



Clinical trial results:

A phase III, observer-blind, multi-centre, multi-country, randomized study to evaluate the immunogenicity and safety of thimerosal-free (TF) Fluarix™ (GSK Biologicals) compared with Fluzone® (Sanofi Pasteur) administered intramuscularly in children (6 to 35 months of age)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-001258-13 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 01 June 2009 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 04 May 2016 |
| First version publication date | 18 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 111751 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00764790 |
| 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, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@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 | 30 September 2009 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 March 2009 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 June 2009 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate the immunological non-inferiority (in terms of GMTs and seroconversion rates) of TF Fluarix (0.5mL) versus Fluzone (0.25mL) in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial IM vaccination.
- To demonstrate the immunological non-inferiority (in terms of GMTs and seroconversion rates) of TF Fluarix (0.25mL) versus Fluzone (0.25mL) in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial IM vaccination

Protection of trial subjects:

All subjects were supervised closely for at least 30 minutes following vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines. Subjects were followed-up from the time the subject consents to participate in the study until she/he is discharged.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2008 |
| 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 | United States: 1289 |
| Country: Number of subjects enrolled | Taiwan: 177 |
| Country: Number of subjects enrolled | Thailand: 275 |
| Country: Number of subjects enrolled | Mexico: 1297 |
| Country: Number of subjects enrolled | Hong Kong: 280 |
| Worldwide total number of subjects | 3318 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|--|------|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 2212 |
| Children (2-11 years) | 1106 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Overall (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind ^[1] |
| Roles blinded | Subject, Carer, Assessor |

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Fluarix Dose A Group |

Arm description:

Subjects were administered 1 or 2 doses* of Fluarix vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Fluarix |
| Investigational medicinal product code | |
| Other name | TRIVALENT INACTIVATED INFLUENZA VACCINE |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One (Day 0) or two (Day 0 and Day 28) doses by intramuscular injection. Two different doses were tested.

| | |
|------------------|----------------------|
| Arm title | Fluarix Dose B Group |
|------------------|----------------------|

Arm description:

Subjects were administered 1 or 2 doses*, half the volume of dose A, of Fluarix vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Fluarix |
| Investigational medicinal product code | |
| Other name | TRIVALENT INACTIVATED INFLUENZA VACCINE |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One (Day 0) or two (Day 0 and Day 28) doses by intramuscular injection. Two different doses were tested.

| | |
|------------------|---------------|
| Arm title | Fluzone Group |
|------------------|---------------|

Arm description:

Subjects were administered 1 or 2 doses* of Fluzone vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|--|--------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Fluzone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One (Day 0) or two (Day 0 and Day 28) doses by intramuscular injection.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: This is an observer-blind study which means that during the course of the study, the vaccine recipient (subject) and those responsible for the evaluation of any study endpoint, were all unaware of which vaccine was administered to a particular subject. To do so, vaccine preparation and vaccination was done by authorized medical personnel who did not participate in any of the study clinical evaluation (i.e. carer and assessor).

| Number of subjects in period 1^[2] | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group |
|---|-----------------------------|-----------------------------|----------------------|
| Started | 1107 | 1106 | 1104 |
| Completed | 1069 | 1065 | 1074 |
| Not completed | 38 | 41 | 30 |
| Consent withdrawn by subject | 10 | 12 | 6 |
| Protocol violation | - | - | 1 |
| Migrated/moved from study area | 4 | 3 | 5 |
| Lost to follow-up | 24 | 26 | 18 |

Notes:

[2] - 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: 1 subject enrolled in the study was allocated a subject number but the study vaccine dose was not administered.

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Fluarix Dose A Group |
|-----------------------|----------------------|

Reporting group description:

Subjects were administered 1 or 2 doses* of Fluarix vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|-----------------------|----------------------|
| Reporting group title | Fluarix Dose B Group |
|-----------------------|----------------------|

Reporting group description:

Subjects were administered 1 or 2 doses*, half the volume of dose A, of Fluarix vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|-----------------------|---------------|
| Reporting group title | Fluzone Group |
|-----------------------|---------------|

Reporting group description:

Subjects were administered 1 or 2 doses* of Fluzone vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| Reporting group values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group |
|---|----------------------|----------------------|---------------|
| Number of subjects | 1107 | 1106 | 1104 |
| 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: months | | | |
| arithmetic mean | 20.9 | 20.9 | 21 |
| standard deviation | ± 8.07 | ± 8.42 | ± 8.23 |
| Gender categorical Units: Subjects | | | |
| Female | 539 | 517 | 560 |
| Male | 568 | 589 | 544 |

| | | | |
|------------------------|-------|--|--|
| Reporting group values | Total | | |
|------------------------|-------|--|--|

| | | | |
|---|------|--|--|
| Number of subjects | 3317 | | |
| 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: months | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1616 | | |
| Male | 1701 | | |

End points

End points reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Fluarix Dose A Group |
|-----------------------|----------------------|

Reporting group description:

Subjects were administered 1 or 2 doses* of Fluarix vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|-----------------------|----------------------|
| Reporting group title | Fluarix Dose B Group |
|-----------------------|----------------------|

Reporting group description:

Subjects were administered 1 or 2 doses*, half the volume of dose A, of Fluarix vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|-----------------------|---------------|
| Reporting group title | Fluzone Group |
|-----------------------|---------------|

Reporting group description:

Subjects were administered 1 or 2 doses* of Fluzone vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age).

* Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

Primary: Geometric Mean Titer (GMT) of serum anti-hemagglutinin (HA) antibodies against each of the influenza vaccine strains

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|-----------------|--|
| End point title | Geometric Mean Titer (GMT) of serum anti-hemagglutinin (HA) antibodies against each of the influenza vaccine strains |
|-----------------|--|

End point description:

GMTs and their 95% confidence interval are presented for all 3 viral strains comprised in the vaccine. Post-vaccination timepoints: Day 28 for primed or Day 56 for unprimed subjects

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|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (PRE), Day 28 or Day 56 (POST)

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|--|-----------------------|------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1018 | 1016 | 1031 | |
| Units: titre | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/Brisbane (PRE) (N=1017; 1013; 1030) | 10.4 (9.7 to 11.1) | 10.6 (9.8 to 11.4) | 10.9 (10.1 to 11.7) | |
| A/Brisbane (POST) (N=1018; 1016; 1031) | 106.1 (93.8 to 120.1) | 131.6 (116.3 to 148.9) | 232.4 (214 to 252.3) | |
| A/Uruguay (PRE) (N=1017; 1013; 1030) | 12.1 (11.1 to 13.2) | 11.2 (10.2 to 12.2) | 11.6 (10.7 to 12.7) | |

| | | | | |
|---------------------------------------|------------------------|------------------------|------------------------|--|
| A/Uruguay (POST) (N=1018; 1016; 1031) | 125.6 (113.3 to 139.3) | 158.7 (143.9 to 175.2) | 280.3 (260.3 to 301.9) | |
| B/Florida (PRE) (N=1017; 1013; 1030) | 8.4 (7.9 to 9) | 8.9 (8.3 to 9.6) | 8.3 (7.7 to 8.8) | |
| B/Florida (POST) (N=1018; 1016; 1031) | 113 (103.4 to 123.4) | 164.4 (150.2 to 180.1) | 176.4 (162.3 to 191.7) | |

Statistical analyses

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|---|--|
| Statistical analysis title | Adjusted GMT ratio anti-A/Brisbane Fluzone/Fluarix |
| Statistical analysis description: | |
| To demonstrate the immunological non-inferiority (in terms of geometric mean titers [GMTs] of Fluarix (Dose B) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination. | |
| Comparison groups | Fluarix Dose B Group v Fluzone Group |
| Number of subjects included in analysis | 2047 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Adjusted GMT ratio |
| Point estimate | 1.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.54 |
| upper limit | 1.98 |

Notes:

[1] - The non-inferiority of the Fluarix Dose B Group as compared to the Fluzone Group was concluded if the upper limit of two-sided 95% CI of the GMT ratio (Fluzone Group over Fluarix Dose B Group) was \leq 1.50 in terms of anti-A/Brisbane titers.

| | |
|---|---|
| Statistical analysis title | Adjusted GMT ratio anti-A/Uruguay Fluzone/Fluarix |
| Statistical analysis description: | |
| To demonstrate the immunological non-inferiority (in terms of geometric mean titers [GMTs] of Fluarix (Dose B) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination. | |
| Comparison groups | Fluarix Dose B Group v Fluzone Group |
| Number of subjects included in analysis | 2047 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | Adjusted GMT ratio |
| Point estimate | 1.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.57 |
| upper limit | 1.89 |

Notes:

[2] - The non-inferiority of the Fluarix Dose B Group as compared to the Fluzone Group was concluded if the upper limit of two-sided 95% CI of the GMT ratio (Fluzone Group over Fluarix Dose B Group) was \leq 1.50 in terms of anti-A/Uruguay titers.

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted GMT ratio anti-B/Florida Fluzone/Fluarix |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of geometric mean titers [GMTs] of Fluarix

(Dose B) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluzone Group v Fluarix Dose B Group |
| Number of subjects included in analysis | 2047 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| Parameter estimate | Adjusted GMT ratio |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.01 |
| upper limit | 1.25 |

Notes:

[3] - The non-inferiority of the Fluarix Dose B Group as compared to the Fluzone Group was concluded if the upper limit of two-sided 95% CI of the GMT ratio (Fluzone Group over Fluarix Dose B Group) was ≤ 1.50 in terms of anti-B/Florida titers.

| | |
|-----------------------------------|--|
| Statistical analysis title | Adjusted GMT ratio anti-A/Brisbane Fluzone/Fluarix |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of geometric mean titers [GMTs] of Fluarix (Dose A) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluzone Group v Fluarix Dose A Group |
| Number of subjects included in analysis | 2049 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Parameter estimate | Adjusted GMT ratio |
| Point estimate | 2.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.86 |
| upper limit | 2.4 |

Notes:

[4] - The non-inferiority of the Fluarix Dose A Group as compared to the Fluzone Group was concluded if the upper limit of two-sided 95% CI of the GMT ratio (Fluzone Group over Fluarix Dose A Group) was ≤ 1.50 in terms of anti-A/Brisbane titers.

| | |
|-----------------------------------|---|
| Statistical analysis title | Adjusted GMT ratio anti-A/Uruguay Fluzone/Fluarix |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of geometric mean titers [GMTs] of Fluarix (Dose A) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluzone Group v Fluarix Dose A Group |
| Number of subjects included in analysis | 2049 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[5] |
| Parameter estimate | Adjusted GMT ratio |
| Point estimate | 2.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.08 |
| upper limit | 2.52 |

Notes:

[5] - The non-inferiority of the Fluarix Dose A Group as compared to the Fluzone Group was concluded if the upper limit of two-sided 95% CI of the GMT ratio (Fluzone Group over Fluarix Dose A Group) was ≤ 1.50 in terms of anti-A/Uruguay titers.

| | |
|---|---|
| Statistical analysis title | Adjusted GMT ratio anti-B/Florida Fluzone/Fluarix |
| Statistical analysis description: | |
| To demonstrate the immunological non-inferiority (in terms of geometric mean titers [GMTs] of Fluarix (Dose A) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination. | |
| Comparison groups | Fluzone Group v Fluarix Dose A Group |
| Number of subjects included in analysis | 2049 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[6] |
| Parameter estimate | Adjusted GMT ratio |
| Point estimate | 1.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.42 |
| upper limit | 1.76 |

Notes:

[6] - The non-inferiority of the Fluarix Dose A Group as compared to the Fluzone Group was concluded if the upper limit of two-sided 95% CI of the GMT ratio (Fluzone Group over Fluarix Dose A Group) was ≤ 1.50 in terms of anti-B/Florida titers.

Primary: Number of subjects seroconverted for the 3 Flu strains

| | |
|--|--|
| End point title | Number of subjects seroconverted for the 3 Flu strains |
| End point description: | |
| Seroconversion rate was defined as the number of subjects with either a pre-vaccination anti-HA titer $< 1:10$ and a post-vaccination titer $\geq 1:40$, or a pre-vaccination titer $\geq 1:10$ and a minimum 4-fold increase at post-vaccination titer. Post-vaccination timepoints: Day 28 for primed or Day 56 for unprimed subjects | |
| End point type | Primary |
| End point timeframe: | |
| Day 28 or Day 56 | |

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|-----------------------------|----------------------|----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1017 | 1013 | 1030 | |
| Units: Subjects | | | | |
| A/Brisbane | 636 | 699 | 929 | |
| A/Uruguay | 747 | 808 | 988 | |
| B/Florida | 812 | 864 | 904 | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | SCR difference A/Brisbane Fluzone/Fluarix Dose B |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of seroconversion rates [SCRs]) of Fluarix (Dose B) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluarix Dose B Group v Fluzone Group |
| Number of subjects included in analysis | 2043 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[7] |
| Parameter estimate | SCR difference |
| Point estimate | 21.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17.82 |
| upper limit | 24.58 |

Notes:

[7] - The non-inferiority of the Fluarix Dose B Group as compared to the Fluzone Group was concluded if the upper limit of the two-sided 95% CI for the difference (Fluzone Group minus Fluarix Dose B Group) in SCR was $\leq 10\%$ for the 3 strains.

| | |
|-----------------------------------|---|
| Statistical analysis title | SCR difference A/Uruguay Fluzone/Fluarix Dose B |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of seroconversion rates [SCRs]) of Fluarix (Dose B) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluarix Dose B Group v Fluzone Group |
| Number of subjects included in analysis | 2043 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[8] |
| Parameter estimate | SCR difference |
| Point estimate | 16.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.46 |
| upper limit | 18.98 |

Notes:

[8] - The non-inferiority of the Fluarix Dose B Group as compared to the Fluzone Group was concluded if the upper limit of the two-sided 95% CI for the difference (Fluzone Group minus Fluarix Dose B Group) in SCR was $\leq 10\%$ for the 3 strains.

| | |
|-----------------------------------|---|
| Statistical analysis title | SCR difference B/Florida Fluzone/Fluarix Dose B |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of seroconversion rates [SCRs]) of Fluarix (Dose B) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluarix Dose B Group v Fluzone Group |
| Number of subjects included in analysis | 2043 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| Parameter estimate | SCR difference |
| Point estimate | 2.48 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.49 |
| upper limit | 5.45 |

Notes:

[9] - The non-inferiority of the Fluarix Dose B Group as compared to the Fluzone Group was concluded if the upper limit of the two-sided 95% CI for the difference (Fluzone Group minus Fluarix Dose B Group) in SCR was $\leq 10\%$ for the 3 strains.

| | |
|-----------------------------------|--|
| Statistical analysis title | SCR difference A/Brisbane Fluzone/Fluarix Dose A |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of seroconversion rates [SCRs]) of Fluarix (Dose A) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluzone Group v Fluarix Dose A Group |
| Number of subjects included in analysis | 2047 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[10] |
| Parameter estimate | SCR difference |
| Point estimate | 27.66 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 24.16 |
| upper limit | 31.14 |

Notes:

[10] - The non-inferiority of the Fluarix Dose A Group as compared to the Fluzone Group was concluded if the upper limit of the two-sided 95% CI for the difference (Fluzone Group minus Fluarix Dose A Group) in SCR was $\leq 10\%$ for the 3 strains.

| | |
|-----------------------------------|---|
| Statistical analysis title | SCR difference A/Uruguay Fluzone/Fluarix Dose A |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of seroconversion rates [SCRs]) of Fluarix (Dose A) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluzone Group v Fluarix Dose A Group |
| Number of subjects included in analysis | 2047 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[11] |
| Parameter estimate | SCR difference |
| Point estimate | 22.47 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19.54 |
| upper limit | 25.49 |

Notes:

[11] - The non-inferiority of the Fluarix Dose A Group as compared to the Fluzone Group was concluded if the upper limit of the two-sided 95% CI for the difference (Fluzone Group minus Fluarix Dose A Group) in SCR was $\leq 10\%$ for the 3 strains.

| | |
|-----------------------------------|---|
| Statistical analysis title | SCR difference B/Florida Fluzone/Fluarix Dose A |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate the immunological non-inferiority (in terms of seroconversion rates [SCRs]) of Fluarix (Dose A) vaccine versus Fluzone vaccine in subjects (6 to 35 months) at approximately 28 days (for

primed subjects) or 56 days (for unprimed subjects) following initial intramuscular vaccination.

| | |
|---|--------------------------------------|
| Comparison groups | Fluarix Dose A Group v Fluzone Group |
| Number of subjects included in analysis | 2047 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[12] |
| Parameter estimate | SCR difference |
| Point estimate | 7.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.75 |
| upper limit | 11.12 |

Notes:

[12] - The non-inferiority of the Fluarix Dose A Group as compared to the Fluzone Group was concluded if the upper limit of the two-sided 95% CI for the difference (Fluzone Group minus Fluarix Dose A Group) in SCR was $\leq 10\%$ for the 3 strains.

Secondary: Number of Seroprotected Subjects for the 3 Flu strains

| | |
|------------------------|--|
| End point title | Number of Seroprotected Subjects for the 3 Flu strains |
| End point description: | A seroprotected subject is a subject with a serum anti-HA titer $\geq 1:40$ Post-vaccination timepoints: Day 28 for primed or Day 56 for unprimed subjects |
| End point type | Secondary |
| End point timeframe: | Day 0 (PRE), Day 28 or Day 56 (POST) |

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|--|----------------------|----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1018 | 1016 | 1031 | |
| Units: Subjects | | | | |
| A/Brisbane (PRE) (N=1017; 1013; 1030) | 185 | 186 | 206 | |
| A/Brisbane (POST) (N=1018; 1016; 1031) | 699 | 754 | 986 | |
| A/Uruguay (PRE) (N=1017; 1013; 1030) | 222 | 193 | 214 | |
| A/Uruguay (POST) (N=1018; 1016; 1031) | 788 | 846 | 1012 | |
| B/Florida (PRE) (N=1017; 1013; 1030) | 171 | 181 | 166 | |
| B/Florida (POST) (N=1018; 1016; 1031) | 872 | 902 | 935 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion factor

| | |
|-----------------|-----------------------|
| End point title | Seroconversion factor |
|-----------------|-----------------------|

End point description:

Seroconversion factor is defined as the fold increase in serum anti-HA GMTs post-vaccination (Day 28 or 56) compared to pre-vaccination (Day 0). Post-vaccination timepoints: Day 28 for primed or Day 56 for unprimed subjects

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 28 or Day 56

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|--|----------------------|----------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1017 | 1013 | 1030 | |
| Units: fold increase | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/Brisbane | 10.2 (9.2 to 11.4) | 12.4 (11.2 to 13.7) | 21.4 (19.9 to 23.1) | |
| A/Uruguay | 10.4 (9.6 to 11.3) | 14.2 (13.1 to 15.4) | 24.1 (22.6 to 25.7) | |
| B/Florida | 13.4 (12.4 to 14.5) | 18.4 (17 to 20) | 21.4 (19.7 to 23.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited local symptoms

| | |
|-----------------|---|
| End point title | Number of subjects reporting solicited local symptoms |
|-----------------|---|

End point description:

Solicited local symptoms assessed included pain, redness and swelling.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During a 4-day follow-up period after vaccination

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|-----------------------------|----------------------|----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1081 | 1086 | 1090 | |
| Units: Subjects | | | | |
| Pain | 403 | 406 | 363 | |
| Redness | 259 | 249 | 253 | |
| Swelling | 152 | 170 | 129 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited general symptoms

| | |
|---|---|
| End point title | Number of subjects reporting solicited general symptoms |
| End point description: | |
| Solicited general symptoms assessed included drowsiness, irritability, loss of appetite, and temperature. | |
| End point type | Secondary |
| End point timeframe: | |
| During a 4-day follow-up period after vaccination | |

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|-----------------------------|----------------------|----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1080 | 1086 | 1090 | |
| Units: Subjects | | | | |
| Drowsiness | 293 | 317 | 298 | |
| Irritability | 386 | 387 | 375 | |
| Loss of appetite | 281 | 273 | 270 | |
| Temperature | 67 | 69 | 72 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited adverse events (AE)

| | |
|---|--|
| End point title | Number of subjects reporting unsolicited adverse events (AE) |
| End point description: | |
| An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product | |
| End point type | Secondary |
| End point timeframe: | |
| During a 28-day follow-up period after vaccination | |

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|---------------------------------|----------------------|----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1107 | 1106 | 1104 | |
| Units: Subjects | | | | |
| Unsolicited adverse events (AE) | 565 | 541 | 562 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAE) and new onset of chronic diseases (NOCD)

| | |
|-----------------|--|
| End point title | Number of subjects reporting serious adverse events (SAE) and new onset of chronic diseases (NOCD) |
|-----------------|--|

End point description:

An SAE is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above. NOCDs assessed include for example: diabetes, asthma, allergies, autoimmune disease, cancer, neuropathic disorders

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the entire study (Day 0 until Month 6)

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|-----------------------------|----------------------|----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1107 | 1106 | 1104 | |
| Units: Subjects | | | | |
| SAE | 35 | 29 | 31 | |
| NOCD | 10 | 8 | 9 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting rare serious events

| | |
|-----------------|--|
| End point title | Number of subjects reporting rare serious events |
|-----------------|--|

End point description:

Rare serious events have an occurrence rate of 1/300 (0.3%).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the entire study (Day 0 until Month 6)

| End point values | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group | |
|-----------------------------|----------------------|----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1107 | 1106 | 1104 | |
| Units: Subjects | | | | |
| Pneumonia | 0 | 0 | 3 | |
| Bronchiolitis | 0 | 3 | 3 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: Day 0 to Month 6; Unsolicited AEs: During the 28-day post-vaccination period; Solicited local and general symptoms: During the 4-day post-vaccination period.

Adverse event reporting additional description:

The occurrence of reported AEs (all/related) was not available and is encoded as equal to the number of subjects affected.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Fluarix Dose A Group |
|-----------------------|----------------------|

Reporting group description:

Subjects were administered 1 or 2 doses* of Fluarix vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age). * Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|-----------------------|----------------------|
| Reporting group title | Fluarix Dose B Group |
|-----------------------|----------------------|

Reporting group description:

Subjects were administered 1 or 2 doses*, half the volume of dose A, of Fluarix vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age). * Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| | |
|-----------------------|---------------|
| Reporting group title | Fluzone Group |
|-----------------------|---------------|

Reporting group description:

Subjects were administered 1 or 2 doses* of Fluzone vaccine (at Day 0 or at Days 0 and 28) intramuscularly, in the non-dominant upper arm (children >12 months of age) or in the anterolateral thigh (children <12 months of age). * Only those subjects who had no history of prior influenza vaccination (i.e. unprimed subjects) received 2 doses.

| Serious adverse events | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group |
|---|----------------------|----------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 35 / 1107 (3.16%) | 29 / 1106 (2.62%) | 31 / 1104 (2.81%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Electric shock | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Foreign body trauma | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 1 / 1106 (0.09%) | 0 / 1104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury corneal | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Skull fracture | | | |
| subjects affected / exposed | 2 / 1107 (0.18%) | 0 / 1106 (0.00%) | 0 / 1104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thermal burn | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 2 / 1104 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Coarctation of the aorta | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Cardiac disorders | | | |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 | | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Febrile convulsion | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Gastrointestinal disorders | | | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Gastritis | | | |
| subjects affected / exposed | 2 / 1107 (0.18%) | 0 / 1106 (0.00%) | 0 / 1104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intussusception | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 2 / 1106 (0.18%) | 0 / 1104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| 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 | | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Asthma | | | |
| subjects affected / exposed | 2 / 1107 (0.18%) | 1 / 1106 (0.09%) | 2 / 1104 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|------------------|------------------|
| Asthmatic crisis | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Idiopathic urticaria | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Acute sinusitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute tonsillitis | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Bronchiolitis | | | |
| subjects affected / exposed | 4 / 1107 (0.36%) | 3 / 1106 (0.27%) | 3 / 1104 (0.27%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 2 / 1106 (0.18%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Croup infectious | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 1 / 1106 (0.09%) | 0 / 1104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 6 / 1107 (0.54%) | 4 / 1106 (0.36%) | 2 / 1104 (0.18%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Gastroenteritis rotavirus | | | |
| subjects affected / exposed | 2 / 1107 (0.18%) | 0 / 1106 (0.00%) | 4 / 1104 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Otitis media | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 2 / 1104 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (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 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 1107 (0.36%) | 4 / 1106 (0.36%) | 3 / 1104 (0.27%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Pneumonia primary atypical | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 0 / 1106 (0.00%) | 0 / 1104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| 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 viral | | | |
| subjects affected / exposed | 1 / 1107 (0.09%) | 1 / 1106 (0.09%) | 0 / 1104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 2 / 1104 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 1107 (0.63%) | 4 / 1106 (0.36%) | 4 / 1104 (0.36%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (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 rash | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 2 / 1104 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| 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 / 1107 (0.00%) | 0 / 1106 (0.00%) | 1 / 1104 (0.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 1107 (0.00%) | 1 / 1106 (0.09%) | 0 / 1104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Fluarix Dose A Group | Fluarix Dose B Group | Fluzone Group |
|---|----------------------|----------------------|---------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 565 / 1107 (51.04%) | 541 / 1106 (48.92%) | 562 / 1104 (50.91%) |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 53 / 1107 (4.79%) | 52 / 1106 (4.70%) | 62 / 1104 (5.62%) |
| occurrences (all) | 53 | 52 | 62 |
| Pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 403 / 1107 (36.40%) | 406 / 1106 (36.71%) | 363 / 1104 (32.88%) |
| occurrences (all) | 403 | 406 | 363 |
| Redness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 259 / 1107 (23.40%) | 249 / 1106 (22.51%) | 253 / 1104 (22.92%) |
| occurrences (all) | 259 | 249 | 253 |
| Swelling | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 152 / 1107 (13.73%) | 170 / 1106 (15.37%) | 129 / 1104 (11.68%) |
| occurrences (all) | 152 | 170 | 129 |
| Drowsiness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 293 / 1107 (26.47%) | 317 / 1106 (28.66%) | 298 / 1104 (26.99%) |
| occurrences (all) | 293 | 317 | 298 |
| Irritability | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 386 / 1107 (34.87%) | 387 / 1106 (34.99%) | 375 / 1104 (33.97%) |
| occurrences (all) | 386 | 387 | 375 |
| Loss of appetite | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed | 281 / 1107 (25.38%) | 273 / 1106 (24.68%) | 270 / 1104 (24.46%) |
| occurrences (all) | 281 | 273 | 270 |
| Temperature alternative assessment type: Systematic | | | |
| subjects affected / exposed | 67 / 1107 (6.05%) | 69 / 1106 (6.24%) | 72 / 1104 (6.52%) |
| occurrences (all) | 67 | 69 | 72 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 62 / 1107 (5.60%) | 42 / 1106 (3.80%) | 60 / 1104 (5.43%) |
| occurrences (all) | 62 | 42 | 60 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 59 / 1107 (5.33%) | 70 / 1106 (6.33%) | 60 / 1104 (5.43%) |
| occurrences (all) | 59 | 70 | 60 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 135 / 1107 (12.20%) | 116 / 1106 (10.49%) | 139 / 1104 (12.59%) |
| occurrences (all) | 135 | 116 | 139 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 139 / 1107 (12.56%) | 119 / 1106 (10.76%) | 123 / 1104 (11.14%) |
| occurrences (all) | 139 | 119 | 123 |
| Pharyngitis | | | |
| subjects affected / exposed | 49 / 1107 (4.43%) | 60 / 1106 (5.42%) | 52 / 1104 (4.71%) |
| occurrences (all) | 49 | 60 | 52 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 22 August 2008 | The rationale for this amendment was to include respiratory rate and heart rate measures at visit Day 0, change in the number of subjects planned (from 150 to 300) for interim analyses and recruitment plan was changed as enrollment plan was not available. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported