



Clinical trial results:

A Combined Phase II/III, Observer-Blind, Randomized, Multi-center Study to Evaluate Safety, Tolerability and Immunogenicity of Trivalent Subunit Influenza Vaccines, Produced Either in Mammalian Cell Culture or in Embryonated Hen Eggs (Fluvirin®), in Healthy Children and Adolescents Aged 3-17 Years

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2007-001534-13 |
| Trial protocol | HU LT FI IT |
| Global end of trial date | 17 July 2008 |

Results information

| | |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Result version number | v2 (current) |
| This version publication date | 28 July 2016 |
| First version publication date | 04 December 2014 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Required for the re-QC project because of the EudraCT system glitch and possible updates to results may be required. Moreover, a change in system user for this study is necessary. |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | V58P12 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00645411 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--------------------------------------------------------------------------------|
| Sponsor organisation name | Novartis Vaccines |
| Sponsor organisation address | Via Fiorentina, 1, Siena, Italy, 53100 |
| Public contact | Posting Director, Novartis Vaccines, RegistryContactVaccinesUS@novartis.com |
| Scientific contact | Posting Director, Novartis Vaccines, RegistryContactVaccinesUS@novartis.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 March 2009 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 July 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Co-Primary:

To demonstrate non-inferiority of the post-vaccination (Day 50) hemagglutination inhibition (HI) geometric mean titer (GMT) of the cell culture-derived influenza vaccine to the corresponding GMT of the egg-derived influenza vaccine for all three strains after two doses administered four weeks apart to a subset of children 3-8 years of age (Cohort 3, immunogenicity subset).

To demonstrate non-inferiority of the percentages of subjects achieving seroconversion or significant increase in antibody titer at Day 50 following administration of the cell culture-derived influenza vaccine to the corresponding percentages of subjects following administration of the egg-derived influenza vaccine for all three strains after two doses administered four weeks apart to a subset of children 3-8 years of age (Cohort 3, immunogenicity subset).

Protection of trial subjects:

Study vaccines were not administered to individuals with known hypersensitivity to any component of the vaccines.

An oral temperature $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$) or serious active infection was a reason for delaying vaccination.

Standard immunization practices were observed and care was taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision was readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine was available in case of any anaphylactic reactions. Care was taken to ensure that the vaccine is not injected into a blood vessel.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment | 08 October 2007 |
| 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 | Finland: 632 |
| Country: Number of subjects enrolled | Italy: 149 |
| Country: Number of subjects enrolled | Lithuania: 248 |
| Country: Number of subjects enrolled | Hungary: 575 |
| Country: Number of subjects enrolled | Croatia: 109 |
| Country: Number of subjects enrolled | Romania: 3 |

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United States: 1888 |
| Worldwide total number of subjects | 3604 |
| EEA total number of subjects | 1716 |

Notes:

| Subjects enrolled per age group | |
|-------------------------------------------|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 3017 |
| Adolescents (12-17 years) | 587 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 14 sites in Finland, 16 in the US, 9 in Croatia, 5 in Italy, 6 in Lithuania, 2 in Romania, 8 in Hungary.

Pre-assignment

Screening details:

All subjects enrolled were included in the trial.

Period 1

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

Arms

| | |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1+2 cTIV (9-17 years) |

Arm description:

All subjects aged 9-17 years received one 0.5 mL IM injection, of Cell Culture-derived trivalent influenza vaccine.

| | |
|----------------------------------------|--------------------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cell culture-derived trivalent influenza vaccine |
| Investigational medicinal product code | |
| Other name | cTIV, Optaflu |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose for Cohorts 1 and 2 and two 0.5 mL doses administered four weeks apart for Cohort 3; all injections were administered IM in the deltoid muscle, preferably of the non-dominant arm.

| | |
|------------------|------------------------------|
| Arm title | Cohort 1+2 eTIV (9-17 years) |
|------------------|------------------------------|

Arm description:

All subjects aged 9-17 years received one 0.5 mL injection, of egg -derived trivalent influenza vaccine.

| | |
|----------------------------------------|-----------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Egg-derived trivalent influenza vaccine |
| Investigational medicinal product code | |
| Other name | eTIV, Fluvirin |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose for Cohorts 1 and 2 and two 0.5 mL doses administered four weeks apart for Cohort 3; all injections were administered IM in the deltoid muscle, preferably of the non-dominant arm.

| | |
|------------------|---------------------------|
| Arm title | Cohort 3 cTIV (3-8 years) |
|------------------|---------------------------|

Arm description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|----------------------------------------|--------------------------------------------------|
| Investigational medicinal product name | Cell culture-derived trivalent influenza vaccine |
| Investigational medicinal product code | |
| Other name | cTIV, Optaflu |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose for Cohorts 1 and 2 and two 0.5 mL doses administered four weeks apart for Cohort 3; all injections were administered IM in the deltoid muscle, preferably of the non-dominant arm.

| | |
|------------------|---------------------------|
| Arm title | Cohort 3 eTIV (3-8 Years) |
|------------------|---------------------------|

Arm description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg - derived trivalent influenza vaccine.

| | |
|----------------------------------------|-----------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Egg-derived trivalent influenza vaccine |
| Investigational medicinal product code | |
| Other name | eTIV, Fluvirin |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose for Cohorts 1 and 2 and two 0.5 mL doses administered four weeks apart for Cohort 3; all injections were administered IM in the deltoid muscle, preferably of the non-dominant arm.

| Number of subjects in period 1 | Cohort 1+2 cTIV (9-17 years) | Cohort 1+2 eTIV (9-17 years) | Cohort 3 cTIV (3-8 years) |
|---------------------------------------|------------------------------|------------------------------|---------------------------|
| Started | 656 | 318 | 1608 |
| Completed | 643 | 312 | 1457 |
| Not completed | 13 | 6 | 151 |
| Consent withdrawn by subject | 2 | 1 | 19 |
| Unable to classify | - | - | 3 |
| Adverse event | - | - | - |
| Inappropriate enrolment | - | - | 4 |
| Lost to follow-up | 10 | 5 | 124 |
| Protocol deviation | 1 | - | 1 |

| Number of subjects in period 1 | Cohort 3 eTIV (3-8 Years) |
|---------------------------------------|---------------------------|
| Started | 1022 |
| Completed | 919 |
| Not completed | 103 |
| Consent withdrawn by subject | 21 |
| Unable to classify | 4 |
| Adverse event | 2 |
| Inappropriate enrolment | 1 |
| Lost to follow-up | 75 |
| Protocol deviation | - |

Baseline characteristics

Reporting groups

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Reporting group title | Cohort 1+2 cTIV (9-17 years) |
| Reporting group description: All subjects aged 9-17 years received one 0.5 mL IM injection, of Cell Culture-derived trivalent influenza vaccine. | |
| Reporting group title | Cohort 1+2 eTIV (9-17 years) |
| Reporting group description: All subjects aged 9-17 years received one 0.5 mL injection, of egg -derived trivalent influenza vaccine. | |
| Reporting group title | Cohort 3 cTIV (3-8 years) |
| Reporting group description: All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine. | |
| Reporting group title | Cohort 3 eTIV (3-8 Years) |
| Reporting group description: All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg -derived trivalent influenza vaccine. | |

| Reporting group values | Cohort 1+2 cTIV (9-17 years) | Cohort 1+2 eTIV (9-17 years) | Cohort 3 cTIV (3-8 years) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------|---------------------------|
| Number of subjects | 656 | 318 | 1608 |
| 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 | | | |
| arithmetic mean | 12.6 | 12.6 | 5.5 |
| standard deviation | ± 2.6 | ± 2.5 | ± 1.7 |
| Gender categorical Units: Subjects | | | |
| Female | 304 | 154 | 795 |
| Male | 352 | 164 | 813 |

| Reporting group values | Cohort 3 eTIV (3-8 Years) | Total | |
|----------------------------------------------------------------|---------------------------|--------|--|
| Number of subjects | 1022 | 3604 | |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) | | 0 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 | | | |
| arithmetic mean | 5.4 | | |
| standard deviation | ± 1.7 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 494 | 1747 | |
| Male | 528 | 1857 | |

End points

End points reporting groups

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Reporting group title | Cohort 1+2 cTIV (9-17 years) |
| Reporting group description: All subjects aged 9-17 years received one 0.5 mL IM injection, of Cell Culture-derived trivalent influenza vaccine. | |
| Reporting group title | Cohort 1+2 eTIV (9-17 years) |
| Reporting group description: All subjects aged 9-17 years received one 0.5 mL injection, of egg -derived trivalent influenza vaccine. | |
| Reporting group title | Cohort 3 cTIV (3-8 years) |
| Reporting group description: All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine. | |
| Reporting group title | Cohort 3 eTIV (3-8 Years) |
| Reporting group description: All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg - derived trivalent influenza vaccine. | |
| Subject analysis set title | cTIV- Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects with at least one vaccination and who provided some postvaccination safety data. | |
| Subject analysis set title | eTIV - Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects with at least one vaccination and who provided some postvaccination safety data. | |
| Subject analysis set title | Cohort 1 cTIV- (9-17 Years)- PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects in the Modified Intention To Treat (MITT) population who received all doses of vaccine correctly, who provided evaluable serum samples at the relevant time points and who had no major protocol violations as defined prior to unblinding. | |
| Subject analysis set title | Cohort 1 eTIV- (9-17 Years)- PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects in the MITT population who received all doses of vaccine correctly, who provided evaluable serum samples at the relevant time points and who had no major protocol violations as defined prior to unblinding. | |
| Subject analysis set title | cTIV - PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects in the MITT population who received all doses of vaccine correctly, who provided evaluable serum samples at the relevant time points and who had no major protocol violations as defined prior to unblinding. | |
| Subject analysis set title | eTIV - PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects in the MITT population who received all doses of vaccine correctly, who provided evaluable serum samples at the relevant time points and who had no major protocol violations as defined prior to unblinding. | |

Primary: 1) Non-inferiority of the Cell Culture-derived Vaccine to the Egg-derived Vaccine in 3-8 Years Old Children in Post Vaccination Geometric Mean Titers

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 1) Non-inferiority of the Cell Culture-derived Vaccine to the Egg-derived Vaccine in 3-8 Years Old Children in Post Vaccination Geometric Mean Titers ^[1] |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

To demonstrate non-inferiority of the post vaccination hemagglutination inhibition (HI) geometric mean titer (GMT) of the cell culture-derived influenza (cTIV) vaccine to the corresponding GMT of the egg-derived (eTIV_f) influenza vaccine, for all three strains, after two injections administered four weeks apart to a subset of children 3-8 years of age.

GMTs were evaluated using two assays, HI egg derived antigen assay and HI cell derived antigen assay. The analysis was performed on the per-protocol dataset

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

End point timeframe:

Day 50 post vaccination

Notes:

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

Justification: There were no statistical analysis done to this endpoint.

| End point values | Cohort 3 cTIV (3-8 years) | Cohort 3 eTIV (3-8 Years) | | |
|-------------------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 524 | 513 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1 (egg derived antigen assay) | 407 (358 to 462) | 477 (419 to 542) | | |
| A/H3N2 (egg derived antigen assay) | 768 (666 to 885) | 1293 (1121 to 1491) | | |
| B (egg derived antigen assay) | 25 (21 to 29) | 44 (38 to 51) | | |
| A/H1N1 (cell derived antigen assay) (N=522,513) | 563 (501 to 634) | 610 (542 to 686) | | |
| A/H3N2 (cell derived antigen assay) (N=522,513) | 858 (744 to 990) | 1329 (1152 to 1533) | | |
| B (cell derived antigen assay) (N=522,513) | 53 (46 to 62) | 62 (53 to 72) | | |

Statistical analyses

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | A/H1N1-Egg derived antigen assay |
|----------------------------|----------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI egg-derived antigen assay

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Method | ANOVA |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 0.85 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.01 |

Notes:

[2] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | A/H3N2-Egg derived antigen assay |
|-----------------------------------|----------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H3N2 influenza strain as measured by HI egg-derived antigen assay.

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| Method | ANOVA |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 0.59 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.72 |

Notes:

[3] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | B-Egg derived antigen assay |
|-----------------------------------|-----------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against influenza B strain as measured by HI egg-derived antigen assay.

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Method | ANOVA |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 0.56 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.46 |
| upper limit | 0.68 |

Notes:

[4] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | A/H1N1-Cell derived antigen assay |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI cell-derived antigen assay.

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[5] |
| Method | ANOVA |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.08 |

Notes:

[5] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | A/H3N1-Cell derived antigen assay |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H3N2 influenza strain as measured by HI cell-derived antigen assay.

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[6] |
| Method | ANOVA |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.78 |

Notes:

[6] - Cell derived vaccine (cTIV) was considered non-inferior to egg-derived vaccine (eTIV) in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | B-Cell derived antigen assay |
|-----------------------------------|------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI cell-derived antigen assay

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[7] |
| Method | ANOVA |
| Parameter estimate | Ratio of GMTs |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.06 |

Notes:

[7] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

Primary: 2) Non-inferiority of the Cell Culture-derived Vaccine to the Egg-derived Vaccine in 3-8 Years Old Children in the Percentage of Subjects Achieving Seroconversion or Significant Increase in Antibody Titers

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 2) Non-inferiority of the Cell Culture-derived Vaccine to the Egg-derived Vaccine in 3-8 Years Old Children in the Percentage of Subjects Achieving Seroconversion or Significant Increase in Antibody Titers ^[8] |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

To demonstrate non-inferiority of the cell culture-derived influenza (cTIV) vaccine to the egg-derived (eTIV_f) influenza vaccine in the percentage of subjects achieving seroconversion or significant increase in antibody titer post vaccination, for all three strains, after two injections administered four weeks apart in children 3-8 years of age.

Seroconversion rate was evaluated using two assays- HI egg derived antigen assay and HI cell derived antigen assay.

The analysis was performed on the per-protocol dataset

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

End point timeframe:

Day 50 post vaccination

Notes:

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

Justification: There were no statistical analysis done to this endpoint.

| End point values | Cohort 3 cTIV (3-8 years) | Cohort 3 eTIV (3-8 Years) | | |
|-------------------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 524 | 513 | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| A/H1N1 (egg derived antigen assay) | 94 (92 to 96) | 96 (94 to 97) | | |
| A/H3N2 (egg derived antigen assay) | 77 (73 to 81) | 86 (82 to 89) | | |
| B (egg derived antigen assay) | 38 (34 to 42) | 53 (49 to 58) | | |
| A/H1N1 (cell derived antigen assay) (N=522,513) | 96 (93 to 97) | 96 (94 to 98) | | |
| A/H3N2 (cell derived antigen assay) (N=522,513) | 80 (76 to 83) | 85 (82 to 88) | | |
| B (cell derived antigen assay) (N=522,513) | 58 (54 to 63) | 58 (54 to 63) | | |

Statistical analyses

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | A/H1N1-Egg derived antigen assay |
|----------------------------|----------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI egg-derived antigen assay.

| | |
|-------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
|-------------------|-------------------------------------------------------|

| | |
|-----------------------------------------|----------------------------------------|
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| Method | Binomial or Miettinen & Nurimen Method |
| Parameter estimate | Difference in % (cTIV minus eTIV) |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | 1 |

Notes:

[9] - cTIV was considered non-inferior to eTIV in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | A/H3N2-Egg derived antigen assay |
|-----------------------------------|----------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H3N2 influenza strain as measured by HI egg-derived antigen assay.

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[10] |
| Method | Binomial or Miettinen & Nurimen Method |
| Parameter estimate | Difference in % (cTIV minus eTIV): |
| Point estimate | -9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13 |
| upper limit | -4 |

Notes:

[10] - cTIV was considered non-inferior to eTIV in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | B-Egg derived antigen assay |
|-----------------------------------|-----------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against influenza B strain as measured by HI egg-derived antigen assay.

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[11] |
| Method | Binomial or Miettinen & Nurimen method |
| Parameter estimate | Difference in % (cTIV minus eTIV): |
| Point estimate | -15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21 |
| upper limit | -9 |

Notes:

[11] - cTIV was considered non-inferior to eTIV in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was $>-10\%$.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | A/H1N1-Cell derived antigen assay |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI cell-derived antigen assay.

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[12] |
| Method | Binominal or Miettinen & Nurimen method |
| Parameter estimate | Difference in % (cTIV minus eTIV) |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | 2 |

Notes:

[12] - cTIV was considered non-inferior to eTIV in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was $>-10\%$.

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | A/H3N2-Cell derived antigen assay |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H3N2 influenza strain as measured by HI cell-derived antigen assay.

| | |
|-----------------------------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[13] |
| Method | Binominal or Miettinen & Nurimen method |
| Parameter estimate | Difference in % (cTIV minus eTIV) |
| Point estimate | -5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.5 |
| upper limit | 0 |

Notes:

[13] - cTIV was considered non-inferior to eTIV_f in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was $>-10\%$.

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | B-Cell derived antigen assay |
|-----------------------------------|------------------------------|

Statistical analysis description:

Non-inferiority of cTIV to eTIV against B influenza strain as measured by HI cell-derived antigen assay.

| | |
|-------------------|-------------------------------------------------------|
| Comparison groups | Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years) |
|-------------------|-------------------------------------------------------|

| | |
|-----------------------------------------|------------------------------------------|
| Number of subjects included in analysis | 1037 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[14] |
| Method | Binominal or Miettinen & Nurminen method |
| Parameter estimate | Difference in % (cTIV minus eTIV) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6 |
| upper limit | 6 |

Notes:

[14] - cTIV was considered non-inferior to eTIV_f in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

Secondary: 3) Geometric Mean Titers After 1 Dose of the Cell Culture-derived or the Egg- derived Influenza Vaccine in 9-17 Years Old Children and Adolescents

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 3) Geometric Mean Titers After 1 Dose of the Cell Culture-derived or the Egg- derived Influenza Vaccine in 9-17 Years Old Children and Adolescents |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

To evaluate immunogenicity in terms of Geometric Mean Titers (GMTs) in children 9-17 years of age after one injection of either cTIV vaccine or eTIV_f.
GMTs were evaluated using two assays, HI egg derived antigen assay and HI cell derived antigen assay. The analysis was performed on the per-protocol dataset.

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

End point timeframe:

Day 29 post vaccination

| End point values | Cohort 1 cTIV- (9-17 Years)- PPS | Cohort 1 eTIV- (9-17 Years)- PPS | | |
|---------------------------------------------|----------------------------------------|----------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 142 | 144 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Baseline (A/H1N1) egg derived antigen assay | 55 (42 to 72) | 78 (60 to 101) | | |
| Day 29 (A/H1N1) egg derived antigen assay | 879 (728 to 1062) | 1107 (918 to 1334) | | |
| Baseline (A/H3N2) egg derived antigen assay | 121 (94 to 155) | 151 (118 to 193) | | |
| Day 29 (A/H3N2) egg derived antigen assay | 706 (607 to 821) | 1857 (1598 to 2157) | | |
| Baseline (B) Egg derived antigen assay | 9.65 (8.2 to 11) | 9.92 (8.45 to 12) | | |
| Day 29 (B) egg derived antigen assay | 58 (48 to 71) | 105 (86 to 129) | | |
| Baseline(A/H1N1)Cell derived assay | 70 (53 to 92) | 90 (69 to 119) | | |
| Day 29 (A/H1N1) cell derived antigen assay | 1076 (886 to 1307) | 1296 (1069 to 1571) | | |

| | | | | |
|-----------------------------------------------|------------------|---------------------|--|--|
| Baseline(A/H3N2)cell derived assay(N=141,144) | 125 (98 to 158) | 144 (114 to 182) | | |
| Day 29 (A/H3N2) cell derived antigen assay | 676 (585 to 783) | 1651 (1429 to 1908) | | |
| Baseline(B)cell derived assay(N=141,144) | 22 (18 to 27) | 25 (21 to 30) | | |
| Day 29 (B) cell derived antigen assay | 136 (113 to 163) | 186 (155 to 222) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 4) Geometric Mean Ratio After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine in 9-17 Year-old Children and Adolescents.

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 4) Geometric Mean Ratio After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine in 9-17 Year-old Children and Adolescents. |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Immunogenicity was evaluated in terms of Geometric Mean Ratio (GMRs) in 9-17 year-old children and adolescents after one injection of either cTIV vaccine or eTIV.

The criterion is met according to European (CHMP) guideline if the mean geometric increase GMR (day29/day1) in HI antibody titer is >2.5.

The analysis was performed on the per-protocol dataset.

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

End point timeframe:

Day 29 post vaccination

| End point values | Cohort 1 cTIV- (9-17 Years)- PPS | Cohort 1 eTIV- (9-17 Years)- PPS | | |
|----------------------------------------------------|----------------------------------------|----------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 142 | 144 | | |
| Units: Ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Day 29 (A/H1N1)egg derived antigen assay | 16 (12 to 21) | 14 (11 to 19) | | |
| Day 29 (A/H3N2) egg derived antigen assay | 5.84 (4.43 to 7.7) | 12 (9.33 to 16) | | |
| Day 29 (B) egg derived antigen assay | 6.03 (4.77 to 7.62) | 11 (8.43 to 13) | | |
| Day29(A/H1N1)cell derived antigen assay(N=141,144) | 15 (12 to 21) | 14 (11 to 19) | | |
| Day29(A/H3N2)cell derived antigen assay(N=141,144) | 5.45 (4.21 to 7.06) | 11 (8.87 to 15) | | |
| Day29(B) cell derived antigen assay(N=141,144) | 6.15 (4.96 to 7.63) | 7.37 (5.96 to 9.12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 5) Percentage of 9-17 Year-old Children and Adolescents Achieving HI Titers ≥ 40 After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine

| | |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 5) Percentage of 9-17 Year-old Children and Adolescents Achieving HI Titers ≥ 40 After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

To evaluate immunogenicity in terms of percentage of 9-17 year-old children and adolescents achieving HI titers ≥ 40 , after one injection of either the cTIV vaccine or the eTIV_f vaccine.

This criterion is met according to European (CHMP) guideline if the percentage of subjects achieving HI titers ≥ 40 is $>70\%$ and according to the US (CBER) guideline is met if the lower bound of the two sided 95%CI for percentage of subjects achieving HI titers ≥ 40 is $\geq 70\%$.

The analysis was performed on PPS

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

End point timeframe:

Day 29 post vaccination

| End point values | Cohort 1 cTIV- (9-17 Years)- PPS | Cohort 1 eTIV- (9-17 Years)- PPS | | |
|----------------------------------------------------|----------------------------------------|----------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 142 | 144 | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Prevaccination(A/H1N1)egg derived antigen assay | 65 (57 to 73) | 75 (67 to 82) | | |
| Day 29 (A/H1N1) egg derived antigen assay | 99 (96 to 100) | 99 (95 to 100) | | |
| Prevaccination(A/H3N2) egg derived antigen assay | 82 (74 to 88) | 86 (79 to 91) | | |
| Day 29 (A/H3N2) egg derived antigen assay | 100 (97 to 100) | 100 (97 to 100) | | |
| Prevaccination(B)egg derived antigen assay | 17 (11 to 24) | 13 (8 to 19) | | |
| Day 29 (B) egg derived antigen assay | 75 (67 to 82) | 84 (77 to 90) | | |
| Prevaccination(H1N1)cell derived assay(N=141,144) | 67 (59 to 75) | 78 (71 to 85) | | |
| Day 29 (A/H1N1)cell derived antigen assay | 99 (96 to 100) | 98 (94 to 100) | | |
| Prevaccination (H3N2)cell derived assay(N=141,144) | 83 (76 to 89) | 86 (79 to 91) | | |
| Day 29 (A/H3N2) cell derived antigen assay | 100 (97 to 100) | 100 (97 to 100) | | |
| Prevaccination (B) cell derived assay(N=141,144) | 40 (32 to 49) | 47 (38 to 55) | | |
| Day 29 (B) cell derived antigen assay | 95 (90 to 98) | 94 (89 to 98) | | |

Statistical analyses

Secondary: 6) Percentage of 9-17 Year-old Children and Adolescents With Seroconversion or Significant Increase After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine

| | |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 6) Percentage of 9-17 Year-old Children and Adolescents With Seroconversion or Significant Increase After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Seroconversion or significant increase as per CHMP criteria is defined as percentage of subjects with a pre vaccination HI titer <10 to a post vaccination titer ≥40 or a pre vaccination HI titer ≥10 and a ≥4-fold increase in post vaccination HI antibody titer.

According to the CHMP criteria, the percentage of subjects achieving seroconversion or significant increase should be >40%.

According to the CBER criteria, the lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion/significant increase should be ≥40%.

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

End point timeframe:

Day 29 post vaccination

| End point values | Cohort 1 cTIV- (9-17 Years)- PPS | Cohort 1 eTIV- (9-17 Years)- PPS | | |
|----------------------------------------------------|----------------------------------------|----------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 142 | 144 | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Day 29 (A/H1N1) egg derived antigen assay | 77 (70 to 84) | 77 (69 to 84) | | |
| Day 29 (A/H3N2) egg derived antigen assay | 56 (48 to 65) | 77 (69 to 84) | | |
| Day 29 (B) egg derived antigen assay | 56 (48 to 65) | 71 (63 to 78) | | |
| Day29(A/H1N1)cell derived antigen assay(N=141,144) | 74 (66 to 81) | 74 (66 to 81) | | |
| Day29(A/H3N2)cell derived antigen assay(N=141,144) | 52 (44 to 61) | 78 (70 to 84) | | |
| Day29(B)cell derived antigen assay (N=141,144) | 63 (55 to 71) | 69 (61 to 76) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 7) Geometric Mean Titers After Two Doses of the Cell Derived or the Egg Derived Vaccine in 3-8 Year-old Children

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | 7) Geometric Mean Titers After Two Doses of the Cell Derived or the Egg Derived Vaccine in 3-8 Year-old Children ^[15] |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

To evaluate immunogenicity in terms of Geometric Mean Titers (GMTs) in children 3-8 years of age after two doses of either cTIV vaccine or eTIV, administered 4 weeks apart.

The analysis was performed on the per-protocol dataset.

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

End point timeframe:

Day 29 and Day 50 post vaccination

Notes:

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

Justification: There were no statistical analysis done to this endpoint.

| End point values | Cohort 3 cTIV (3-8 years) | Cohort 3 eTIV (3-8 Years) | | |
|-------------------------------------------------------|------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 524 | 513 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Baseline (A/H1N1) egg derived antigen assay | 16 (14 to 18) | 15 (13 to 17) | | |
| Day29(A/H1N1)egg derived antigen assay(N=515,507) | 152 (124 to 186) | 157 (128 to 192) | | |
| Day50(A/H1N1)egg derived antigen assay | 407 (358 to 462) | 477 (419 to 542) | | |
| Baseline (A/H3N2) egg derived antigen assay | 68 (58 to 80) | 74 (63 to 87) | | |
| Day29(A/H3N2)egg derived antigen assay(N=515,507) | 584 (478 to 713) | 1075 (880 to 1312) | | |
| Day50(A/H3N2)egg derived antigen assay | 768 (666 to 885) | 1293 (1121 to 1491) | | |
| Baseline (B) egg derived antigen assay | 6.16 (5.86 to 6.48) | 6.24 (5.93 to 6.56) | | |
| Day29(B) egg derived antigen assay (N=515,507) | 19 (16 to 22) | 27 (23 to 33) | | |
| Day 50 (B) egg derived antigen assay | 25 (21 to 29) | 44 (38 to 51) | | |
| Baseline (A/H1N1) cell derived antigen assay | 19 (16 to 22) | 17 (14 to 19) | | |
| Day 29 (A/H1N1) cell derived antigen assay | 234 (194 to 283) | 192 (159 to 232) | | |
| Day50(A/H1N1)cell derived antigen assay(N=522,513) | 563 (501 to 634) | 610 (542 to 686) | | |
| Baseline (A/H3N2) cell derived antigen assay | 75 (64 to 88) | 85 (72 to 99) | | |
| Day 29 (A/H3N2) cell derived antigen assay | 653 (536 to 795) | 1099 (903 to 1339) | | |
| Day50(A/H3N2)cell derived antigen assay(N=522,513) | 858 (744 to 990) | 1329 (1152 to 1533) | | |
| Baseline (B) cell derived antigen assay | 8.22 (7.59 to 8.9) | 8.72 (8.05 to 9.45) | | |
| Day 29 (B) cell derived antigen assay | 29 (24 to 36) | 36 (30 to 44) | | |
| Day50 (B) cell derived antigen assay(N=522,513) | 53 (46 to 62) | 62 (53 to 72) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 8) Geometric Mean Ratio After Two Doses of the Cell-derived or the Egg-derived Vaccine in 3-8 Year-old Children

| | |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | 8) Geometric Mean Ratio After Two Doses of the Cell-derived or the Egg-derived Vaccine in 3-8 Year-old Children ^[16] |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

End point description:

To evaluate immunogenicity in terms of Geometric Mean Ratio (GMR) in children 3-8 years of age after two doses of either the cTIV vaccine or the eTIV vaccine, administered 4 weeks apart according to the CHMP criteria.

The criterion is met according to the European (CHMP) guideline if the mean geometric increase(GMR day 29/day 1 and GMR day 50/day 1) in HI antibody titer is >2.5

The analysis was performed on the per-protocol dataset.

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

End point timeframe:

Day 29 and Day 50 post vaccination

Notes:

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

Justification: There were no statistical analysis done to this endpoint.

| End point values | Cohort 3 cTIV (3-8 years) | Cohort 3 eTIV (3-8 Years) | | |
|----------------------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 524 | 513 | | |
| Units: Ratios | | | | |
| number (confidence interval 95%) | | | | |
| Day29 (A/H1N1)egg derived antigen assay(N=515,507) | 9.58 (8.37 to 11) | 11 (9.36 to 12) | | |
| Day 50 (A/H1N1) egg derived antigen assay | 25 (23 to 28) | 33 (29 to 36) | | |
| Day29 (A/H3N2)egg derived antigen assay(N=515,507) | 8.65 (7.4 to 10) | 15 (13 to 17) | | |
| Day 50 (A/H3N2) egg derived antigen assay | 11 (9.84 to 13) | 17 (15 to 20) | | |
| Day 29 (B) egg derived assay (N=515,507) | 3.04 (2.59 to 3.57) | 4.36 (3.71 to 5.12) | | |
| Day 50 (B) egg derived antigen assay | 3.99 (3.49 to 4.57) | 7.04 (6.15 to 8.07) | | |
| Day 29 (A/H1N1) cell derived antigen assay | 13 (11 to 14) | 12 (10 to 13) | | |
| Day50(A/H1N1)cell derived antigen assay(N=522,513) | 30 (27 to 34) | 37 (33 to 42) | | |
| Day 29 (A/H3N2) cell derived antigen assay | 8.73 (7.54 to 10) | 13 (11 to 15) | | |
| Day50(A/H3N2)cell derived antigen assay(N=522,513) | 12 (10 to 13) | 16 (14 to 18) | | |
| Day 29 (B) cell derived antigen assay | 3.59 (3.08 to 4.19) | 4.14 (3.55 to 4.82) | | |
| Day 50 (B) cell derived antigen assay(N=522,513) | 6.5 (5.75 to 7.34) | 7.06 (6.24 to 7.99) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 9) Percentage of 3-8 Year-old Children Achieving HI Titers ≥ 40 After Two Doses of the Cell Culture Derived or the Egg Derived Influenza Vaccine.

| | |
|-----------------|-----------------------------------------------------------------|
| End point title | 9) Percentage of 3-8 Year-old Children Achieving HI Titers ≥ 40 |
|-----------------|-----------------------------------------------------------------|

End point description:

To evaluate immunogenicity in terms of HI titers ≥ 40 , in children 3-8 years of age after two doses of either cTIV vaccine or eTIV_f vaccine, administered 4 weeks apart.
The criterion is met according to European (CHMP) guideline if the percentage of subjects achieving HI titers ≥ 40 is $>70\%$ and according to the US (CBER) guideline if the lower bound of the two sided 95%CI for percentage of subjects achieving HI titers ≥ 40 is $\geq 70\%$.
The analysis was performed on the per-protocol dataset.

End point type Secondary

End point timeframe:

Day 29 and Day 50 post vaccination

Notes:

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

Justification: There were no statistical analysis done to this endpoint.

| End point values | Cohort 3 cTIV (3-8 years) | Cohort 3 eTIV (3-8 Years) | | |
|----------------------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 524 | 513 | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Prevaccination (A/H1N1) egg derived antigen assay | 35 (30 to 39) | 31 (27 to 35) | | |
| Day29(A/H1N1)egg derived antigen assay (N=515,507) | 72 (68 to 76) | 68 (64 to 72) | | |
| Day 50 (A/H1N1) egg derived antigen assay | 96 (94 to 98) | 97 (95 to 98) | | |
| Prevaccination (A/H3N2) egg derived antigen assay | 67 (62 to 71) | 70 (66 to 74) | | |
| Day29(A/H3N2)egg derived antigen assay(N=515,507) | 87 (84 to 90) | 85 (82 to 88) | | |
| Day50 (A/H3N2) egg derived antigen assay | 96 (94 to 98) | 94 (91 to 96) | | |
| Prevaccination (B) egg derived antigen assay | 4 (3 to 7) | 4 (3 to 6) | | |
| Day 29 (B) egg derived antigen assay (N=515,507) | 35 (30 to 39) | 40 (36 to 45) | | |
| Day 50 (B) egg derived antigen assay | 40 (35 to 44) | 55 (51 to 95) | | |
| Prevaccination (A/H1N1) cell derived antigen assay | 36 (32 to 40) | 33 (29 to 38) | | |
| Day 29 (A/H1N1) cell derived antigen assay | 82 (78 to 85) | 76 (72 to 80) | | |
| Day50(A/H1N1)cell derived antigen assay(N=522,513) | 98 (97 to 99) | 98 (96 to 99) | | |
| Prevaccination (A/H3N2) cell derived antigen assay | 71 (67 to 75) | 75 (71 to 79) | | |
| Day 29 (A/H3N2) cell derived antigen assay | 89 (86 to 92) | 85 (82 to 88) | | |
| Day50(A/H3N2)cell derived antigen assay(N=522,513) | 98 (96 to 99) | 93 (91 to 95) | | |
| Prevaccination (B) cell derived antigen assay | 11 (8 to 14) | 12 (10 to 16) | | |
| Day 29 (B) cell derived antigen assay | 43 (39 to 47) | 45 (40 to 49) | | |
| Day 50 (B) cell derived antigen assay (N=522,513) | 60 (56 to 65) | 62 (57 to 66) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 10) Percentage of 3-8 Year-old Children Achieving Seroconversion or Significant Increase in HI Titers After Two Doses of the Cell Culture-derived or the Egg-derived Influenza Vaccine.

| | |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 10) Percentage of 3-8 Year-old Children Achieving Seroconversion or Significant Increase in HI Titers After Two Doses of the Cell Culture-derived or the Egg-derived Influenza Vaccine. ^[18] |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Seroconversion or significant increase as per CHMP criteria is defined as percentage of subjects with a pre vaccination HI titer <10 to a post vaccination titer ≥40 or a prevaccination HI titer ≥10 and a ≥4-fold increase in post vaccination HI antibody titer.

According to the CHMP criteria, the percentage of subjects achieving seroconversion or significant increase should be >40%.

According to the CBER criteria, the lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion/significant increase should be ≥40%.

The analysis was performed on the per-protocol dataset.

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

End point timeframe:

Day 29 and Day 50 post vaccination

Notes:

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

Justification: There were no statistical analysis done to this endpoint.

| End point values | Cohort 3 cTIV (3-8 years) | Cohort 3 eTIV (3-8 Years) | | |
|----------------------------------------------------|------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 524 | 513 | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Day29(A/H1N1) egg derived antigen assay(N=515,507) | 70 (66 to 74) | 67 (63 to 72) | | |
| Day 50 (H1N1) egg derived antigen assay | 94 (92 to 96) | 96 (94 to 97) | | |
| Day29(A/H3N2) egg derived antigen assay(N=515,507) | 65 (61 to 70) | 78 (74 to 81) | | |
| Day 50 (A/H3N2) egg derived antigen assay | 77 (73 to 81) | 86 (82 to 89) | | |
| Day29(B) egg derived antigen assay(N=515,507) | 33 (29 to 37) | 38 (34 to 43) | | |
| Day 50 (B) egg derived antigen assay | 38 (34 to 42) | 53 (49 to 58) | | |
| Day 29 (A/H1N1) cell derived antigen assay | 79 (75 to 83) | 75 (70 to 78) | | |
| Day50(A/H1N1)cell derived antigen assay(N=522,513) | 96 (93 to 97) | 96 (94 to 98) | | |
| Day 29 (A/H3N2) cell derived antigen assay | 70 (66 to 74) | 76 (72 to 80) | | |

| | | | | |
|----------------------------------------------------|---------------|---------------|--|--|
| Day50(A/H3N2)cell derived antigen assay(N=522,513) | 80 (76 to 83) | 85 (82 to 88) | | |
| Day 29 (B) cell derived antigen assay | 40 (36 to 44) | 41 (37 to 45) | | |
| Day 50(B)cell derived antigen assay(N=522,513) | 58 (54 to 63) | 58 (54 to 63) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 11) Number of 9-17 Year-old Children and Adolescents Reporting Local and Systemic Reactions After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine

| | |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 11) Number of 9-17 Year-old Children and Adolescents Reporting Local and Systemic Reactions After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine ^[19] |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

To evaluate safety and tolerability in terms of number of 9-17 year-old children and adolescents (cohorts 1 and 2) reporting local and systemic reactions following of one injection of the cTIV or the eTIV vaccine .

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

End point timeframe:

Up to 7 days after vaccination

Notes:

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

Justification: There were no statistical analysis done to this endpoint.

| End point values | Cohort 1+2 cTIV (9-17 years) | Cohort 1+2 eTIV (9-17 years) | | |
|-------------------------------------------------|------------------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 652 | 316 | | |
| Units: Participants | | | | |
| Any Local | 276 | 141 | | |
| Injection site pain | 220 | 120 | | |
| Injection site erythema | 91 | 45 | | |
| Injection site induration | 44 | 28 | | |
| Injection site ecchymosis | 34 | 10 | | |
| Injection site swelling | 32 | 17 | | |
| Any Systemic | 188 | 95 | | |
| Chills | 26 | 13 | | |
| Malaise | 60 | 34 | | |
| Myalgia | 99 | 59 | | |
| Arthralgia | 27 | 17 | | |
| Headache | 92 | 44 | | |
| Sweating | 14 | 3 | | |
| Fatigue | 57 | 41 | | |
| Fever ($\geq 38^{\circ}\text{C}$) (N=651,316) | 5 | 3 | | |
| Any Other | 44 | 37 | | |
| Stayed at home (N=649,316) | 9 | 10 | | |
| Analgesic Medication Used | 42 | 31 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 12) Number of 3-8 Year-old Children Reporting Local and Systemic Reactions After One and Two Doses of the Cell Culture-derived or Egg-derived Influenza Vaccine.

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 12) Number of 3-8 Year-old Children Reporting Local and Systemic Reactions After One and Two Doses of the Cell Culture-derived or Egg-derived Influenza Vaccine. ^[20] |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

To evaluate the safety and tolerability of the cTIV and the eTIV_f influenza vaccines in 3-8 year-old children terms of number of participants reporting local and systemic reactions after each vaccination.

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

End point timeframe:

Up to 7 days after each vaccination

Notes:

[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: There were no statistical analysis done to this endpoint.

| End point values | Cohort 3 cTIV (3-8 years) | Cohort 3 eTIV (3-8 Years) | | |
|-----------------------------------------------------------|------------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1599 | 1013 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Injection site pain | 653 | 398 | | |
| Injection site erythema | 337 | 206 | | |
| Injection site induration | 141 | 84 | | |
| Injection site ecchymosis | 144 | 99 | | |
| Injection site swelling | 119 | 85 | | |
| Chills | 70 | 68 | | |
| Malaise | 156 | 117 | | |
| Myalgia | 202 | 119 | | |
| Arthralgia | 65 | 28 | | |
| Headache | 182 | 144 | | |
| Sweating | 47 | 28 | | |
| Fatigue | 210 | 170 | | |
| Fever ($\geq 38^{\circ}\text{C}$) | 75 | 60 | | |
| Oral temp; 38 to $<38.9^{\circ}\text{C}$ (N=1598,1013) | 48 | 43 | | |
| Oral temp; 39 to $< 40^{\circ}\text{C}$ (N=1598,1013) | 16 | 15 | | |
| Oral temp; $\geq 40^{\circ}\text{C}$ (N=1598,1013) | 6 | 1 | | |
| Stayed at home (N=1586, 1004)) | 77 | 63 | | |
| Analgesic Medication Used | 221 | 148 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study period (Day 1-181 for Cohorts 1 and 2, and Day 1-209 for cohort 3)

Adverse event reporting additional description:

Solicited AEs - day 1 through day 7 after vaccination.

All AEs- day 1 through day 29 (cohort 1&2); day 1 through day 50 (cohort 3).

SAEs, onset of chronic illness, and AEs that lead to withdrawal from the study and associated concomitant medications-day 29 to day 181 (cohort 1&2); day 50 through day 209 (cohort 3)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Cohort 1 & 2 cTIV (9-17 years) |
|-----------------------|--------------------------------|

Reporting group description:

All subjects aged 9-17 years received one 0.5 mL IM injection, of Cell Culture-derived trivalent influenza vaccine.

| | |
|-----------------------|--------------------------------|
| Reporting group title | Cohort 1 & 2 eTIV (9-17 years) |
|-----------------------|--------------------------------|

Reporting group description:

All subjects aged 9-17 years received one 0.5 mL injection, of egg -derived trivalent influenza vaccine.

| | |
|-----------------------|--------------------------------------------|
| Reporting group title | Cohort 3 cTIV(3-8 years)-First vaccination |
|-----------------------|--------------------------------------------|

Reporting group description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine.

| | |
|-----------------------|--------------------------------------------|
| Reporting group title | Cohort 3 eTIV(3-8 years)-First vaccination |
|-----------------------|--------------------------------------------|

Reporting group description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg - derived trivalent influenza vaccine.

| | |
|-----------------------|---------------------------------------------|
| Reporting group title | Cohort 3 cTIV(3-8 years)-Second vaccination |
|-----------------------|---------------------------------------------|

Reporting group description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine.

| | |
|-----------------------|---------------------------------------------|
| Reporting group title | Cohort 3 eTIV(3-8 years)-Second vaccination |
|-----------------------|---------------------------------------------|

Reporting group description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg - derived trivalent influenza vaccine.

| Serious adverse events | Cohort 1 & 2 cTIV (9-17 years) | Cohort 1 & 2 eTIV (9-17 years) | Cohort 3 cTIV(3-8 years)-First vaccination |
|---------------------------------------------------|--------------------------------|--------------------------------|--------------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 652 (0.77%) | 3 / 316 (0.95%) | 2 / 1599 (0.13%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Body height below normal | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed | 1 / 652 (0.15%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Contusion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 1 / 1599 (0.06%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye injury | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Congenital, familial and genetic disorders | | | |
| Thalassaemia beta | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Surgical and medical procedures | | | |
| Tonsillectomy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 | | | |
| Post procedural haemorrhage | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|------------------|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 652 (0.15%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Appendix disorder | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 652 (0.15%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Reproductive system and breast disorders | | | |
| Ovarian torsion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 1 / 316 (0.32%) | 0 / 1599 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchitis chronic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Psychiatric disorders | | | |
| Major depression | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 652 (0.15%) | 0 / 316 (0.00%) | 0 / 1599 (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 | | | |
| Abscess limb | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Infectious mononucleosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 1 / 1599 (0.06%) |
| 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 | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 1 / 316 (0.32%) | 0 / 1599 (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 |
| Otitis media chronic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Pelvic abscess | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 652 (0.15%) | 0 / 316 (0.00%) | 0 / 1599 (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 | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 bacterial | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 1 / 316 (0.32%) | 0 / 1599 (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 |
| Respiratory tract infection viral | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Streptococcal bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 652 (0.00%) | 1 / 316 (0.32%) | 0 / 1599 (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 | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 652 (0.15%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 652 (0.15%) | 0 / 316 (0.00%) | 0 / 1599 (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 |
| Diabetes mellitus | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed | 0 / 652 (0.00%) | 0 / 316 (0.00%) | 0 / 1599 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 3 eTIV(3-8 years)-First vaccination | Cohort 3 cTIV(3-8 years)-Second vaccination | Cohort 3 eTIV(3-8 years)-Second vaccination |
|---------------------------------------------------|--------------------------------------------|---------------------------------------------|---------------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 7 / 1557 (0.45%) | 5 / 977 (0.51%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Body height below normal | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 2 / 1557 (0.13%) | 0 / 977 (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 |
| Contusion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 1 / 1557 (0.06%) | 0 / 977 (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 |
| Eye injury | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 1 / 1557 (0.06%) | 0 / 977 (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 |
| Congenital, familial and genetic disorders | | | |
| Thalassaemia beta | | | |
| alternative assessment type: Non- | | | |

| | | | |
|-------------------------------------------------|------------------|------------------|-----------------|
| systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 1 / 1557 (0.06%) | 0 / 977 (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 |
| Surgical and medical procedures | | | |
| Tonsillectomy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 1 / 977 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Post procedural haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 1 / 977 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 |
| Appendix disorder | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 |
| Reproductive system and breast disorders | | | |
| Ovarian torsion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 | | | |
| Bronchitis chronic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 1 / 977 (0.10%) |
| 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 | | | |
| Major depression | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 | | | |
| Abscess limb | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 1 / 977 (0.10%) |
| 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 | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 1 / 1557 (0.06%) | 1 / 977 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 |
| Influenza | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 chronic | | | |

| | | | |
|-------------------------------------------------|------------------|------------------|-----------------|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 1 / 977 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic abscess | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 |
| Pharyngotonsillitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 1 / 1557 (0.06%) | 0 / 977 (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 bacterial | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 tract infection viral | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 1 / 1557 (0.06%) | 0 / 977 (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 |
| Streptococcal bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|-------------------------------------------------|------------------|------------------|-----------------|
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 0 / 1557 (0.00%) | 0 / 977 (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 |
| Diabetes mellitus | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 1013 (0.00%) | 1 / 1557 (0.06%) | 0 / 977 (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 | Cohort 1 & 2 cTIV (9-17 years) | Cohort 1 & 2 eTIV (9-17 years) | Cohort 3 cTIV(3-8 years)-First vaccination |
|-------------------------------------------------------|-----------------------------------|-----------------------------------|--------------------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 328 / 652 (50.31%) | 168 / 316 (53.16%) | 799 / 1599 (49.97%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 99 / 652 (15.18%) | 47 / 316 (14.87%) | 143 / 1599 (8.94%) |
| occurrences (all) | 125 | 56 | 167 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 57 / 652 (8.74%) | 41 / 316 (12.97%) | 155 / 1599 (9.69%) |
| occurrences (all) | 67 | 47 | 171 |
| Injection site erythema | | | |
| subjects affected / exposed | 91 / 652 (13.96%) | 45 / 316 (14.24%) | 197 / 1599 (12.32%) |
| occurrences (all) | 94 | 45 | 198 |
| Injection site haemorrhage | | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------|----------------------------|
| subjects affected / exposed occurrences (all) | 34 / 652 (5.21%) 37 | 10 / 316 (3.16%) 11 | 98 / 1599 (6.13%) 106 |
| Injection site induration subjects affected / exposed occurrences (all) | 44 / 652 (6.75%) 44 | 28 / 316 (8.86%) 29 | 87 / 1599 (5.44%) 89 |
| Injection site pain subjects affected / exposed occurrences (all) | 220 / 652 (33.74%) 227 | 120 / 316 (37.97%) 122 | 451 / 1599 (28.21%) 462 |
| Malaise alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 60 / 652 (9.20%) 68 | 34 / 316 (10.76%) 41 | 103 / 1599 (6.44%) 118 |
| Pyrexia subjects affected / exposed occurrences (all) | 12 / 652 (1.84%) 13 | 5 / 316 (1.58%) 7 | 88 / 1599 (5.50%) 96 |
| Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 10 / 652 (1.53%) 10 | 4 / 316 (1.27%) 4 | 124 / 1599 (7.75%) 130 |
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) | 99 / 652 (15.18%) 107 | 59 / 316 (18.67%) 67 | 141 / 1599 (8.82%) 150 |

| Non-serious adverse events | Cohort 3 eTIV(3-8 years)-First vaccination | Cohort 3 cTIV(3-8 years)-Second vaccination | Cohort 3 eTIV(3-8 years)-Second vaccination |
|------------------------------------------------------------------------------------------|--------------------------------------------|---------------------------------------------|---------------------------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 507 / 1013 (50.05%) | 670 / 1557 (43.03%) | 413 / 977 (42.27%) |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 111 / 1013 (10.96%) 135 | 94 / 1557 (6.04%) 110 | 73 / 977 (7.47%) 89 |
| General disorders and administration site conditions | | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------------------------|---------------------------|
| Fatigue subjects affected / exposed occurrences (all) | 119 / 1013 (11.75%) 143 | 99 / 1557 (6.36%) 110 | 82 / 977 (8.39%) 92 |
| Injection site erythema subjects affected / exposed occurrences (all) | 138 / 1013 (13.62%) 139 | 209 / 1557 (13.42%) 211 | 118 / 977 (12.08%) 121 |
| Injection site haemorrhage subjects affected / exposed occurrences (all) | 60 / 1013 (5.92%) 67 | 52 / 1557 (3.34%) 58 | 43 / 977 (4.40%) 51 |
| Injection site induration subjects affected / exposed occurrences (all) | 44 / 1013 (4.34%) 45 | 66 / 1557 (4.24%) 66 | 51 / 977 (5.22%) 51 |
| Injection site pain subjects affected / exposed occurrences (all) | 251 / 1013 (24.78%) 261 | 421 / 1557 (27.04%) 430 | 266 / 977 (27.23%) 278 |
| Malaise alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 78 / 1013 (7.70%) 85 | 76 / 1557 (4.88%) 86 | 50 / 977 (5.12%) 56 |
| Pyrexia subjects affected / exposed occurrences (all) | 73 / 1013 (7.21%) 84 | 63 / 1557 (4.05%) 70 | 44 / 977 (4.50%) 49 |
| Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 75 / 1013 (7.40%) 87 | 70 / 1557 (4.50%) 75 | 51 / 977 (5.22%) 52 |
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) | 76 / 1013 (7.50%) 88 | 100 / 1557 (6.42%) 28 | 67 / 977 (6.86%) 22 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22301476>