



Clinical trial results:

A Phase 2, Randomized, Controlled, Observer-Blind, Clinical Study to Evaluate the Humoral and Cell Mediated Immunity and Safety of Two Intramuscular Doses of FludacTM or AgrippalTM in Previously Unvaccinated Healthy Subjects Aged 6 to < 36 Months.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2010-023791-63 |
| Trial protocol | DE BE |
| Global end of trial date | 14 February 2012 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 28 July 2016 |
| First version publication date | 20 March 2015 |
| 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 | V70_34 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01342796 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000149-PIP01-07 |
| 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 | 17 May 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 February 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To explore the cell mediated immune (CMI) responses to two 0.25 mL Intramuscular (IM) injections of Thiomersal free MF59C.1-adjuvanted influenza vaccine (aTIV) or to two 0.25 mL IM injections of non-adjuvanted trivalent influenza vaccine (TIV) as determined by the quality and quantity of the antigen-specific T- cells responses after in-vitro restimulation of peripheral blood mononuclear cells in previously unvaccinated healthy children aged 6 to <36 months.

Protection of trial subjects:

This clinical study was designated, implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations (CFR) Title 21, and Japanese Ministry of Health, Labor and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 21 May 2011 |
| 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 | Belgium: 84 |
| Worldwide total number of subjects | 84 |
| EEA total number of subjects | 84 |

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) | 43 |

| | |
|---------------------------|----|
| Children (2-11 years) | 41 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 90 subjects were planned for this study. Overall, 84 subjects were enrolled .

Pre-assignment

Screening details:

Subjects were randomized into one of two treatment groups in a 1:1 ratio to receive either aTIV or TIV.

Period 1

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | aTIV (6 to < 24 months) |

Arm description:

Subjects aged between 6 to <24 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | MF59C.1-adjuvanted subunit trivalent influenza vaccine (purified viral envelope-glycoproteins neuraminidase (NA) and hemagglutinin (HA)) |
| Investigational medicinal product code | |
| Other name | Fluad |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Vaccination consisted of one 0.25 mL dose administered IM in the deltoid muscle, preferably of the non-dominant arm.

| | |
|------------------|-------------------------|
| Arm title | aTIV (24 to <36 months) |
|------------------|-------------------------|

Arm description:

Subjects aged between 24 to <36 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | MF59C.1-adjuvanted subunit trivalent influenza vaccine (purified viral envelope-glycoproteins neuraminidase (NA) and hemagglutinin (HA)) |
| Investigational medicinal product code | |
| Other name | Fluad |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Vaccination consisted of one 0.25 mL dose administered IM in the deltoid muscle, preferably of the non-dominant arm.

| | |
|--|---|
| Arm title | TIV (6 to <24 months) |
| Arm description: Subjects aged between 6 to <24 months who received two doses of inactivated unadjuvanted trivalent influenza vaccine on days 1 and 29. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Egg-derived trivalent subunit influenza vaccine |
| Investigational medicinal product code | |
| Other name | Agrippal |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Vaccination consisted of one 0.25 mL dose administered IM in the deltoid muscle, preferably of the non-dominant arm.

| | |
|---|---|
| Arm title | TIV (24 to <36 months) |
| Arm description: Subjects aged between 24 to <36 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Egg-derived trivalent subunit influenza vaccine |
| Investigational medicinal product code | |
| Other name | Agrippal |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Vaccination consisted of one 0.25 mL dose administered IM in the deltoid muscle, preferably of the non-dominant arm.

| Number of subjects in period 1 | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) |
|---------------------------------------|-------------------------|-------------------------|-----------------------|
| Started | 22 | 21 | 21 |
| Completed | 21 | 19 | 20 |
| Not completed | 1 | 2 | 1 |
| Consent withdrawn by subject | 1 | 1 | - |
| Inappropriate enrollment | - | 1 | - |
| Lost to follow-up | - | - | 1 |

| Number of subjects in period 1 | TIV (24 to <36 months) |
|---------------------------------------|------------------------|
| Started | 20 |
| Completed | 18 |
| Not completed | 2 |
| Consent withdrawn by subject | - |
| Inappropriate enrollment | - |
| Lost to follow-up | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | aTIV (6 to < 24 months) |
|-----------------------|-------------------------|

Reporting group description:

Subjects aged between 6 to <24 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29.

| | |
|-----------------------|-------------------------|
| Reporting group title | aTIV (24 to <36 months) |
|-----------------------|-------------------------|

Reporting group description:

Subjects aged between 24 to <36 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29.

| | |
|-----------------------|-----------------------|
| Reporting group title | TIV (6 to <24 months) |
|-----------------------|-----------------------|

Reporting group description:

Subjects aged between 6 to <24 months who received two doses of inactivated unadjuvanted trivalent influenza vaccine on days 1 and 29.

| | |
|-----------------------|------------------------|
| Reporting group title | TIV (24 to <36 months) |
|-----------------------|------------------------|

Reporting group description:

Subjects aged between 24 to <36 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29.

| Reporting group values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) |
|--|-------------------------|-------------------------|-----------------------|
| Number of subjects | 22 | 21 | 21 |
| Age categorical Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous Units: months | | | |
| arithmetic mean | 13.1 | 27.6 | 13.1 |
| standard deviation | ± 5.4 | ± 2.8 | ± 5.6 |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 7 | 11 |
| Male | 13 | 14 | 10 |

| Reporting group values | TIV (24 to <36 months) | Total | |
|------------------------|------------------------|-------|--|
| Number of subjects | 20 | 84 | |

| | | | |
|---|-------|----|--|
| Age categorical Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 0 | |
| Newborns (0-27 days) | | 0 | |
| Infants and toddlers (28 days-23 months) | | 0 | |
| Children (2-11 years) | | 0 | |
| Adolescents (12-17 years) | | 0 | |
| Adults (18-64 years) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous Units: months | | | |
| arithmetic mean | 30 | | |
| standard deviation | ± 3.7 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 7 | 34 | |
| Male | 13 | 50 | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | aTIV (6 to < 24 months) |
| Reporting group description: Subjects aged between 6 to <24 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29. | |
| Reporting group title | aTIV (24 to <36 months) |
| Reporting group description: Subjects aged between 24 to <36 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29. | |
| Reporting group title | TIV (6 to <24 months) |
| Reporting group description: Subjects aged between 6 to <24 months who received two doses of inactivated unadjuvanted trivalent influenza vaccine on days 1 and 29. | |
| Reporting group title | TIV (24 to <36 months) |
| Reporting group description: Subjects aged between 24 to <36 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29. | |
| Subject analysis set title | Per Protocol Set/Serology |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects in the full analysis set who received the relevant dose of vaccine correctly on Day 1, who provided evaluable serum samples with the relevant time windows and had no major protocol violations. | |
| Subject analysis set title | Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects in the Exposed Set (all enrolled subjects who actually received a study vaccine) who provided post-baseline safety data. | |
| Subject analysis set title | Per Protocol Set/CMI |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects in the full analysis set who received the relevant dose of vaccine correctly on Day 1, who provided evaluable serum samples with the relevant time windows and had no major protocol violations. | |
| Primary: 1. Proportion of Cytokine Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane strains/B/Florida/Staphylococcus enterotoxin B (SEB)/Tetanus toxoid strains. | |
| End point title | 1. Proportion of Cytokine Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane strains/B/Florida/Staphylococcus enterotoxin B (SEB)/Tetanus toxoid strains. ^[1] |
| End point description: Immunogenicity was measured in terms Proportion of Cytokine γ producing CD4+ T cells (Mean Cells per Million Total Cells (95% CI) in Response to In vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/Staphylococcus enterotoxin B (SEB) at day 1 and day 50. Data are reported based on the Per Protocol Set (PPS). | |
| End point type | Primary |

End point timeframe:

Day 1 and day 50.

Notes:

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

Justification: There were no statistical analysis done.

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|---|-------------------------|-------------------------|--------------------------|--------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Mean Cells per Million Total Cells | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| A/H1N1 (Day 1; N=16,8,17,8) | 624 (422 to 826) | 621 (405 to 836) | 616 (420 to 812) | 710 (495 to 926) |
| A/H1N1 (Day 50; N=16,8,17,8) | 1262 (968 to 1556) | 1953 (1189 to 2718) | 1073 (788 to 1358) | 1120 (356 to 1885) |
| A/H3N2 (Day 1; N=16,9,18,13) | 438 (234 to 642) | 613 (369 to 851) | 506 (313 to 698) | 398 (195 to 601) |
| A/H3N2 (Day 50; N=16,9,18,13) | 1117 (861 to 1373) | 1641 (1211 to 2071) | 635 (394 to 876) | 658 (603 to 1013) |
| B/Brisbane (Day 1; N=14,5,17,7) | 644 (423 to 864) | 526 (180 to 873) | 623 (422 to 823) | 966 (673 to 1258) |
| B/Brisbane (Day 50; N=14,5,17,7) | 2184 (1750 to 2618) | 2683 (1372 to 3994) | 933 (539 to 1327) | 1187 (113 to 2261) |
| B/Florida (Day 1; N=7,2,11,7) | 708 (211 to 1205) | 410 (-118.7 to 938) | 791 (395 to 1187) | 721 (439 to 1004) |
| B/Florida (Day 50; N=7,2,11,7) | 1857 (1281 to 2433) | 1008 (135 to 1881) | 972 (513 to 1431) | 1057 (615 to 1499) |
| SEB (Day 1; N=8,2,11,6) | 75308 (50618 to 99997) | 88595 (54063 to 123126) | 111107 (90052 to 132162) | 101313 (81376 to 121249) |
| SEB (Day 50; N=8,2,11,6) | 88688 (63452 to 113924) | 55772 (-2700 to 114244) | 101174 (80115 to 122233) | 111908 (78955 to 144861) |
| Tetanus Toxoid (Day 1; N=8,2,10,6) | 1270 (719 to 1821) | 1154 (-874.8 to 3183) | 1351 (858 to 1844) | 1397 (226 to 2568) |
| Tetanus Toxoid (Day 50; N=8,2,10,6) | 1244 (772 to 1717) | 860 (116 to 1604) | 1177 (755 to 1600) | 1328 (900 to 1757) |

Statistical analyses

No statistical analyses for this end point

Primary: 2. Proportion of IL-2 Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid strains.

| | |
|-----------------|---|
| End point title | 2. Proportion of IL-2 Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid strains. ^[2] |
|-----------------|---|

End point description:

Immunogenicity was measured in terms of the Proportion of IL-2 producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid at day 1 and day 50. Data are reported based on the Per Protocol Set (PPS).

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

End point timeframe:

Day 1 and day 50.

Notes:

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

Justification: There were no statistical analysis done.

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|---|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Mean Cells per Million Total Cells | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| A/H1N1 (Day 1; N=16,8,17,8) | 285 (195 to 376) | 242 (119 to 364) | 167 (79 to 254) | 356 (233 to 478) |
| A/H1N1 (Day 50; N=16,8,17,8) | 891 (593 to 1189) | 1308 (683 to 1932) | 597 (308 to 886) | 774 (149 to 1399) |
| A/H3N2 (Day 1; N=16,9,18,13) | 199 (109 to 290) | 216 (97 to 336) | 153 (68 to 238) | 219 (119 to 318) |
| A/H3N2 (Day 50; N=16,9,18,13) | 754 (519 to 989) | 1177 (810 to 1544) | 407 (185 to 629) | 342 (37 to 647) |
| B/Brisbane (Day 1; N=14,5,17,7) | 294 (195 to 394) | 179 (-112.5 to 470) | 192 (101 to 283) | 552 (306 to 798) |
| B/Brisbane (Day 50; N=14,5,17,7) | 1612 (1187 to 2037) | 1813 (798 to 2828) | 618 (234 to 1002) | 700 (-130.3 to 1531) |
| B/Florida (Day 1; N=7,2,11,7) | 457 (159 to 755) | 26 (-304.7 to 357) | 181 (-57.24 to 419) | 407 (231 to 584) |
| B/Florida (Day 50; N=7,2,11,7) | 1404 (923 to 1885) | 585 (-91.75 to 1262) | 487 (109 to 865) | 571 (264 to 878) |
| SEB (Day 1; N=8,2,11,16) | 65580 (42981 to 88179) | 81296 (46182 to 116409) | 98178 (78905 to 117450) | 86057 (65784 to 106330) |
| SEB (Day 50; N=8,2,11,16) | 75418 (53564 to 97273) | 48228 (-6205 to 102660) | 89792 (71551 to 108033) | 96476 (65156 to 127795) |
| Tetanus Toxoid (Day 1; N=8,2,10,6) | 596 (288 to 905) | 563 (-231.4 to 1360) | 635 (359 to 911) | 717 (256 to 1177) |
| Tetanus Toxoid (Day 50; N=8,2,10,6) | 656 (285 to 1027) | 584 (-496.8 to 1664) | 681 (349 to 1013) | 887 (268 to 1507) |

Statistical analyses

No statistical analyses for this end point

Primary: 3. Proportion of IFN-γProducing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid strains.

| | |
|-----------------|---|
| End point title | 3. Proportion of IFN-γProducing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid strains. ^[3] |
|-----------------|---|

End point description:

Immunogenicity was measured in terms of the Proportion of IFN-γproducing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid strains at day 1 and day 50. Data are reported based on the Per Protocol Set (PPS).

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

End point timeframe:

Day 1 and Day 50.

Notes:

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

Justification: There were no statistical analysis done.

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|---|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Mean Cells per Million Total Cells arithmetic mean (confidence interval 95%) | | | | |
| A/H1N1 (Day 1; N=16,8,17,8) | 110 (54 to 165) | 66 (2.63 to 129) | 115 (61 to 169) | 127 (64 to 190) |
| A/H1N1 (Day 50; N=16,8,17,8) | 186 (98 to 275) | 348 (114 to 583) | 166 (80 to 251) | 303 (69 to 537) |
| A/H3N2 (Day 1; N=16,9,18,13) | 76 (32 to 121) | 75 (21 to 130) | 65 (23 to 107) | 92 (47 to 138) |
| A/H3N2 (Day 50; N=16,9,18,13) | 82 (47 to 118) | 357 (174 to 540) | 117 (83 to 150) | 117 (-35.01 to 269) |
| B/Brisbane (Day 1; N=14,5,17,7) | 84 (47 to 122) | 40 (-88.84 to 168) | 80 (45 to 114) | 192 (83 to 301) |
| B/Brisbane (Day 50; N=14,5,17,7) | 373 (218 to 529) | 204 (45 to 364) | 119 (-22.68 to 260) | 213 (82 to 344) |
| B/Florida (Day 1; N=7,2,11,7) | 116 (55 to 177) | 53 (-133 to 238) | 61 (13 to 110) | 135 (36 to 234) |
| B/Florida (Day 50; N=7,2,11,7) | 196 (31 to 361) | 181 (-9.667 to 372) | 182 (52 to 312) | 133 (34 to 231) |
| SEB (Day 1; N=8,2,11,6) | 3252 (1877 to 4627) | 2803 (-1842 to 7447) | 3741 (2569 to 4914) | 6056 (3375 to 8738) |
| SEB (Day 50; N=8,2,11,6) | 3291 (1738 to 4844) | 4674 (636 to 8712) | 4098 (2775 to 5420) | 5543 (3386 to 7700) |
| Tetanus Toxoid (Day 1; N=8,2,10,6) | 98 (16 to 181) | 305 (39 to 571) | 145 (71 to 219) | 136 (-17.56 to 289) |
| Tetanus Toxoid (Day 50; N=8,2,10,6) | 129 (63 to 196) | 73 (-79.23 to 225) | 181 (121 to 240) | 133 (51 to 215) |

Statistical analyses

No statistical analyses for this end point

Primary: 4. Proportion of TNF- α Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid strains.

| | |
|-----------------|--|
| End point title | 4. Proportion of TNF- α Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid strains. ^[4] |
|-----------------|--|

End point description:

Immunogenicity was measured in terms of Proportion of TNF- α producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/Tetanus toxoid strains at day 1 and day 50. Data are reported based on the Per Protocol Set (PPS).

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

End point timeframe:

Day 1 and day 50.

Notes:

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

Justification: There were no statistical analysis done.

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|---|-------------------------|-------------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Mean Cells per Million Total Cells | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| A/H1N1 (Day 1; N=16,8,17,8) | 109 (72 to 145) | 139 (32 to 246) | 96 (61 to 132) | 180 (73 to 287) |
| A/H1N1 (Day 50; N=16,8,17,8) | 372 (271 to 473) | 614 (276 to 951) | 212 (114 to 310) | 369 (31 to 706) |
| A/H3N2 (Day 1; N=16,9,18,13) | 56 (35 to 76) | 115 (58 to 173) | 64 (45 to 84) | 69 (21 to 117) |
| A/H3N2 (Day 50; N=16,9,18,13) | 394 (234 to 553) | 542 (340 to 743) | 179 (28 to 329) | 203 (37 to 369) |
| B/Brisbane (Day 1; N=14,5,17,7) | 118 (88 to 148) | 49 (-116.5 to 214) | 89 (62 to 117) | 258 (118 to 397) |
| B/Brisbane (Day 50; N=14,5,17,7) | 855 (550 to 1160) | 1031 (410 to 1653) | 247 (-29.07 to 522) | 284 (-224.8 to 794) |
| B/Florida (Day 1; N=7,2,11,7) | 152 (82 to 222) | 44 (-275.1 to 362) | 106 (50 to 162) | 250 (80 to 421) |
| B/Florida (Day 50; N=7,2,11,7) | 691 (366 to 1016) | 398 (191 to 605) | 229 (-27.79 to 487) | 308 (204 to 412) |
| SEB (Day 1; N=8,2,11,6) | 25901 (14384 to 37417) | 23891 (4929 to 42852) | 37632 (27811 to 47453) | 38312 (27364 to 49259) |
| SEB (Day 50; N=8,2,11,6) | 34801 (23595 to 46006) | 22816 (-1592 to 47223) | 33427 (23980 to 42874) | 38540 (25651 to 51430) |
| Tetanus Toxoid (Day 1; N=8,2,10,6) | 446 (171 to 722) | 685 (18 to 1351) | 486 (239 to 732) | 587 (202 to 972) |
| Tetanus Toxoid (Day 50; N=8,2,10,6) | 421 (224 to 618) | 201 (-591.2 to 992) | 581 (405 to 757) | 802 (346 to 1257) |

Statistical analyses

No statistical analyses for this end point

Primary: 5. Proportion of IL-21 Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/ Tetanus toxoid strains.

| | |
|-----------------|---|
| End point title | 5. Proportion of IL-21 Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/ Tetanus toxoid strains. ^[5] |
|-----------------|---|

End point description:

Immunogenicity was measured in terms of Proportion of IL-21 producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/ Tetanus toxoid strains day 1 and day 50. Data are reported based on the Per Protocol Set (PPS).

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

End point timeframe:

Day 1 and day 50.

Notes:

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

Justification: There were no statistical analysis done.

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|---|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Mean Cells per Million Total Cells | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| A/H1N1 (Day 1; N=16,8,17,8) | 128 (11 to 246) | 126 (5.87 to 246) | 177 (63 to 291) | 218 (98 to 338) |
| A/H1N1 (Day 50; N=16,8,17,8) | 209 (125 to 292) | 423 (241 to 605) | 164 (83 to 244) | 168 (-13.7 to 350) |
| A/H3N2 (Day 1; N=16,9,18,13) | 85 (-47.3 to 218) | 104 (3.92 to 205) | 188 (63 to 312) | 104 (20 to 187) |
| A/H3N2 (Day 50; N=16,9,18,13) | 121 (79 to 162) | 381 (153 to 608) | 76 (37 to 115) | 156 (-33.04 to 345) |
| B/Brisbane (Day 1; N=14,5,17,7) | 157 (12 to 301) | 202 (-7.426 to 412) | 246 (114 to 377) | 230 (53 to 407) |
| B/Brisbane (Day 50; N=14,5,17,7) | 353 (198 to 508) | 306 (-37.86 to 650) | 222 (82 to 363) | 255 (-35.78 to 545) |
| B/Florida (Day 1; N=7,2,11,7) | 141 (-239 to 520) | 271 (-182.3 to 724) | 466 (163 to 769) | 243 (0.55 to 485) |
| B/Florida (Day 50; N=7,2,11,7) | 519 (172 to 865) | 152 (-360.9 to 664) | 241 (-32.12 to 513) | 386 (112 to 659) |
| SEB (Day 1; N=8,2,11,6) | 625 (15 to 1236) | 339 (-1215 to 1893) | 637 (116 to 1157) | 707 (-190.5 to 1603) |
| SEB (Day 50; N=8,2,11,6) | 482 (292 to 672) | 574 (115 to 1033) | 370 (208 to 532) | 500 (238 to 762) |
| Tetanus Toxoid (Day 1; N=8,2,10,6) | 509 (-13.31 to 1032) | 192 (-1376 to 1759) | 632 (165 to 1100) | 665 (-240.2 to 1570) |
| Tetanus Toxoid (Day 50; N=8,2,10,6) | 581 (272 to 891) | 253 (-69.17 to 576) | 370 (93 to 646) | 316 (132 to 499) |

Statistical analyses

No statistical analyses for this end point

Primary: 6. Proportion of IL-13 Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/ Tetanus toxoid strains.

| | |
|-----------------|---|
| End point title | 6. Proportion of IL-13 Producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/ Tetanus toxoid strains. ^[6] |
|-----------------|---|

End point description:

Immunogenicity was measured in terms of Proportion of IL-13 producing CD4+ T cells in Response to In Vitro Pulse With A/H1N1/A/H3N2/B/Brisbane/B/Florida/SEB/ Tetanus toxoid at day 1 and day 50. Data are reported based on the Per Protocol Set (PPS).

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

End point timeframe:

Day 1 and Day 50.

Notes:

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

Justification: There were no statistical analysis done.

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|---|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Mean Cells per Million Total Cells | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| A/H1N1 (Day 1; N=16,8,17,8) | 251 (128 to 374) | 228 (55 to 401) | 217 (98 to 337) | 107 (-66.17 to 279) |
| A/H1N1 (Day 50; N=16,8,17,8) | 143 (-17.82 to 305) | 395 (169 to 622) | 398 (242 to 554) | 198 (-28.8 to 425) |
| A/H3N2 (Day 1; N=16,9,18,13) | 205 (94 to 317) | 323 (147 to 500) | 198 (93 to 304) | 137 (-9.455 to 284) |
| A/H3N2 (Day 50; N=16,9,18,13) | 239 (120 to 358) | 509 (217 to 801) | 229 (117 to 342) | 231 (-8.971 to 471) |
| B/Brisbane (Day 1; N=14,5,17,7) | 199 (52 to 346) | 174 (-39.68 to 387) | 188 (55 to 322) | 144 (-36.68 to 324) |
| B/Brisbane (Day 50; N=14,5,17,7) | 179 (104 to 255) | 559 (174 to 944) | 118 (50 to 187) | 285 (-39.75 to 611) |
| B/Florida (Day 1; N=7,2,11,7) | 203 (-30.97 to 438) | 85 (-78.43 to 248) | 132 (-54.71 to 319) | 45 (-42.78 to 132) |
| B/Florida (Day 50; N=7,2,11,7) | 85 (3.81 to 167) | 136 (-95.56 to 367) | 99 (34 to 164) | 80 (-42.17 to 202) |
| SEB (Day 1; N=8,2,11,6) | 934 (475 to 1394) | 585 (-594.4 to 1718) | 571 (179 to 963) | 1433 (799 to 2088) |
| SEB (Day 50; N=8,2,11,6) | 624 (422 to 826) | 1565 (-238.8 to 3369) | 728 (557 to 899) | 1245 (290 to 2200) |
| Tetanus Toxoid (Day 1; N=8,2,10,6) | 250 (46 to 454) | 63 (-151 to 276) | 294 (112 to 477) | 154 (31 to 277) |
| Tetanus Toxoid (Day 50; N=8,2,10,6) | 273 (-27.74 to 574) | 142 (-543.2 to 827) | 267 (-2.3 to 536) | 321 (-62.18 to 704) |

Statistical analyses

No statistical analyses for this end point

Primary: 12. Number of Subjects Reporting Unsolicited Adverse Events After Receiving two doses of aTIV and TIV.

| | |
|-----------------|---|
| End point title | 12. Number of Subjects Reporting Unsolicited Adverse Events After Receiving two doses of aTIV and TIV. ^[7] |
|-----------------|---|

End point description:

The number of subjects reporting unsolicited AEs between Day 1 and the study termination i.e., Day 50, after receiving two doses of aTIV and TIV. Data are reported based on the Safety Set.

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

End point timeframe:

Day 1 to Day 50 post vaccination.

Notes:

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

Justification: There were no statistical analysis done.

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|-------------------------------|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Number of Subjects | | | | |
| Any Adverse Event (AE) | 9 | 11 | 11 | 7 |
| At least possibly related AE | 0 | 1 | 2 | 1 |
| Any SAE | 0 | 0 | 1 | 1 |
| At least possibly related SAE | 0 | 0 | 0 | 0 |
| AE leading to discontinuation | 0 | 0 | 0 | 0 |
| Death | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Geometric mean HI titer (GMTs) against the three vaccine strains after two doses of aTIV and TIV.

| | |
|-----------------|--|
| End point title | 7. Geometric mean HI titer (GMTs) against the three vaccine strains after two doses of aTIV and TIV. |
|-----------------|--|

End point description:

The immunogenicity was assessed in terms of GMT in subjects aged 6 to < 36 months against each of three vaccine strains after receiving two doses of aTIV and two doses of TIV. Data are reported based on the Per Protocol Set (PPS).

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

End point timeframe:

Day 1 and Day 50.

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|--|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1 (Day 1; N=16,9,17,13) | 16 (5.72 to 43) | 43 (9.56 to 195) | 16 (5.87 to 42) | 152 (43 to 532) |
| A/H1N1 (Day 50; N=16,9,17,13) | 944 (527 to 1690) | 1709 (1068 to 2734) | 209 (119 to 367) | 893 (606 to 1317) |
| A/H3N2 (Day 1; N=16,9,17,13) | 5.45 (3.51 to 8.46) | 7.35 (4.42 to 12) | 6.65 (4.34 to 10) | 5 (3.28 to 7.63) |
| A/H3N2 (Day 50; N=16,9,17,13) | 1115 (731 to 1700) | 1377 (688 to 2757) | 210 (140 to 316) | 193 (109 to 343) |
| B/Brisbane (Day 1; N=16,9,17,13) | 9.17 (5.69 to 15) | 6.8 (3.14 to 15) | 6.52 (4.1 to 10) | 15 (8.06 to 29) |

| | | | | |
|-----------------------------------|------------------|------------------|---------------|----------------|
| B/Brisbane (Day 50; N=16,9,17,13) | 255 (146 to 444) | 372 (170 to 812) | 40 (23 to 68) | 68 (36 to 130) |
|-----------------------------------|------------------|------------------|---------------|----------------|

Statistical analyses

No statistical analyses for this end point

Secondary: 8. Geometric Mean Ratio (GMRs) against the three vaccine strains after two doses of aTIV and TIV.

| | |
|--|---|
| End point title | 8. Geometric Mean Ratio (GMRs) against the three vaccine strains after two doses of aTIV and TIV. |
| End point description: The immunogenicity was assessed in terms of GMR in subjects aged 6 to < 36 months against each of three vaccine strains after receiving two doses of aTIV and two doses of TIV. Data are reported based on the Per Protocol Set (PPS). | |
| End point type | Secondary |
| End point timeframe: Day 50 to Day 1. | |

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|--|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1 (Day 50/Day 1; N=16,9,17,13) | 60 (27 to 133) | 27 (11 to 67) | 13 (6.15 to 29) | 7.59 (3.63 to 16) |
| A/H3N2 (Day 50/Day 1; N=16,9,17,13) | 197 (119 to 327) | 196 (90 to 426) | 33 (20 to 53) | 38 (20 to 72) |
| B/Brisbane (Day 50/Day 1; N=16,9,17,13) | 33 (19 to 56) | 35 (17 to 72) | 5.21 (3.08 to 8.82) | 6.13 (3.34 to 11) |

Statistical analyses

No statistical analyses for this end point

Secondary: 9. Percentage of subjects achieving seroconversion or a significant increase in HI antibody titer after receiving two doses of aTIV and TIV by age cohort.

| | |
|---|--|
| End point title | 9. Percentage of subjects achieving seroconversion or a significant increase in HI antibody titer after receiving two doses of aTIV and TIV by age cohort. |
| End point description: The immunogenicity was assessed in terms of percentage of subjects aged 6 to <36 months with seroconversion (defined as a change in HI titer of <10 on day 1 to a HI titer > 40 at day 50) or | |

significant increase in HI titers (defined as a 4 fold or greater increase in titer in a subject with a day 1 titer > 10) after administration of two doses of aTIV against two doses of TIV. In the interpretation of HI immunogenicity results, the CHMP criteria (CPMP/BWP/214/96) for healthy adults were taken in consideration as the proportion of subjects achieving seroconversion or significant increase in HI titer should be > 40%. Data are reported based on the Per Protocol Set (PPS).

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: Day 50. | |

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|-----------------------------------|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Percentages of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| A/H1N1 (Day 50; N=16,9,17,13) | 100 (79 to 100) | 100 (66 to 100) | 76 (50 to 93) | 69 (39 to 91) |
| A/H3N2 (Day 50; N=16,9,17,13) | 100 (79 to 100) | 100 (66 to 100) | 88 (64 to 99) | 100 (75 to 100) |
| B/Brisbane (Day 50; N=16,9,17,13) | 100 (79 to 100) | 100 (66 to 100) | 47 (23 to 72) | 62 (32 to 86) |

Statistical analyses

No statistical analyses for this end point

Secondary: 10. Percentage of subjects with a HI titer \geq 40 against the three vaccine strains after two doses of aTIV and TIV.

| | |
|-----------------|---|
| End point title | 10. Percentage of subjects with a HI titer \geq 40 against the three vaccine strains after two doses of aTIV and TIV. |
|-----------------|---|

End point description:

The immunogenicity was assessed in terms of percentage of subjects aged 6 to < 36 months with seroprotection as measured by HI assay against each of three vaccine strains after receiving two doses of aTIV and two doses of TIV. In the interpretation of HI immunogenicity results, the CHMP criteria (CPMP/BWP/214/96) for healthy adults were taken in consideration which defined The proportion of subjects achieving an HI titer \geq 40 should be > 70%. Data are reported based on the Per Protocol Set (PPS).

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: Day 1 and Day 50. | |

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|-----------------------------------|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Percentages of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| A/H1N1 (Day 1; N=16,9,17,13) | 25 (7 to 52) | 56 (21 to 86) | 24 (7 to 50) | 77 (46 to 95) |
| A/H1N1 (Day 50; N=16,9,17,13) | 100 (79 to 100) | 100 (66 to 100) | 88 (64 to 99) | 100 (75 to 100) |
| A/H3N2 (Day 1; N=16,9,17,13) | 0 (0 to 21) | 11 (0 to 48) | 6 (0 to 29) | 0 (0 to 25) |
| A/H3N2 (Day 50; N=16,9,17,13) | 100 (79 to 100) | 100 (66 to 100) | 94 (71 to 100) | 100 (75 to 100) |
| B/Brisbane (Day 1; N=16,9,17,13) | 25 (7 to 52) | 11 (0 to 48) | 12 (1 to 36) | 31 (9 to 61) |
| B/Brisbane (Day 50; N=16,9,17,13) | 100 (79 to 100) | 100 (66 to 100) | 47 (23 to 72) | 69 (39 to 91) |

Statistical analyses

No statistical analyses for this end point

Secondary: 11. Number of Subjects Reporting Solicited Adverse Events and Other Indicators of Reactogenicity After Receiving two doses of aTIV and TIV by injection.

| | |
|-----------------|--|
| End point title | 11. Number of Subjects Reporting Solicited Adverse Events and Other Indicators of Reactogenicity After Receiving two doses of aTIV and TIV by injection. |
|-----------------|--|

End point description:

The number of subjects reporting solicited local and systemic adverse events and other solicited adverse events after receiving two doses of aTIV and TIV are reported. Data are reported based on the Safety Set.

| | |
|----------------------|----------------------------------|
| End point type | Secondary |
| End point timeframe: | Day 1 to Day 7 post vaccination. |

| End point values | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) | TIV (24 to <36 months) |
|--|-------------------------|-------------------------|-----------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 21 | 21 | 20 |
| Units: Number of Subjects | | | | |
| Any Local (vac.1; N=22,21,20,19) | 9 | 9 | 6 | 4 |
| Injection site induration (vac.1; N=22,20,20,19) | 1 | 1 | 1 | 1 |
| Injection site erythema (vac.1; N=22,20,20,19) | 4 | 3 | 0 | 0 |
| Injection site ecchymosis (vac.1; N=22,20,20,19) | 3 | 1 | 0 | 0 |
| Injection site swelling (vac.1; N=22,20,20,19) | 0 | 1 | 0 | 0 |
| Injection site tenderness (vac.1; N=22,20,20,19) | 4 | 6 | 5 | 4 |
| Any Systemic (vac.1; N=22,20,20,19) | 10 | 14 | 12 | 10 |

| | | | | |
|--|----|---|----|---|
| Diarrhea (vac.1; N=22,20,20,19) | 2 | 6 | 6 | 2 |
| Eat Change (vac.1; N=22,20,20,19) | 2 | 5 | 5 | 3 |
| Irritability (vac.1; N=22,20,20,19) | 5 | 3 | 2 | 2 |
| Shivering (vac.1; N=22,20,20,19) | 1 | 1 | 1 | 0 |
| Sleepiness (vac.1; N=22,20,20,19) | 3 | 6 | 3 | 5 |
| Unusual Crying (vac.1; N=22,20,20,19) | 0 | 3 | 2 | 1 |
| Vomiting (vac.1; N=22,20,20,19) | 0 | 3 | 3 | 1 |
| Other (vac.1; N=22,20,20,19) | 2 | 9 | 5 | 3 |
| Analgesic (vac.1; N=22,20,20,19) | 2 | 6 | 5 | 3 |
| Stayed home (vac.1; N=22,20,20,19) | 2 | 6 | 1 | 1 |
| Fever ($\geq 38^{\circ}\text{C}$) (vac.1; N=22,20,20,19) | 3 | 8 | 6 | 3 |
| Any Local (vac.2; N=20,19,20,18) | 6 | 4 | 4 | 3 |
| Injection site induration (vac.2; N=20,19,20,18) | 1 | 2 | 1 | 1 |
| Injection site erythema (vac.2; N=20,19,20,18) | 2 | 2 | 1 | 1 |
| Injection site ecchymosis (vac.2; N=20,19,20,18) | 0 | 0 | 1 | 1 |
| Injection site swelling (vac.2; N=20,19,20,18) | 1 | 0 | 1 | 0 |
| Injection site tenderness (vac.2; N=20,19,20,18) | 3 | 2 | 3 | 2 |
| Any Systemic (vac.2; N=20,19,20,18) | 10 | 9 | 10 | 6 |
| Diarrhea (vac.2; N=20,19,20,18) | 3 | 2 | 2 | 1 |
| Eat Change (vac.2; N=20,19,20,18) | 4 | 4 | 3 | 2 |
| Irritability (vac.2; N=20,19,20,18) | 3 | 3 | 4 | 2 |
| Shivering (vac.2; N=20,19,20,18) | 0 | 0 | 0 | 0 |
| Sleepiness (vac.2; N=20,19,20,18) | 2 | 5 | 5 | 2 |
| Unusual Crying (vac.2; N=20,19,20,18) | 2 | 4 | 2 | 2 |
| Vomiting (vac.2; N=20,19,20,18) | 0 | 2 | 0 | 0 |
| Other (vac.2; N=20,19,20,18) | 8 | 4 | 0 | 3 |
| Analgesic (vac.2; N=20,19,20,18) | 7 | 2 | 0 | 3 |
| Stayed home (vac.2; N=20,19,20,18) | 3 | 2 | 0 | 1 |
| Fever ($\geq 38^{\circ}\text{C}$) (vac.2; N=20,19,20,18) | 6 | 5 | 2 | 3 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All solicited AEs and unsolicited AEs were collected from Day 1 to Day 7; all unsolicited SAEs, medically attended AEs, AEs leading to withdrawal from the study were collected from Day 1 to Day 50.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | aTIV (6 to < 24 months) |
|-----------------------|-------------------------|

Reporting group description:

Subjects aged between 6 to <24 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29.

| | |
|-----------------------|-------------------------|
| Reporting group title | aTIV (24 to <36 months) |
|-----------------------|-------------------------|

Reporting group description:

Subjects aged between 24 to <36 months who received two doses of MF59C.1-adjuvanted subunit trivalent influenza vaccine on days 1 and 29.

| | |
|-----------------------|-----------------------|
| Reporting group title | TIV (6 to <24 months) |
|-----------------------|-----------------------|

Reporting group description:

Subjects aged between 6 to <24 months who received two doses of inactivated unadjuvanted trivalent influenza vaccine on days 1 and 29.

| | |
|-----------------------|------------------------|
| Reporting group title | TIV (24 to <36 months) |
|-----------------------|------------------------|

Reporting group description:

Subjects aged between 24 to <36 months who received two doses of inactivated unadjuvanted trivalent influenza vaccine on days 1 and 29.

| Serious adverse events | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) |
|---|-------------------------|-------------------------|-----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Infections and infestations | | | |
| Varicella | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 21 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 21 (0.00%) | 1 / 21 (4.76%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | TIV (24 to <36 months) | | |
|---|------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Infections and infestations | | | |
| Varicella | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | aTIV (6 to < 24 months) | aTIV (24 to <36 months) | TIV (6 to <24 months) |
|---|-------------------------|-------------------------|-----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 22 (86.36%) | 18 / 21 (85.71%) | 17 / 21 (80.95%) |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 7 / 21 (33.33%) | 7 / 21 (33.33%) |
| occurrences (all) | 7 | 11 | 11 |
| General disorders and administration site conditions | | | |
| Crying | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 4 / 21 (19.05%) | 4 / 21 (19.05%) |
| occurrences (all) | 2 | 7 | 6 |
| Injection site erythema | | | |
| subjects affected / exposed | 5 / 22 (22.73%) | 3 / 21 (14.29%) | 1 / 21 (4.76%) |
| occurrences (all) | 6 | 5 | 1 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 1 / 21 (4.76%) | 1 / 21 (4.76%) |
| occurrences (all) | 3 | 1 | 2 |
| Injection site induration | | | |

| | | | |
|--|-----------------------|------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 2 | 2 / 21 (9.52%) 3 | 2 / 21 (9.52%) 3 |
| Injection site pain subjects affected / exposed occurrences (all) | 5 / 22 (22.73%) 7 | 6 / 21 (28.57%) 8 | 5 / 21 (23.81%) 8 |
| Pyrexia subjects affected / exposed occurrences (all) | 8 / 22 (36.36%) 13 | 11 / 21 (52.38%) 18 | 9 / 21 (42.86%) 12 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | 3 / 21 (14.29%) 3 | 2 / 21 (9.52%) 2 |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 2 / 21 (9.52%) 2 | 0 / 21 (0.00%) 0 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 5 / 22 (22.73%) 6 | 6 / 21 (28.57%) 10 | 8 / 21 (38.10%) 10 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 3 / 21 (14.29%) 5 | 3 / 21 (14.29%) 3 |
| Psychiatric disorders Eating Disorder subjects affected / exposed occurrences (all) | 5 / 22 (22.73%) 6 | 6 / 21 (28.57%) 9 | 7 / 21 (33.33%) 10 |
| Irritability subjects affected / exposed occurrences (all) | 6 / 22 (27.27%) 8 | 5 / 21 (23.81%) 7 | 5 / 21 (23.81%) 7 |
| Infections and infestations Bronchiolitis subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 1 / 21 (4.76%) 1 | 2 / 21 (9.52%) 2 |
| Tonsillitis subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 21 (0.00%) 0 | 0 / 21 (0.00%) 0 |
| Upper respiratory tract infection | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 21 (0.00%) | 2 / 21 (9.52%) |
| occurrences (all) | 0 | 0 | 2 |
| Varicella | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 21 (4.76%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |

| | | | |
|---|------------------------|--|--|
| Non-serious adverse events | TIV (24 to <36 months) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 20 (60.00%) | | |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 5 / 20 (25.00%) | | |
| occurrences (all) | 8 | | |
| General disorders and administration site conditions | | | |
| Crying | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | | |
| occurrences (all) | 5 | | |
| Injection site erythema | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences (all) | 1 | | |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injection site induration | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | | |
| occurrences (all) | 2 | | |
| Injection site pain | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | | |
| occurrences (all) | 7 | | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 20 (30.00%) | | |
| occurrences (all) | 7 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | | |
| occurrences (all) | 2 | | |
| Bronchitis | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 3 | | |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | | |
| Psychiatric disorders | | | |
| Eating Disorder subjects affected / exposed occurrences (all) | 4 / 20 (20.00%) 6 | | |
| Irritability subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 5 | | |
| Infections and infestations | | | |
| Bronchiolitis subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | | |
| Tonsillitis subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | | |
| Varicella subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 24 March 2011 | 1. Allowed for a 0.25 ml presentation of aTIV to be used; 2. Incorporated changes to safety reporting section in line with new SAE SOP effective from APR 11; 3. Removal of requirement to enter data in EDC following the day 8 and day 36 telephone calls; 4. Incorporated corrections to statistical section. |
| 19 August 2011 | 1. Extension of study to new season 2011/2012; 2. Correction to visit windows; 3. Increase in sample size to 90 to make up for higher than expected number of nonevaluable subjects in season 1. |

Notes:

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/25037034>