaccine, the GMT ratio of Influsplit Tetra_LP/ Influsplit Tetra_IP and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination antibody titer as covariate.	
Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio (D-QIV_LP/ D-QIV_IP) is $\leq 1.5$ .	
Comparison groups	Influsplit Tetra_IP 3-17y Group v Influsplit Tetra_LP 3-17y Group
Number of subjects included in analysis	805
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	$\leq 1.5$
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.11

Statistical analysis title	Non-inferiority of (HI) antibodies
Statistical analysis description:	
The adjusted GMT of HI antibodies for H3N2 strain at post-vaccination of each vaccine, the GMT ratio of Influsplit Tetra_LP/Influsplit Tetra_IP and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination antibody titer as covariate. Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio is $\leq 1.5$ .	



Comparison groups	Influsplit Tetra_IP 3-17y Group v Influsplit Tetra_LP 3-17y Group
Number of subjects included in analysis	805
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	$\leq 1.5$
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.18

<b>Statistical analysis title</b>	Non-inferiority of (HI) antibodies
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Statistical analysis description:

The adjusted GMT of HI antibodies for Yamagata strain at post-vaccination of each vaccine, the GMT ratio of Influsplit Tetra\_LP/Influsplit Tetra\_IP and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination antibody titer as covariate.

Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio is  $\leq 1.5$ .

Comparison groups	Influsplit Tetra_IP 3-17y Group v Influsplit Tetra_LP 3-17y Group
Number of subjects included in analysis	805
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	$\leq 1.5$
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.16

<b>Statistical analysis title</b>	Non-inferiority of (HI) antibodies
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Statistical analysis description:

The adjusted GMT of HI antibodies for Victoria strain at post-vaccination of each vaccine, the GMT ratio of Influsplit Tetra\_LP/Influsplit Tetra\_IP and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination antibody titer as covariate.

Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio is  $\leq 1.5$ .

Comparison groups	Influsplit Tetra_IP 3-17y Group v Influsplit Tetra_LP 3-17y Group
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Number of subjects included in analysis	805
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 1.5
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.21

**Primary: Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 6-35 months by calculating serum antihaemagglutination (HA) antibody titers against the 4 vaccine strains.**

End point title	Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 6-35 months by calculating serum antihaemagglutination (HA) antibody titers against the 4 vaccine strains. <sup>[34]</sup>
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End point description:

HI antibody titres were expressed as adjusted geometric mean titers (GMTs) and adjusted GMT ratios. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), FluA/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Primary
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End point timeframe:

At Day 28 post last vaccination

Notes:

[34] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	431	424		
Units: Adjusted GMTs				
number (not applicable)				
H1N1 [N=431,424]	98	105.3		
H3N2 [N=431,423]	47.7	56.3		
Yamagata [N=431,423]	99.2	106.4		
Victoria [N=431,423]	32.2	37.7		

**Statistical analyses**

Statistical analysis title	Non-inferiority of (HI) antibodies
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**Statistical analysis description:**

The adjusted GMT of HI antibodies for H1N1 strain at post-vaccination of each vaccine, the GMT ratio of Influsplit Tetra\_LP/Influsplit Tetra\_IP and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination antibody titer as covariate.

Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio is  $\leq 1.5$ .

Comparison groups	Influsplit Tetra_IP 6-35m Group v Influsplit Tetra_LP 6-35m Group
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	$\leq 1.5$
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.28

**Statistical analysis title**

Non-inferiority of (HI) antibodies

**Statistical analysis description:**

The adjusted GMT of HI antibodies for H3N2 strain at post-vaccination of each vaccine, the GMT ratio of Influsplit Tetra\_LP/Influsplit Tetra\_IP and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination antibody titer as covariate.

Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio is  $\leq 1.5$ .

Comparison groups	Influsplit Tetra_IP 6-35m Group v Influsplit Tetra_LP 6-35m Group
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	$\leq 1.5$
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.39

**Statistical analysis title**

Non-inferiority of (HI) antibodies

**Statistical analysis description:**

The adjusted GMT of HI antibodies for Yamagata strain at post-vaccination of each vaccine, the GMT ratio of Influsplit Tetra\_LP/Influsplit Tetra\_IP and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination antibody titer as covariate.

Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio is  $\leq 1.5$ .

Comparison groups	Influsplit Tetra_LP 6-35m Group v Influsplit Tetra_IP 6-35m Group
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	$\leq 1.5$
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.27

<b>Statistical analysis title</b>	Non-inferiority of (HI) antibodies
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Statistical analysis description:

The adjusted GMT of HI antibodies for Victoria strain at post-vaccination of each vaccine, the GMT ratio of Influsplit Tetra\_LP/Influsplit Tetra\_IP and the 2-sided 95% CI on each GMT ratio were computed after fitting an ANCOVA model on the logarithm10 transformation of the titers, including the vaccine group as fixed effect and the pre-vaccination antibody titer as covariate.

Non-inferiority criterion (for each of the 4 strains): UL of the 95% CI for the GMT ratio is  $\leq 1.5$ .

Comparison groups	Influsplit Tetra_IP 6-35m Group v Influsplit Tetra_LP 6-35m Group
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	$\leq 1.5$
Method	ANCOVA
Parameter estimate	Adjusted GMT ratio
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.38

## **Secondary: Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 18-49 years by calculating serum anti-haemagglutination (HA) antibody titers against the 4 vaccine strains**

End point title	Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 18-49 years by calculating serum anti-haemagglutination (HA) antibody titers against the 4 vaccine strains <sup>[35]</sup>
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End point description:

HI antibody titres were expressed as Geometric mean titers (GMTs). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 0 and Day 21

Notes:

[35] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	58		
Units: Titers				
geometric mean (confidence interval 95%)				
[H1N1, Day 0]	48.3 (33.4 to 69.7)	53.6 (36.8 to 78)		
[H1N1, Day 21]	655.7 (493.1 to 871.9)	632.2 (498.8 to 801.3)		
[H3N2, Day 0]	16.7 (12.6 to 22.2)	16 (11.9 to 21.5)		
[H3N2, Day 21]	80.5 (63.2 to 102.7)	73 (59 to 90.5)		
[Yamagata, Day 0]	133.3 (98.4 to 180.6)	101.6 (76.2 to 135.4)		
[Yamagata, Day 21]	591.4 (475.1 to 736.3)	598.6 (480.9 to 745)		
[Victoria, Day 0]	38.6 (29.5 to 50.5)	34.8 (25.2 to 48.1)		
[Victoria, Day 21]	263.4 (209 to 331.9)	302.9 (244 to 376.1)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of seroconverted subjects aged 18-49 years for anti-Haemagglutination Inhibition (HI) antibodies against each of the four vaccine influenza strains.

End point title	Number of seroconverted subjects aged 18-49 years for anti-Haemagglutination Inhibition (HI) antibodies against each of the four vaccine influenza strains. <sup>[36]</sup>
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End point description:

A seroconverted subject was defined as a vaccinated subject with either a pre-vaccination titer less than (<) 1:10 and a post-vaccination titer greater than or equal to ( $\geq$ ) 1:40, or a pre-vaccination titer  $\geq$  1:10 and at least a 4-fold increase in post-vaccination titer. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 21

Notes:

[36] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Subjects				
H1N1	42	42		
H3N2	30	29		
Yamagata	27	36		
Victoria	36	40		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects aged 18-49 years, who were seroprotected for haemagglutination inhibition (HI) antibodies against each of the four vaccine influenza strains.

End point title	Number of subjects aged 18-49 years, who were seroprotected for haemagglutination inhibition (HI) antibodies against each of the four vaccine influenza strains. <sup>[37]</sup>
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End point description:

A seroprotected subject was defined as a vaccinated subject with a serum HI titer greater than or equal to ( $\geq$ ) 1:40 that usually is accepted as indicating protection in adults. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 0 and Day 21

Notes:

[37] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	58		
Units: Subjects				
[H1N1, Day 0]	35	35		
[H1N1, Day 21]	56	57		
[H3N2, Day 0]	15	14		
[H3N2, Day 21]	49	49		
[Yamagata, Day 0]	52	50		

[Yamagata, Day 21]	57	57		
[Victoria, Day 0]	34	32		
[Victoria, Day 21]	57	57		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains in subjects aged 18-49 years.

End point title	Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains in subjects aged 18-49 years. <sup>[38]</sup>
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End point description:

MGI was defined as the fold increase in serum haemagglutination inhibition (HI) GMTs post-vaccination compared to pre-vaccination (Day 0). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 21

Notes:

[38] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1	13.6 (8.9 to 20.8)	11.5 (7.7 to 17)		
H3N2	4.8 (3.6 to 6.5)	4.6 (3.6 to 5.7)		
Yamagata	4.4 (3.3 to 6)	6 (4.3 to 8.2)		
Victoria	6.8 (5 to 9.2)	8.6 (6 to 12.3)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects aged 5-17 years reporting myalgia across doses.

End point title	Number of subjects aged 5-17 years reporting myalgia across doses.
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End point description:

Any = occurrence of any myalgia symptom regardless of intensity grade or relationship to vaccination.

End point type	Secondary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

End point values	Influsplit Tetra_IP 5-17y Group	Influsplit Tetra_LP 5-17y Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	340	338		
Units: Subjects				
Any Myalgia	71	88		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 3-17 years by calculating serum anti-haemagglutination (HA) antibody titers against the 4 vaccine strains

End point title	Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 3-17 years by calculating serum anti-haemagglutination (HA) antibody titers against the 4 vaccine strains <sup>[39]</sup>
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End point description:

HI antibody titres were expressed as Geometric mean titers (GMTs). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 0 and Day 28 post last vaccination

Notes:

[39] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	402		
Units: Titers				
geometric mean (confidence interval 95%)				
[H1N1, Day 0]	80.2 (69.2 to 93)	87.7 (76.1 to 101)		
[H1N1, Day 28]	698 (629.6 to 773.9)	694.1 (625.8 to 769.7)		



[H3N2, Day 0]	38.9 (34.6 to 43.8)	41.9 (37.1 to 47.3)		
[H3N2, Day 28]	158.2 (143.7 to 174.2)	171.4 (156.3 to 188)		
[Yamagata, Day 0]	58.1 (49.7 to 68)	70.8 (60.4 to 83)		
[Yamagata, Day 28]	479 (434.1 to 528.5)	527.6 (475.5 to 585.3)		
[Victoria, Day 0]	27.3 (23.8 to 31.3)	28.8 (25 to 33.1)		
[Victoria, Day 28]	237.6 (210.4 to 268.3)	253.7 (222.7 to 289.1)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of seroconverted subjects aged 3-17 years for anti-Haemagglutination Inhibition (HI) antibodies against each of the four vaccine influenza strains.

End point title	Number of seroconverted subjects aged 3-17 years for anti-Haemagglutination Inhibition (HI) antibodies against each of the four vaccine influenza strains. <sup>[40]</sup>
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End point description:

A seroconverted subject was defined as a vaccinated subject with either a pre-vaccination titer less than (<) 1:10 and a post-vaccination titer greater than or equal to (≥) 1:40, or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 28 post last vaccination

Notes:

[40] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	402		
Units: Subjects				
H1N1	274	269		
H3N2	192	183		
Yamagata	273	268		
Victoria	285	287		

## Statistical analyses

**Secondary: Number of subjects aged 3-17 years, who were seroprotected for haemagglutination inhibition (HI) antibodies against each of the four vaccine influenza strains.**

End point title	Number of subjects aged 3-17 years, who were seroprotected for haemagglutination inhibition (HI) antibodies against each of the four vaccine influenza strains. <sup>[41]</sup>
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## End point description:

A seroprotected subject was defined as a vaccinated subject with a serum HI titer greater than or equal to ( $\geq$ ) 1:40 that usually is accepted as indicating protection in adults. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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## End point timeframe:

At Day 0 and Day 28 post last vaccination

## Notes:

[41] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	402		
Units: Subjects				
[H1N1, Day 0]	308	314		
[H1N1, Day 28]	393	395		
[H3N2, Day 0]	245	252		
[H3N2, Day 28]	377	378		
[Yamagata, Day 0]	266	281		
[Yamagata, Day 28]	396	395		
[Victoria, Day 0]	192	195		
[Victoria, Day 28]	375	374		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains in subjects aged 3-17 years.**

End point title	Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains in subjects aged 3-17 years. <sup>[42]</sup>
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## End point description:

MGI was defined as the fold increase in serum haemagglutination inhibition (HI) GMTs post-vaccination compared to pre-vaccination (Day 0). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 28 post last vaccination

Notes:

[42] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 3-17y Group	Influsplit Tetra_LP 3-17y Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	403	402		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1	8.7 (7.6 to 10)	7.9 (6.9 to 9.1)		
H3N2	4.1 (3.7 to 4.5)	4.1 (3.7 to 4.6)		
Yamagata	8.2 (7.2 to 9.4)	7.4 (6.5 to 8.5)		
Victoria	8.7 (7.7 to 9.8)	8.8 (7.7 to 10)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 6-35 months by calculating serum anti-haemagglutination (HA) antibody titers against the 4 vaccine strains

End point title	Humoral immune response in terms of haemagglutination inhibition (HI) antibodies in subjects aged 6-35 months by calculating serum anti-haemagglutination (HA) antibody titers against the 4 vaccine strains <sup>[43]</sup>
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End point description:

HI antibody titres were expressed as Geometric mean titers (GMTs). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 0 and Day 28 post last vaccination

Notes:

[43] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6- 35m Group	Influsplit Tetra_LP 6- 35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	427		
Units: Titers				
geometric mean (confidence interval 95%)				

H1N1, Day 0 [N=431,424]	11.1 (9.6 to 12.8)	11.2 (9.7 to 12.9)		
H1N1, Day 28 [N=432,427]	97.5 (82.1 to 115.7)	105.5 (88.2 to 126.1)		
H3N2, Day 0 [N=431,423]	7.5 (6.8 to 8.2)	8.4 (7.5 to 9.3)		
H3N2, Day 28 [N=432,427]	45.2 (39 to 52.3)	59.9 (51.7 to 69.4)		
Yamagata, Day 0 [N=431,423]	8.3 (7.5 to 9.1)	7.9 (7.2 to 8.6)		
Yamagata, Day 28 [N=432,427]	100.8 (87.8 to 115.8)	105.4 (91.8 to 121)		
Victoria, Day 0 [N=431,423]	5.7 (5.4 to 6.1)	5.7 (5.4 to 6.1)		
Victoria, Day 28 [N=432,427]	32.1 (28.1 to 36.7)	38 (33.2 to 43.5)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of seroconverted subjects aged 6-35 months for anti-Haemagglutination Inhibition (HI) antibodies against each of the four vaccine influenza strains.

End point title	Number of seroconverted subjects aged 6-35 months for anti-Haemagglutination Inhibition (HI) antibodies against each of the four vaccine influenza strains. <sup>[44]</sup>
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End point description:

A seroconverted subject was defined as a vaccinated subject with either a pre-vaccination titer less than (<) 1:10 and a post-vaccination titer greater than or equal to (≥) 1:40, or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 28 post last vaccination

Notes:

[44] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	427		
Units: Subjects				
H1N1	287	275		
H3N2	217	236		
Yamagata	318	321		
Victoria	213	211		

## Statistical analyses

**Secondary: Number of subjects aged 6-35 months, who were seroprotected for haemagglutination inhibition (HI) antibodies against each of the four vaccine influenza strains.**

End point title	Number of subjects aged 6-35 months, who were seroprotected for haemagglutination inhibition (HI) antibodies against each of the four vaccine influenza strains. <sup>[45]</sup>
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## End point description:

A seroprotected subject was defined as a vaccinated subject with a serum HI titer greater than or equal to ( $\geq$ ) 1:40 that usually is accepted as indicating protection in adults. The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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## End point timeframe:

At Day 0 and Day 28 post last vaccination

## Notes:

[45] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	427		
Units: Subjects				
H1N1, Day 0 [N=431,424]	84	83		
H1N1, Day 28 [N=432,427]	303	289		
H3N2, Day 0 [N=431,423]	55	67		
H3N2, Day 28 [N=432,427]	232	259		
Yamagata, Day 0 [N=431,423]	53	49		
Yamagata, Day 28 [N=432,427]	329	331		
Victoria, Day 0 [N=431,423]	17	16		
Victoria, Day 28 [N=432,427]	214	217		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains in subjects aged 6-35 months.**

End point title	Mean geometric increase (MGI) for haemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains in subjects aged 6-35 months. <sup>[46]</sup>
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## End point description:

MGI was defined as the fold increase in serum haemagglutination inhibition (HI) GMTs post-vaccination compared to pre-vaccination (Day 0). The vaccine strains assessed were Flu A/Christchurch/16/2010 (H1N1), Flu A/Texas/50/2012 (H3N2), Flu B/Massachusetts/02/2012 (Yamagata) and Flu B/Brisbane/60/2008 (Victoria).

End point type	Secondary
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End point timeframe:

At Day 28 post last vaccination

Notes:

[46] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	427		
Units: Fold increase				
geometric mean (confidence interval 95%)				
H1N1	8.8 (7.8 to 10)	9.5 (8.3 to 10.8)		
H3N2	6 (5.4 to 6.8)	7.1 (6.3 to 7.9)		
Yamagata	12.2 (10.8 to 13.8)	13.3 (11.8 to 15)		
Victoria	5.6 (5 to 6.3)	6.6 (5.8 to 7.4)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects aged 6-35 months reporting fever $\geq 38^{\circ}\text{C}$ after Dose 1 and after Dose 2.

End point title	Number of subjects aged 6-35 months reporting fever $\geq 38^{\circ}\text{C}$ after Dose 1 and after Dose 2. <sup>[47]</sup>
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End point description:

Any fever = all subjects with a documented temperature of  $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$  by any route and all subjects reporting temperature  $< 38^{\circ}\text{C}$  but with missing values (MC) for at least one day during the solicited period. Fever = temperature of  $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$  by any route

End point type	Secondary
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End point timeframe:

During 7 days (Days 0-6) post-vaccination

Notes:

[47] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	470		
Units: Subjects				
Any Fever, Dose 1 [N=462,470]	42	44		
Fever ( $\geq 38^{\circ}\text{C}$ ), Dose 1 [N=462,470]	39	42		
Any Fever, Dose 2 [N=420,421]	41	40		

Fever ( $\geq 38^{\circ}\text{C}$ ), Dose 2 [N=420,421]	40	40		
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects aged 6-35 months reporting solicited local adverse events (AEs).

End point title	Number of subjects aged 6-35 months reporting solicited local adverse events (AEs). <sup>[48]</sup>
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End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of the specified solicited local symptom regardless of its intensity. Grade 3 pain = significant pain at rest and pain that prevented normal everyday activities. Grade 3 redness and swelling = greater than 50 millimeters (mm) i.e. > 50mm.

End point type	Secondary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[48] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6- 35m Group	Influsplit Tetra_LP 6- 35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	470		
Units: Subjects				
Any Pain, Dose 1 [N=462,470]	69	77		
Grade 3 Pain, Dose 1 [N=462,470]	1	2		
Any Redness, Dose 1 [N=462,470]	88	86		
Grade 3 Redness, Dose 1 [N=462,470]	0	0		
Any Swelling, Dose 1 [N=462,470]	33	42		
Grade 3 Swelling, Dose 1 [N=462,470]	0	0		
Any Pain, Dose 2 [N=420,421]	47	48		
Grade 3 Pain, Dose 2 [N=420,421]	1	4		
Any Redness, Dose 2 [N=420,421]	61	66		
Grade 3 Redness, Dose 2 [N=420,421]	0	0		
Any Swelling, Dose 2 [N=420,421]	32	27		
Grade 3 Swelling, Dose 2 [N=420,421]	0	1		
Any Pain, Across Doses [N=462,470]	89	98		
Grade 3 Pain, Across Doses [N=462,470]	2	4		
Any Redness, Across Doses [N=462,470]	106	106		
Grade 3 Redness, Across Doses [N=462,470]	0	0		

Any Swelling, Across Doses [N=462,470]	50	51		
Grade 3 Swelling, Across Doses [N=462,470]	0	1		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects aged 6 months to <5 years, reporting fever $\geq 38^{\circ}\text{C}$ ( $100.4^{\circ}\text{F}$ ) and $>39.0^{\circ}\text{C}$ ( $102.2^{\circ}\text{F}$ ) across doses.

End point title	Number of subjects aged 6 months to <5 years, reporting fever $\geq 38^{\circ}\text{C}$ ( $100.4^{\circ}\text{F}$ ) and $>39.0^{\circ}\text{C}$ ( $102.2^{\circ}\text{F}$ ) across doses.
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End point description:

Any fever = all subjects with a documented temperature of  $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$  by any route and all subjects reporting temperature  $< 38^{\circ}\text{C}$  but with missing values (MC) for at least one day during the solicited period. Grade 3 fever = temperature above  $39.0^{\circ}\text{C}/102.2^{\circ}\text{F}$ . Data of 2 independent groups were pooled.

End point type	Secondary
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End point timeframe:

During the 2 days (Day 0-Day 1) post-vaccination period

End point values	Influsplit Tetra_IP 6m- <5y Group	Influsplit Tetra_LP 6m- <5y Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	532	542		
Units: Subjects				
Any Fever	29	31		
Fever ( $\geq 38^{\circ}\text{C}$ )	28	31		
Grade 3 Fever	4	1		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects aged 6-35 months reporting any, grade 3 and related solicited general symptoms.

End point title	Number of subjects aged 6-35 months reporting any, grade 3 and related solicited general symptoms. <sup>[49]</sup>
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End point description:

Solicited general symptoms assessed were drowsiness, irritability/fussiness, loss of appetite and fever. Any was defined as any solicited general symptom reported irrespective of intensity and relationship to vaccination. Related was defined as symptoms assessed by the investigator to have a causal relationship to vaccination. Grade 3 irritability/fussiness was defined as crying that could not be comforted/prevented normal activity. Grade 3 loss of appetite was defined as not eating at all. Grade 3 drowsiness was defined as drowsiness that prevented normal activity. Any fever was defined as subjects with a documented temperature of greater than or equal to ( $\geq$ )  $38^{\circ}\text{C}/100.4^{\circ}\text{F}$  by any route and all subjects reporting temperature less than ( $<$ )  $38^{\circ}\text{C}$  but with missing values (MC) for at least one day



during the solicited period. Grade 3 fever was defined as temperature greater than (>)39.0°C.

End point type	Secondary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[49] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6- 35m Group	Influsplit Tetra_LP 6- 35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	470		
Units: Subjects				
Any Drowsiness, Dose 1 [N=462,470]	87	77		
Grade 3 Drowsiness, Dose 1 [N=462,470]	3	7		
Related Drowsiness, Dose 1 [N=462,470]	54	50		
Any Irritability, Dose 1 [N=462,470]	124	96		
Grade 3 Irritability, Dose 1 [N=462,470]	10	10		
Related Irritability, Dose 1 [N=462,470]	75	58		
Any Loss of appetite, Dose 1 [N=462,470]	94	76		
Grade 3 Loss of appetite, Dose 1 [N=462,470]	9	8		
Related Loss of appetite, Dose 1 [N=462,470]	47	40		
Any Fever, Dose 1 [N=462,470]	42	44		
Fever (≥38.0°C), Dose 1 [N=462,470]	39	42		
Grade 3 Fever, Dose 1 [N=462,470]	8	5		
Related Fever, Dose 1 [N=462,470]	16	23		
≥38.0°C Related Fever, Dose 1 [N=462,470]	14	22		
Any Drowsiness, Dose 2 [N=420,421]	63	58		
Grade 3 Drowsiness, Dose 2 [N=420,421]	6	7		
Related Drowsiness, Dose 2 [N=420,421]	46	35		
Any Irritability, Dose 2 [N=420,421]	87	87		
Grade 3 Irritability, Dose 2 [N=420,421]	5	8		
Related Irritability, Dose 2 [N=420,421]	59	50		
Any Loss Of Appetite, Dose 2 [N=420,421]	64	69		
Grade 3 Loss Of Appetite, Dose 2 [N=420,421]	4	10		
Related Loss Of Appetite, Dose 2 [N=420,421]	39	37		
Any Fever, Dose 2 [N=420,421]	41	40		
Fever (≥38.0°C), Dose 2 [N=420,421]	40	40		
Grade 3 Fever, Dose 2 [N=420,421]	10	9		
Related Fever, Dose 2 [N=420,421]	19	17		
≥38.0°C Related Fever, Dose 2 [N=420,421]	19	17		

Any Drowsiness, Across Doses [N=462,470]	115	103		
Grade 3 Drowsiness, Across Doses [N=462,470]	8	13		
Related Drowsiness, Across Doses [N=462,470]	78	66		
Any Irritability, Across Doses [N=462,470]	155	141		
Grade 3 Irritability, Across Doses [N=462,470]	15	17		
Related Irritability, Across Doses [N=462,470]	98	87		
Any Loss Of Appetite, Across Doses [N=462,470]	127	116		
Grade 3 Loss Of Appetite, Across Doses [N=462,470]	13	17		
Related Loss Of Appetite, Across Doses [N=462,470]	69	61		
Any Fever, Across Doses [N=462,470]	76	70		
Fever ( $\geq 38.0^{\circ}\text{C}$ ), Across Doses [N=462,470]	72	69		
Grade 3 Fever, Across Doses [N=462,470]	18	14		
Related Fever, Across Doses [N=462,470]	32	35		
$\geq 38.0^{\circ}\text{C}$ Related Fever, Across Doses [N=462,470]	30	34		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of solicited local AEs in subjects aged 6-35 months.

End point title	Duration of solicited local AEs in subjects aged 6-35 months. <sup>[50]</sup>
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End point description:

Duration was defined as number of days with any grade of local symptoms.

"9999" as results when about the Influsplit Tetra\_LP 5-17y Group are placeholder values for confidence interval results being not applicable/missing.

End point type	Secondary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[50] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6- 35m Group	Influsplit Tetra_LP 6- 35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	77		
Units: Days				
median (full range (min-max))				
Pain, Dose 1 [N=69,77]	1 (1 to 6)	1 (1 to 7)		

Pain, Dose 2 [N=47,48]	2 (1 to 5)	2 (1 to 6)		
Redness, Dose 2 [N=2,1]	1.5 (1 to 2)	1 (1 to 1)		
Swelling, Dose 2 [N=NA,1]	9999 (9999 to 9999)	3 (3 to 3)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of solicited general AEs in subjects aged 6-35 months.

End point title	Duration of solicited general AEs in subjects aged 6-35
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End point description:

Duration was defined as number of days with any grade of general symptoms.

End point type	Secondary
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End point timeframe:

During the 7-day (Days 0-6) post-vaccination period

Notes:

[51] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	96		
Units: Days				
median (full range (min-max))				
Drowsiness, Dose 1 [N=87,77]	2 (1 to 7)	2 (1 to 7)		
Drowsiness, Dose 2 [N=63,58]	2 (1 to 7)	2 (1 to 7)		
Irritability, Dose 1 [N=124,96]	2 (1 to 7)	2 (1 to 7)		
Irritability, Dose 2 [N=87,87]	2 (1 to 7)	2 (1 to 7)		
Loss of appetite, Dose 1 [N=94,76]	2 (1 to 7)	2 (1 to 7)		
Loss of appetite, Dose 2 [N=64,69]	2 (1 to 7)	2 (1 to 7)		
Fever, Dose 1 [N=42,44]	2 (1 to 5)	1 (1 to 4)		
Fever, Dose 2 [N=41,40]	1 (1 to 5)	2 (1 to 5)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects aged 6-35 months reporting solicited oculorespiratory syndrome (ORS) like symptoms.

End point title	Number of subjects aged 6-35 months reporting solicited oculorespiratory syndrome (ORS) like symptoms. <sup>[52]</sup>
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End point description:

Oculorespiratory syndrome (ORS) was defined as the occurrence within 24 hours after vaccination of

one or more of the following newly onset symptoms: bilateral red eyes, cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, sore throat, facial swelling. Any = occurrence of any ORS symptom regardless of intensity grade or relationship to vaccination. Grade 3 = ORS symptoms that prevented normal activities. Related = ORS symptom assessed by the investigator as causally related to the vaccination.

End point type	Secondary
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End point timeframe:

During a 3 day (Days 0-2) follow-up period after vaccination

Notes:

[52] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	470		
Units: Subjects				
Any Chest Tightness, Dose 1 [N=462,470]	2	1		
Grade 3 Chest Tightness, Dose 1 [N=462,470]	0	0		
Related Chest Tightness, Dose 1 [N=462,470]	0	0		
Any Cough, Dose 1 [N=462,470]	47	50		
Grade 3 Cough, Dose 1 [N=462,470]	3	3		
Related Cough, Dose 1 [N=462,470]	16	13		
Any Difficulty Breathing, Dose 1 [N=462,470]	15	12		
Grade 3 Difficulty Breathing, Dose 1 [N=462,470]	1	1		
Related Difficulty Breathing, Dose 1 [N=462,470]	4	2		
Any Hoarseness, Dose 1 [N=462,470]	13	11		
Grade 3 Hoarseness, Dose 1 [N=462,470]	0	0		
Related Hoarseness, Dose 1 [N=462,470]	1	4		
Any Red Eyes, Dose 1 [N=462,470]	10	11		
Grade 3 Red Eyes, Dose 1 [N=462,470]	0	0		
Related Red Eyes, Dose 1 [N=462,470]	6	5		
Any Sore throat, Dose 1 [N=462,470]	6	7		
Grade 3 Sore throat, Dose 1 [N=462,470]	0	0		
Related Sore throat, Dose 1 [N=462,470]	1	3		
Any Swallowing Difficulty, Dose 1 [N=462,470]	1	5		
Grade 3 Swallowing Difficulty, Dose 1 [N=462,470]	0	0		
Related Swallowing Difficulty, Dose 1 [N=462,470]	0	2		
Any Swelling of the face, Dose 1 [N=462,470]	4	3		
Grade 3 Swelling of the face, Dose 1 [N=462,470]	0	0		

Related Swelling of the face, Dose 1 [N=462,470]	1	1		
Any Wheezing, Dose 1 [N=462,470]	9	12		
Grade 3 Wheezing, Dose 1 [N=462,470]	1	1		
Related Wheezing, Dose 1 [N=462,470]	3	3		
Any Chest Tightness, Dose 2 [N=420,421]	9	4		
Grade 3 Chest Tightness, Dose 2 [N=420,421]	0	2		
Related Chest Tightness, Dose 2 [N=420,421]	0	1		
Any Cough, Dose 2 [N=420,421]	37	53		
Grade 3 Cough, Dose 2 [N=420,421]	5	3		
Related Cough, Dose 2 [N=420,421]	8	8		
Any Difficulty Breathing, Dose 2 [N=420,421]	19	18		
Grade 3 Difficulty Breathing, Dose 2 [N=420,421]	1	2		
Related Difficulty Breathing, Dose 2 [N=420,421]	5	3		
Any Hoarseness, Dose 2 [N=420,421]	13	9		
Grade 3 Hoarseness, Dose 2 [N=420,421]	0	1		
Related Hoarseness, Dose 2 [N=420,421]	1	1		
Any Red Eyes, Dose 2 [N=420,421]	10	11		
Grade 3 Red Eyes, Dose 2 [N=420,421]	0	0		
Related Red Eyes, Dose 2 [N=420,421]	6	1		
Any Sore Throat, Dose 2 [N=420,421]	7	11		
Grade 3 Sore Throat, Dose 2 [N=420,421]	1	1		
Related Sore Throat, Dose 2 [N=420,421]	0	2		
Any Swallowing Difficulty, Dose 2 [N=420,421]	8	7		
Grade 3 Swallowing Difficulty, Dose 2 [N=420,421]	2	1		
Related Swallowing Difficulty, Dose 2 [N=420,421]	0	1		
Any Swelling of the face, Dose 2 [N=420,421]	5	4		
Grade 3 Swelling of the face, Dose 2 [N=420,421]	0	0		
Related Swelling of the face, Dose 2 [N=420,421]	1	1		
Any Wheezing, Dose 2 [N=420,421]	11	16		
Grade 3 Wheezing, Dose 2 [N=420,421]	3	1		
Related Wheezing, Dose 2 [N=420,421]	4	3		
Any Chest Tightness, Across Doses [N=462,470]	10	5		
Grade 3 Chest Tightness, Across Doses [N=462,470]	0	2		
Related Chest Tightness, Across Doses [N=462,470]	0	1		
Any Cough, Across Doses [N=462,470]	73	85		
Grade 3 Cough, Across Doses [N=462,470]	8	6		
Related Cough, Across Doses [N=462,470]	22	18		

Any Difficulty Breathing, Across Doses [N=462,470]	31	25		
Grade3 DifficultyBreathing,Across Doses[N=462,470]	2	3		
Related DifficultyBreathing,AcrossDoses[N=462,470]	8	4		
Any Hoarseness, Across Doses [N=462,470]	23	17		
Grade 3 Hoarseness, Across Doses [N=462,470]	0	1		
Related Hoarseness, Across Doses [N=462,470]	2	5		
Any Red Eyes, Across Doses [N=462,470]	18	19		
Grade 3 Red Eyes, Across Doses [N=462,470]	0	0		
Related Red Eyes, Across Doses [N=462,470]	10	5		
Any Sore Throat, Across Doses [N=462,470]	12	17		
Grade 3 Sore Throat, Across Doses [N=462,470]	1	1		
Related Sore Throat, Across Doses [N=462,470]	1	5		
Any Swallowing Difficulty, Across Doses[N=462,470]	8	12		
Grade3 SwallowingDifficulty,AcrossDoses[N=462,470]	2	1		
Related SwallowingDifficulty,AcrossDoses[N=462,470]	0	3		
Any Swelling of the face, Across Doses [N=462,470]	9	7		
Grade3 Swelling of the face,AcrossDoses[N=462,470]	0	0		
Related Swelling of the face,AcrossDoses[N=462,470]	2	2		
Any Wheezing, Across Doses [N=462,470]	19	26		
Grade 3 Wheezing, Across Doses [N=462,470]	4	2		
Related Wheezing, Across Doses [N=462,470]	7	5		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects aged 6-35 months reporting the occurrence of all Medically Attended Events (MAEs)

End point title	Number of subjects aged 6-35 months reporting the occurrence of all Medically Attended Events (MAEs) <sup>[53]</sup>
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End point description:

MAEs were defined as adverse events with medically-attended visits that were not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Any was defined as any occurrence of MAE(s). Grade 3 was a MAE that prevented normal activities. Related was defined as a MAE assessed by the investigator to be causally related to the study vaccination.

End point type	Secondary
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End point timeframe:

During the entire study period (approximately 28 days (primed subjects) and 56 days (unprimed subjects) following vaccination

Notes:

[53] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	466	474		
Units: Subjects				
Any MAE(s)	235	252		
Grade 3 MAE(s)	35	29		
Related MAE(s)	2	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects aged 6-35 months reporting any, grade 3 and related unsolicited adverse events (AEs).

End point title	Number of subjects aged 6-35 months reporting any, grade 3 and related unsolicited adverse events (AEs). <sup>[54]</sup>
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End point description:

An unsolicited AE was defined as an untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as occurrence of any unsolicited symptom regardless of intensity grade or relation to vaccination. Grade 3 unsolicited AE was defined as an event that prevented normal activity. Related unsolicited AE was defined as an event assessed by the investigator to be causally related to the study vaccination.

End point type	Secondary
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End point timeframe:

During the 28-day (Days 0-27) follow-up period after vaccination

Notes:

[54] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	466	474		
Units: Subjects				
Any Unsolicited AEs	243	262		
Grade 3 Unsolicited AEs	33	31		
Related Unsolicited AEs	6	3		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects aged 6-35 months, reporting any and related serious adverse events (SAEs)

End point title	Number of subjects aged 6-35 months, reporting any and related serious adverse events (SAEs) <sup>[55]</sup>
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End point description:

A serious adverse event was defined as any untoward medical occurrence that: resulted in death, was life threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

End point type	Secondary
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End point timeframe:

During the entire study period [approximately 28 days (primed subjects) and 56 days (unprimed subjects)]

Notes:

[55] - 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: Descriptive analyses were performed based on the vaccine groups / vaccine administered in the study

End point values	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	466	474		
Units: Subjects				
Any SAEs	7	11		
Related SAEs	0	0		

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events: From Day 0 to Day 56; Solicited local and general symptoms: During the 7-day (Days 0-6) post-vaccination period; Unsolicited adverse events: During the 28-day (Days 0-27) post-vaccination period.

Adverse event reporting additional description:

For the systematically assessed other (non-serious) adverse events, the number of participants at risk included those from Total Vaccinated Cohort who had the symptom sheet completed.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	Influsplit Tetra_IP Adult Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 18 to 49 years received 1 dose of Influsplit Tetra™ vaccine produced by investigational process (IP) at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm.

Reporting group title	Influsplit Tetra_LP Adult Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP aged between 18 to 49 years received 1 dose of Influsplit Tetra™ vaccine produced by currently licensed process (LP) at Day 0. Influsplit Tetra™ vaccine produced by currently LP was administered intramuscularly in the deltoid region of left or non-dominant arm.

Reporting group title	Influsplit Tetra_IP 3-17y Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 3 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by IP at Day 0. Influsplit Tetra™ vaccine produced by IP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Reporting group title	Influsplit Tetra_LP 3-17y Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP group aged between 3 years to <9 years received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Subjects aged 9-17 years received only 1 dose of Influsplit Tetra™ vaccine produced by LP at Day 0. Influsplit Tetra™ vaccine produced by LP was administered intramuscularly in the deltoid region of left or non-dominant arm (Day 0) and in the deltoid region of right or dominant arm (Day 28).

Reporting group title	Influsplit Tetra_IP 6-35m Group
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Reporting group description:

Subjects in the Influsplit Tetra\_IP group aged between 6 months to 35 months received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by investigational process (IP). Influsplit Tetra™ vaccine produced by IP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects ≥ 12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right or dominant arm in subjects ≥ 12 months of age (Day 28).

Reporting group title	Influsplit Tetra_LP 6-35m Group
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Reporting group description:

Subjects in the Influsplit Tetra\_LP group aged between 6 months to 35 months received 1 dose (primed subjects) at Day 0 and 2 doses (unprimed subjects) at Days 0 and 28 of Influsplit Tetra™ vaccine produced by licensed process (LP). Influsplit Tetra™ vaccine produced by LP was administered intramuscularly the anterolateral region of left thigh for subjects below 12 months of age and in the deltoid region of left or non-dominant arm in subjects ≥ 12 months of age (Day 0) and in the anterolateral region of right thigh for subjects below 12 months of age and in the deltoid region of right

<b>Serious adverse events</b>	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group	Influsplit Tetra_IP 3- 17y Group
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 410 (0.24%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural inflammation			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 410 (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			
Febrile convulsion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Asthma			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 410 (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			

Meningitis viral			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 410 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Bronchitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Bronchiolitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Adenovirus infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Bronchopneumonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Epstein-Barr virus infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Haemophilus infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Otitis media			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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 respiratory syncytial viral			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Pseudocroup			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Viral infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 410 (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

<b>Serious adverse events</b>	Influsplit Tetra_LP 3-17y Group	Influsplit Tetra_IP 6-35m Group	Influsplit Tetra_LP 6-35m Group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 411 (0.00%)	7 / 466 (1.50%)	11 / 474 (2.32%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Injury, poisoning and procedural complications			
Post procedural inflammation			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	0 / 474 (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			
Febrile convulsion			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 411 (0.00%)	1 / 466 (0.21%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 411 (0.00%)	1 / 466 (0.21%)	0 / 474 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	0 / 474 (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			
Meningitis viral			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	0 / 474 (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
Gastroenteritis			
subjects affected / exposed	0 / 411 (0.00%)	3 / 466 (0.64%)	2 / 474 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 411 (0.00%)	2 / 466 (0.43%)	2 / 474 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	2 / 474 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenovirus infection			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 411 (0.00%)	1 / 466 (0.21%)	0 / 474 (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
Epstein-Barr virus infection			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus infection			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 411 (0.00%)	1 / 466 (0.21%)	0 / 474 (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
Pseudocroup			

subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 411 (0.00%)	1 / 466 (0.21%)	0 / 474 (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
Viral infection			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	1 / 474 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 411 (0.00%)	1 / 466 (0.21%)	0 / 474 (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 %

<b>Non-serious adverse events</b>	Influsplit Tetra_IP Adult Group	Influsplit Tetra_LP Adult Group	Influsplit Tetra_IP 3-17y Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 60 (90.00%)	46 / 60 (76.67%)	335 / 410 (81.71%)
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	5 / 410 (1.22%)
occurrences (all)	0	0	5
Nervous system disorders			
Headache			
alternative assessment type: Systematic			

subjects affected / exposed	31 / 60 (51.67%)	16 / 60 (26.67%)	85 / 410 (20.73%)
occurrences (all)	31	16	85
Somnolence			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	16 / 410 (3.90%)
occurrences (all)	0	0	16
General disorders and administration site conditions			
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 60 (15.00%)	7 / 60 (11.67%)	21 / 410 (5.12%)
occurrences (all)	9	7	21
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	32 / 60 (53.33%)	20 / 60 (33.33%)	97 / 410 (23.66%)
occurrences (all)	32	20	97
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	41 / 60 (68.33%)	32 / 60 (53.33%)	252 / 410 (61.46%)
occurrences (all)	41	32	252
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 60 (5.00%)	2 / 60 (3.33%)	34 / 410 (8.29%)
occurrences (all)	3	2	34
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 60 (25.00%)	11 / 60 (18.33%)	109 / 410 (26.59%)
occurrences (all)	15	11	109
Decreased appetite			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	13 / 410 (3.17%)
occurrences (all)	0	0	13
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	10 / 410 (2.44%)
occurrences (all)	0	0	10



Gastrointestinal disorders Dysphagia alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Gastrointestinal disorder alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Oropharyngeal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 60 (5.00%)	1 / 60 (1.67%)	0 / 410 (0.00%)
	3	1	0
	6 / 60 (10.00%)	6 / 60 (10.00%)	38 / 410 (9.27%)
	6	6	38
	4 / 60 (6.67%)	2 / 60 (3.33%)	15 / 410 (3.66%)
	4	2	15
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Wheezing subjects affected / exposed occurrences (all)	3 / 60 (5.00%)	2 / 60 (3.33%)	43 / 410 (10.49%)
	3	2	43
	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 410 (0.24%)
	0	0	1
Skin and subcutaneous tissue disorders Erythema alternative assessment type: Systematic subjects affected / exposed occurrences (all)	24 / 60 (40.00%)	18 / 60 (30.00%)	131 / 410 (31.95%)
	24	18	131
Musculoskeletal and connective tissue disorders Arthralgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Myalgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	8 / 60 (13.33%)	5 / 60 (8.33%)	35 / 410 (8.54%)
	8	5	35
	21 / 60 (35.00%)	13 / 60 (21.67%)	72 / 410 (17.56%)
	21	13	72

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	4 / 60 (6.67%) 4	4 / 410 (0.98%) 4
Bronchitis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	5 / 410 (1.22%) 5
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	2 / 410 (0.49%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	13 / 410 (3.17%) 13

<b>Non-serious adverse events</b>	Influsplit Tetra_LP 3-17y Group	Influsplit Tetra_IP 6- 35m Group	Influsplit Tetra_LP 6-35m Group
Total subjects affected by non-serious adverse events subjects affected / exposed	330 / 411 (80.29%)	347 / 466 (74.46%)	352 / 474 (74.26%)
Cardiac disorders Dyspnoea subjects affected / exposed occurrences (all)	13 / 411 (3.16%) 13	31 / 466 (6.65%) 31	25 / 474 (5.27%) 25
Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Somnolence subjects affected / exposed occurrences (all)	84 / 411 (20.44%) 84  11 / 411 (2.68%) 11	0 / 466 (0.00%) 0  115 / 466 (24.68%) 115	1 / 474 (0.21%) 1  103 / 474 (21.73%) 103
General disorders and administration site conditions Chills alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Fatigue alternative assessment type: Systematic	31 / 411 (7.54%) 31	1 / 466 (0.21%) 1	0 / 474 (0.00%) 0

subjects affected / exposed	101 / 411 (24.57%)	0 / 466 (0.00%)	0 / 474 (0.00%)
occurrences (all)	101	0	0
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	264 / 411 (64.23%)	89 / 466 (19.10%)	98 / 474 (20.68%)
occurrences (all)	264	89	98
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	28 / 411 (6.81%)	129 / 466 (27.68%)	127 / 474 (26.79%)
occurrences (all)	28	129	127
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	110 / 411 (26.76%)	50 / 466 (10.73%)	51 / 474 (10.76%)
occurrences (all)	110	50	51
Decreased appetite			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 411 (3.89%)	127 / 466 (27.25%)	116 / 474 (24.47%)
occurrences (all)	16	127	116
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 411 (3.89%)	155 / 466 (33.26%)	141 / 474 (29.75%)
occurrences (all)	16	155	141
Gastrointestinal disorders			
Dysphagia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 411 (0.00%)	0 / 466 (0.00%)	0 / 474 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
alternative assessment type: Systematic			
subjects affected / exposed	32 / 411 (7.79%)	0 / 466 (0.00%)	0 / 474 (0.00%)
occurrences (all)	32	0	0
Oropharyngeal pain			
alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	21 / 411 (5.11%) 21	12 / 466 (2.58%) 12	17 / 474 (3.59%) 17
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Systematic subjects affected / exposed occurrences (all)	44 / 411 (10.71%) 44	86 / 466 (18.45%) 86	100 / 474 (21.10%) 100
Wheezing subjects affected / exposed occurrences (all)	7 / 411 (1.70%) 7	19 / 466 (4.08%) 19	26 / 474 (5.49%) 26
Skin and subcutaneous tissue disorders Erythema alternative assessment type: Systematic subjects affected / exposed occurrences (all)	128 / 411 (31.14%) 128	106 / 466 (22.75%) 106	107 / 474 (22.57%) 107
Musculoskeletal and connective tissue disorders Arthralgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	42 / 411 (10.22%) 42	0 / 466 (0.00%) 0	0 / 474 (0.00%) 0
Myalgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	90 / 411 (21.90%) 90	0 / 466 (0.00%) 0	0 / 474 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 411 (1.46%) 6	26 / 466 (5.58%) 26	29 / 474 (6.12%) 29
Bronchitis subjects affected / exposed occurrences (all)	4 / 411 (0.97%) 4	39 / 466 (8.37%) 39	56 / 474 (11.81%) 56
Gastroenteritis subjects affected / exposed occurrences (all)	4 / 411 (0.97%) 4	31 / 466 (6.65%) 31	37 / 474 (7.81%) 37
Upper respiratory tract infection			

subjects affected / exposed	17 / 411 (4.14%)	62 / 466 (13.30%)	73 / 474 (15.40%)
occurrences (all)	17	62	73

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	<p>Amendment 1:</p> <p>As a result of the recent meeting (25 June 2014) of the United States Advisory Committee on Immunization Practices (ACIP), a slightly modified influenza vaccination dosing schedule will be recommended for the 2014-15 influenza season for children 6 months to &lt; 9 years of age since the vaccine strains did not change from last year's (2013-14) influenza season.</p> <p>Consequently, the dosing schedule described in the initial protocol (dated 07 April 2014) could result in one extra dose for some study participants compared to the ACIP recommendation for the 2014-15 influenza season.</p> <p>Therefore, the definitions of vaccine primed and unprimed subjects have been changed in the current protocol amendment (see 'Glossary of Terms' section) to harmonize with the ACIP recommendations for the 2014-15 influenza season, in order to follow the updated recommended ACIP dosing schedule.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported