



Clinical trial results:

Immunogenicity and Safety of the Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (SP306) as a Booster in Japanese Adolescents

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-005628-25 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 11 November 2012 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 19 February 2016 |
| First version publication date | 19 February 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | Td540 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01689324 |
| WHO universal trial number (UTN) | U1111-1124-7671 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Sanofi K.K. |
| Sponsor organisation address | 3-20-2, Nishi Shinjuku, Shinjuku-ku, Tokyo, Japan, 163-1488 |
| Public contact | Medical Director, Sanofi K.K, +81 3 6301 3603, Toshihiro.emori@sanofi.com |
| Scientific contact | Medical Director, Sanofi K.K, +81 3 6301 3603, Toshihiro.emori@sanofi.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 | 04 February 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 November 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the immunogenicity of Adacel (SP306) when administered as a single dose in Japanese adolescents.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Subjects who were enrolled in the study were previously vaccinated with 4 doses of pediatric diphtheria, pertussis and tetanus (DTaP) vaccine.

Evidence for comparator:

Not applicable

| | |
|---|-------------------|
| Actual start date of recruitment | 12 September 2012 |
| 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 | Japan: 43 |
| Worldwide total number of subjects | 43 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 25 |
| Adolescents (12-17 years) | 18 |
| Adults (18-64 years) | 0 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study subjects were enrolled from 12 September 2012 through 14 October 2012 in 3 clinic centers in Japan.

Pre-assignment

Screening details:

A total of 43 subjects that met all the inclusion criteria but none of the exclusion criteria were enrolled and vaccinated in the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|------------------|-------------|
| Arm title | Study Group |
|------------------|-------------|

Arm description:

Subjects received a single booster dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (TDaP; Adacel®) intramuscularly.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Adacel®) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL, intramuscular in the deltoid, 1 injection on Day 0.

| | |
|---------------------------------------|-------------|
| Number of subjects in period 1 | Study Group |
| Started | 43 |
| Completed | 43 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Study Group |
|-----------------------|-------------|

Reporting group description:

Subjects received a single booster dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (TDaP; Adacel®) intramuscularly.

| Reporting group values | Study Group | Total | |
|--|-------------|-------|--|
| Number of subjects | 43 | 43 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 43 | 43 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 11.4 | | |
| standard deviation | ± 0.5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | 23 | |
| Male | 20 | 20 | |

End points

End points reporting groups

| | |
|--|-------------|
| Reporting group title | Study Group |
| Reporting group description: Subjects received a single booster dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (TDaP; Adacel®) intramuscularly. | |

Primary: Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens Following Vaccination With ADACEL®

| | |
|--|--|
| End point title | Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens Following Vaccination With ADACEL® ^[1] |
| End point description: Seroprotection was defined as the percentage of subjects with antibody concentration levels ≥ 0.1 IU/mL post-vaccination. | |
| End point type | Primary |
| End point timeframe: Day 28 post-vaccination | |

Notes:

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

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Study Group | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Diphtheria | 100 | | | |
| Tetanus | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Booster Response to Diphtheria and Tetanus Antigens Following Vaccination With ADACEL®

| | |
|---|---|
| End point title | Percentage of Subjects With Booster Response to Diphtheria and Tetanus Antigens Following Vaccination With ADACEL® ^[2] |
| End point description: Diphtheria booster response was defined as a ≥ 4 -fold rise in pre- to post-vaccination antitoxin concentration in a subject with a pre-vaccination antitoxin concentration ≤ 2.56 IU/mL; or a ≥ 2 -fold rise in a subject with a pre-vaccination antitoxin concentration > 2.56 IU/mL. Tetanus booster response was defined as a ≥ 4 -fold rise in pre- to post-vaccination antitoxin concentration in a subject with a pre-vaccination antitoxin concentration ≤ 2.7 IU/mL; or a ≥ 2 -fold rise in a subject with a pre-vaccination antitoxin concentration > 2.7 IU/mL. | |
| End point type | Primary |

End point timeframe:

Day 28 post-vaccination

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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Study Group | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Diphtheria | 98 | | | |
| Tetanus | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Booster Response to Pertussis Antigens Following Vaccination with ADACEL®

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Booster Response to Pertussis Antigens Following Vaccination with ADACEL® ^[3] |
|-----------------|--|

End point description:

Booster responses were defined as: Pre-vaccination antibody concentrations less than the lower limit of quantitation (LLOQ) and post-vaccination levels $\geq 4X$ LLOQ; or Pre-vaccination antibody concentrations \geq LLOQ but $< 4X$ LLOQ, and a 4-fold rise (i.e., post-/pre-vaccination ≥ 4), or Pre-vaccination antibody concentrations $\geq 4X$ LLOQ and a 2-fold rise (i.e., post-/pre-vaccination ≥ 2).

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

End point timeframe:

Day 28 post-vaccination

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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Study Group | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Pertussis toxoid | 63 | | | |
| Filamentous hemagglutinin | 88 | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens Pre-Vaccination With ADACEL®

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens Pre-Vaccination With ADACEL® |
|-----------------|---|

End point description:

Seroprotection was defined as the percentage of subjects with antibody concentration of ≥ 0.1 IU/mL.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Day 0 pre-vaccination

| End point values | Study Group | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Diphtheria | 63 | | | |
| Tetanus | 91 | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens Pre-Vaccination and Post-Vaccination With ADACEL®

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens Pre-Vaccination and Post-Vaccination With ADACEL® |
|-----------------|--|

End point description:

Seroprotection was defined as the percentage of subjects with antibody concentration of ≥ 0.01 IU/mL.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Day 0 (pre-vaccination) and Day 28 post-vaccination

| End point values | Study Group | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Diphtheria (pre-vaccination) | 100 | | | |
| Diphtheria (post-vaccination) | 100 | | | |
| Tetanus (pre-vaccination) | 100 | | | |
| Tetanus (post-vaccination) | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens Pre-Vaccination and Post-Vaccination With ADACEL®

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Seroprotection Against Diphtheria and Tetanus Antigens Pre-Vaccination and Post-Vaccination With ADACEL® |
|-----------------|--|

End point description:

Seroprotection was defined as the percentage of subjects with antibody concentrations ≥ 1.0 IU/mL.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Day 0 (pre-vaccination) and Day 28 post-vaccination

| End point values | Study Group | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Diphtheria (pre-vaccination) | 12 | | | |
| Diphtheria (post-vaccination) | 100 | | | |
| Tetanus (pre-vaccination) | 30 | | | |
| Tetanus (post-vaccination) | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Concentrations With Respect to Diphtheria and Tetanus Antibodies Pre- and Post-Vaccination with ADACEL®

| | |
|-----------------|--|
| End point title | Geometric Mean Concentrations With Respect to Diphtheria and Tetanus Antibodies Pre- and Post-Vaccination with ADACEL® |
|-----------------|--|

End point description:

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Day 0 (pre-vaccination) and Day 28 post-vaccination

| End point values | Study Group | | | |
|--|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Titers (1/dil) | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Diphtheria (pre-vaccination) | 0.22 (0.14 to 0.35) | | | |
| Diphtheria (post-vaccination) | 8.58 (6.76 to 10.88) | | | |
| Tetanus (pre-vaccination) | 0.46 (0.33 to 0.64) | | | |
| Tetanus (post-vaccination) | 37.8 (30.16 to 47.38) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Concentrations With Respect to Pertussis Antibodies Pre- and Post-Vaccination with ADACEL®

| | |
|------------------------|---|
| End point title | Geometric Mean Concentrations With Respect to Pertussis Antibodies Pre- and Post-Vaccination with ADACEL® |
| End point description: | Pertussis immune response was measured using Japanese standard enzyme-linked immunosorbent assay. |
| End point type | Other pre-specified |
| End point timeframe: | Day 0 (pre-vaccination) and Day 28 post-vaccination |

| End point values | Study Group | | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Titers (1/dil) | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Pertussis toxoid (pre-vaccination) | 12.21 (7.82 to 19.05) | | | |
| Pertussis toxoid (post-vaccination) | 46.92 (33.65 to 65.42) | | | |
| Filamentous hemagglutinin (pre-vaccination) | 34.79 (23.47 to 51.57) | | | |
| Filamentous hemagglutinin (post-vaccination) | 204 (164.26 to 253.36) | | | |
| Pertactin (pre-vaccination) | 10.64 (6.28 to 18.03) | | | |

| | | | | |
|---|----------------------------|--|--|--|
| Pertactin (post-vaccination) | 272.82 (197.63 to 376.62) | | | |
| Fimbriae types 2 and 3 (pre-vaccination) | 7.78 (5.42 to 11.17) | | | |
| Fimbriae types 2 and 3 (post-vaccination) | 748.28 (443.23 to 1263.27) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Booster Response to Pertussis Antigens Following Vaccination with ADACEL®

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Booster Response to Pertussis Antigens Following Vaccination with ADACEL® |
|-----------------|---|

End point description:

Booster responses were defined as: Pre-vaccination antibody concentrations less than the lower limit of quantitation (LLOQ) and a post-vaccination level $\geq 4X$ LLOQ; or Pre-vaccination antibody concentrations \geq LLOQ but $< 4X$ LLOQ, and a 4-fold rise (i.e., post-/pre-vaccination ≥ 4), or Pre-vaccination antibody concentrations $\geq 4X$ LLOQ and a 2-fold rise (i.e., post-/pre-vaccination ≥ 2).

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Day 28 post-vaccination

| End point values | Study Group | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Pertactin | 93 | | | |
| Fimbriae Types 2 and 3 | 98 | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects Reporting Solicited Injection Site and Systemic Reactions Following Vaccination With ADACEL®

| | |
|-----------------|---|
| End point title | Number of Subjects Reporting Solicited Injection Site and Systemic Reactions Following Vaccination With ADACEL® |
|-----------------|---|

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Grade 3: Pain, Significant, prevents daily activity; Erythema and Swelling, > 100 mm.

Solicited systemic reactions: Fever (Temperature), Headache, Malaise, and Myalgia. Grade 3: Fever, $\geq 39^{\circ}\text{C}$; Headache, Malaise, and Myalgia, Significant, prevents daily activity.

| | |
|------------------------------------|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| Day 0 up to Day 7 post-vaccination | |

| End point values | Study Group | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 43 | | | |
| Units: Number of subjects | | | | |
| number (not applicable) | | | | |
| Solicited Injection site Pain | 37 | | | |
| Grade 3 Solicited Injection site Pain | 0 | | | |
| Solicited Injection site Erythema | 9 | | | |
| Grade 3 Solicited Injection site Erythema | 0 | | | |
| Solicited Injection site Swelling | 12 | | | |
| Grade 3 Solicited Injection site Swelling | 1 | | | |
| Fever | 9 | | | |
| Grade 3 Fever | 1 | | | |
| Headache | 8 | | | |
| Grade 3 Headache | 0 | | | |
| Malaise | 11 | | | |
| Grade 3 Malaise | 0 | | | |
| Myalgia | 17 | | | |
| Grade 3 Myalgia | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 (post-vaccination) up to 1 month post-vaccination.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Study Group |
|-----------------------|-------------|

Reporting group description:

Subjects received a single booster dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (TDaP; Adacel®) intramuscularly.

| Serious adverse events | Study Group | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | Study Group | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 43 (90.70%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | | |
| occurrences (all) | 8 | | |
| General disorders and administration site conditions | | | |
| Injection site Pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 37 / 43 (86.05%) | | |
| occurrences (all) | 37 | | |
| Injection site Erythema | | | |

| | | | |
|--|------------------------|--|--|
| alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 9 / 43 (20.93%) 9 | | |
| Injection site Swelling alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 12 / 43 (27.91%) 12 | | |
| Fever alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 9 / 43 (20.93%) 9 | | |
| Malaise alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 11 / 43 (25.58%) 11 | | |
| Musculoskeletal and connective tissue disorders Myalgia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 17 / 43 (39.53%) 17 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 7 / 43 (16.28%) 9 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 11 November 2012 | Revised observational endpoints and immunogenicity assessment methods to note that the pertussis immune response would be characterized by a Japanese laboratory using a enzyme-linked immunosorbent assay kit, and updated the storage and shipment procedures. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported