



Clinical trial results:

A phase III, multi-centre, open study to assess antibody persistence after completion of the 3-dose primary vaccination course with GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine in study 10PN-PD-DIT-048 (111654) in Singapore as well as the safety, reactogenicity and immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when given as a booster dose at 18-21 months of age

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2012-000819-82 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 17 February 2011 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 19 November 2022 |
| First version publication date | 28 June 2015 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Correction of full data set and alingment between registry. |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 113266 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01119625 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline Biologicals |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, B-1330 |
| Public contact | Clinical Trials Call Center , GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clinical Trials Call Center , GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 December 2011 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 February 2011 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 February 2011 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the antibody persistence induced by the GSK Biologicals' 10-valent pneumococcal conjugate vaccine (commercial lot versus phase III clinical lot), when co-administered with DTPa-IPV/Hib 13-16 months after completion of the 3-dose primary vaccination course in study 10PN-PD-DIT-048 (111654).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 12 July 2010 |
| 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 | Singapore: 238 |
| Worldwide total number of subjects | 238 |
| 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) | 238 |
| Children (2-11 years) | 0 |
| 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:

This booster study was conducted in Singapore only whereas the primary vaccination phase (NCT00808444) was conducted in Singapore and Malaysia.

Pre-assignment

Screening details:

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

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group |

Arm description:

Children primed with 3 doses of clinical lot of Synflorix + Rotarix co-administered with Infanrix-hexa in the primary phase of the study (NCT00808444) and boosted, with commercial lot of Synflorix coadministered with Infanrix-IPV/Hib. The Synflorix vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

| | |
|--|----------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Pneumococcal vaccine GSK1024850A |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One dose, administered intramuscularly in the right deltoid or anterolateral thigh.

| | |
|--|-------------------|
| Investigational medicinal product name | Infanrix-IPV/Hib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One dose, administered intramuscularly in the left deltoid or anterolateral thigh.

| | |
|------------------|--|
| Arm title | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group |
|------------------|--|

Arm description:

Children primed with 3 doses of commercial lot of Synflorix co-administered with Rotarix and Infanrix-hexa in the primary phase of the study (NCT00808444) and boosted, with commercial lot of Synflorix co-administered with Infanrix-IPV/Hib. The Synflorix vaccine (commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

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

| | |
|---|----------------------------------|
| Investigational medicinal product name | Pneumococcal vaccine GSK1024850A |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| One dose, administered intramuscularly in the right deltoid or anterolateral thigh. | |
| Investigational medicinal product name | Infanrix-IPV/Hib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| One dose, administered intramuscularly in the left deltoid or anterolateral thigh. | |

| Number of subjects in period 1 | Synflorix Clinical- Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix-IPV/Hib Group |
|--------------------------------|--|---|
| | | |
| Started | 118 | 120 |
| Completed | 115 | 116 |
| Not completed | 3 | 4 |
| Consent withdrawn by subject | 2 | 1 |
| out of window period | - | 1 |
| Lost to follow-up | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group |
|-----------------------|--|

Reporting group description:

Children primed with 3 doses of clinical lot of Synflorix + Rotarix co-administered with Infanrix-hexa in the primary phase of the study (NCT00808444) and boosted, with commercial lot of Synflorix coadministered with Infanrix-IPV/Hib. The Synflorix vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

| | |
|-----------------------|--|
| Reporting group title | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group |
|-----------------------|--|

Reporting group description:

Children primed with 3 doses of commercial lot of Synflorix co-administered with Rotarix and Infanrix-hexa in the primary phase of the study (NCT00808444) and boosted, with commercial lot of Synflorix co-administered with Infanrix-IPV/Hib. The Synflorix vaccine (commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

| Reporting group values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | Total |
|--|--|--|-------|
| Number of subjects | 118 | 120 | 238 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 118 | 120 | 238 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | 18.8 | 18.9 | |
| standard deviation | ± 0.84 | ± 0.87 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 62 | 49 | 111 |
| Male | 56 | 71 | 127 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group |
| Reporting group description: Children primed with 3 doses of clinical lot of Synflorix + Rotarix co-administered with Infanrix-hexa in the primary phase of the study (NCT00808444) and boosted, with commercial lot of Synflorix coadministered with Infanrix-IPV/Hib. The Synflorix vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh. | |
| Reporting group title | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group |
| Reporting group description: Children primed with 3 doses of commercial lot of Synflorix co-administered with Rotarix and Infanrix-hexa in the primary phase of the study (NCT00808444) and boosted, with commercial lot of Synflorix co-administered with Infanrix-IPV/Hib. The Synflorix vaccine (commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh. | |

Primary: Concentrations of antibodies against vaccine pneumococcal serotypes

| | |
|--|--|
| End point title | Concentrations of antibodies against vaccine pneumococcal serotypes ^[1] |
| End point description: Vaccine pneumococcal serotypes assessed were serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). Pneumococcal serotype specific total immunoglobuline G (IgG) antibodies were measured by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL. | |
| End point type | Primary |
| End point timeframe: Before booster vaccination at Month 0 | |

Notes:

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

Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 111 | 112 | | |
| Units: µg/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-1 [Pre-booster] (N=111;112) | 0.48 (0.4 to 0.57) | 0.35 (0.3 to 0.41) | | |
| Anti-4 [Pre-booster] (N=107;106) | 0.56 (0.48 to 0.67) | 0.48 (0.4 to 0.58) | | |
| Anti-5 [Pre-booster] (N=103;103) | 0.76 (0.65 to 0.89) | 0.54 (0.47 to 0.63) | | |
| Anti-6B [Pre-booster] (N=103;102) | 0.34 (0.29 to 0.4) | 0.32 (0.25 to 0.41) | | |
| Anti-7F [Pre-booster] (N=104;105) | 0.88 (0.75 to 1.03) | 0.91 (0.78 to 1.07) | | |

| | | | | |
|------------------------------------|---------------------|---------------------|--|--|
| Anti-9V [Pre-booster] (N=105;102) | 0.9 (0.77 to 1.06) | 0.73 (0.62 to 0.85) | | |
| Anti-14 [Pre-booster] (N=105;100) | 1.06 (0.86 to 1.31) | 0.91 (0.75 to 1.11) | | |
| Anti-18C [Pre-booster] (N=109;108) | 0.83 (0.69 to 1.01) | 0.78 (0.65 to 0.93) | | |
| Anti-19F [Pre-booster] (N=103;103) | 1.1 (0.87 to 1.4) | 0.96 (0.82 to 1.13) | | |
| Anti-23F [Pre-booster] (N=108;106) | 0.66 (0.51 to 0.84) | 0.47 (0.38 to 0.58) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Concentrations of antibodies against protein D (PD)

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|-----------------|--|
| End point title | Concentrations of antibodies against protein D (PD) ^[2] |
|-----------------|--|

End point description:

Anti-PD antibodies were determined using an ELISA assay. Concentration of specific PD antibodies was determined, using a standard reference serum. The cut-off of the assay is 100 ELISA units per millilitre (EU/mL).

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

End point timeframe:

Before booster vaccination at Month 0

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 118 | | |
| Units: EU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-PD [pre-booster] | 801.6 (693.1 to 927.1) | 619.7 (530.1 to 724.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and grade 3 solicited local adverse events (AEs)

| | |
|-----------------|---|
| End point title | Number of subjects reporting any and grade 3 solicited local adverse events (AEs) |
|-----------------|---|

End point description:

Solicited AEs = AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period. Solicited local symptoms assessed were pain, redness and swelling. Any = occurrence of any local symptom regardless of intensity grade. Grade 3 pain = cried when limb was moved/spontaneously painful. Grade 3 redness/swelling = redness/swelling above 30 millimetre (mm).

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

End point timeframe:

Within 4 days (Days 0-3) after booster vaccination

| End point values | Synflorix Clinical- Commercial + Infanrix- IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix- IPV/Hib Group | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 117 | | |
| Units: Subjects | | | | |
| Any pain | 61 | 70 | | |
| Grade 3 pain | 8 | 13 | | |
| Any redness | 66 | 61 | | |
| Grade 3 redness | 0 | 0 | | |
| Any swelling | 45 | 49 | | |
| Grade 3 swelling | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related solicited general adverse events (AEs)

| | |
|-----------------|--|
| End point title | Number of subjects reporting any, grade 3 and related solicited general adverse events (AEs) |
|-----------------|--|

End point description:

Solicited general symptoms assessed were drowsiness, irritability, loss of appetite and fever (= axillary temperature equal to or above 37.5 degrees Celsius (°C)). Any= occurrence of any general symptom regardless of intensity grade or relationship to vaccination Grade 3 drowsiness = drowsiness which prevented normal activity. Grade 3 irritability = crying that could not be comforted/ prevented normal activity. Grade 3 loss of appetite = not eating at all. Grade 3 fever = temperature greater than (>) 39.5°C. Related = solicited symptom assessed by the investigator as causally related to study vaccination.

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

End point timeframe:

Within 4 days (Days 0-3) after booster vaccination

| End point values | Synflorix Clinical- Commercial + Infanrix- IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix- IPV/Hib Group | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 117 | | |
| Units: Subjects | | | | |
| Any drowsiness | 38 | 49 | | |
| Grade 3 drowsiness | 2 | 2 | | |
| Related drowsiness | 38 | 48 | | |
| Fever $\geq 37.5^{\circ}\text{C}$ | 56 | 75 | | |
| Fever $> 39.5^{\circ}\text{C}$ | 1 | 1 | | |
| Related fever | 55 | 72 | | |
| Any irritability | 51 | 67 | | |
| Grade 3 irritability | 3 | 5 | | |
| Related irritability | 50 | 67 | | |
| Any loss of appetite | 42 | 49 | | |
| Grade 3 loss of appetite | 1 | 1 | | |
| Related loss of appetite | 41 | 47 | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Number of subjects reporting unsolicited adverse events (AEs) |
|-----------------|---|

End point description:

Unsolicited AEs = Any AE (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product) reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms was reported as an unsolicited adverse event.

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

End point timeframe:

Within 31 days (Days 0-30) after booster vaccination

| End point values | Synflorix Clinical- Commercial + Infanrix- IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix- IPV/Hib Group | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 118 | 120 | | |
| Units: Subjects | | | | |
| Unsolicited AEs | 18 | 25 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs)

| | |
|-----------------|--|
| End point title | Number of subjects reporting serious adverse events (SAEs) |
|-----------------|--|

End point description:

SAEs assessed include medical occurrences that results in death, are life threatening, require hospitalization or prolongation of hospitalization, results in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subjects.

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

End point timeframe:

During the entire study period, from the booster vaccination, at Month 0, up to the study end, at Month 1

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 118 | 120 | | |
| Units: Subjects | | | | |
| SAEs | 0 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against cross-reactive pneumococcal serotypes

| | |
|-----------------|--|
| End point title | Concentrations of antibodies against cross-reactive pneumococcal serotypes |
|-----------------|--|

End point description:

Cross-reactive pneumococcal serotypes assessed were serotypes 6A and 19A. Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). The antibody concentrations against the cross-reactive pneumococcal serotypes 6A and 19A were determined by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL.

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

End point timeframe:

Before booster vaccination at Month 0

| End point values | Synflorix Clinical- Commercial + Infanrix- IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix- IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 112 | 111 | | |
| Units: µg/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-6A [pre-booster] (N=109;111) | 0.23 (0.18 to 0.28) | 0.21 (0.16 to 0.26) | | |
| Anti-19A [pre-booster] (N=112;109) | 0.18 (0.14 to 0.22) | 0.19 (0.15 to 0.24) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against diphtheria and tetanus

| | |
|--|---|
| End point title | Concentrations of antibodies against diphtheria and tetanus |
| End point description: | |
| Concentrations were expressed as geometric mean concentrations (GMCs) in International units per millilitre (IU/mL). The cut-off of the assay was 0.1 IU/mL. | |
| End point type | Secondary |
| End point timeframe: | |
| Before booster vaccination at Month 0 | |

| End point values | Synflorix Clinical- Commercial + Infanrix- IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix- IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 49 | | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-diphtheria [pre-booster] (N=42;49) | 0.32 (0.25 to 0.39) | 0.3 (0.24 to 0.39) | | |
| Anti-tetanus [pre-booster] (N=43;48) | 0.51 (0.43 to 0.61) | 0.47 (0.38 to 0.59) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against pertussis toxoid (PT), filamentous

haemagglutinin (FHA) and pertactin (PRN)

| | |
|-----------------|--|
| End point title | Concentrations of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) |
|-----------------|--|

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in ELISA units per millilitre (EU/mL). The cut-off of the assay was 5 EU/mL.

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

End point timeframe:

Before booster vaccination at Month 0

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 47 | | |
| Units: EU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-PT [pre-booster] (N=41;45) | 5.7 (4.5 to 7.2) | 6.5 (4.7 to 8.9) | | |
| Anti-FHA [pre-booster] (N=40;46) | 19.5 (15.1 to 25.3) | 29.2 (21.5 to 39.6) | | |
| Anti-PRN [pre-booster] (N=42;47) | 14.8 (10.7 to 20.6) | 15.1 (11.1 to 20.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against polyribosyl-ribitol phosphate (PRP)

| | |
|-----------------|--|
| End point title | Concentrations of antibodies against polyribosyl-ribitol phosphate (PRP) |
|-----------------|--|

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). The cut-off of the assay was 0.15 µg/mL.

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

End point timeframe:

Before booster vaccination at Month 0

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 57 | | |
| Units: µg/mL | | | | |

| | | | | |
|--|--------------------|---------------------|--|--|
| geometric mean (confidence interval 95%) | | | | |
| Anti-PRP [pre-booster] | 0.68 (0.5 to 0.92) | 0.85 (0.65 to 1.11) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Titers of antibodies against poliovirus types 1, 2 and 3

| | |
|------------------------|--|
| End point title | Titers of antibodies against poliovirus types 1, 2 and 3 |
| End point description: | Titers were expressed as geometric mean titers (GMTs). The cut-off of the assay was 8. |
| End point type | Secondary |
| End point timeframe: | Before booster vaccination at Month 0 |

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 25 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-polio 1 [pre-booster] | 40.7 (23.2 to 71.3) | 32.8 (19.1 to 56.3) | | |
| Anti-polio 2 [pre-booster] | 38.7 (26.5 to 56.7) | 34.9 (18.8 to 64.7) | | |
| Anti-polio 3 [pre-booster] | 40.7 (24.4 to 67.8) | 43.3 (24 to 78) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against vaccine pneumococcal serotypes

| | |
|------------------------|---|
| End point title | Concentrations of antibodies against vaccine pneumococcal serotypes |
| End point description: | Vaccine pneumococcal serotypes assessed were serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). Pneumococcal serotype specific total immunoglobulin G (IgG) antibodies were measured by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL. |
| End point type | Secondary |

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

| End point values | Synflorix Clinical- Commercial + Infanrix- IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix- IPV/Hib Group | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 109 | 111 | | |
| Units: µg/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-1 [pre-booster] (N=109;109) | 0.48 (0.4 to 0.57) | 0.35 (0.3 to 0.41) | | |
| Anti-1 [post-booster] (N=107;111) | 7.14 (6.12 to 8.32) | 6.29 (5.38 to 7.35) | | |
| Anti-4 [pre-booster] (N=105;103) | 0.56 (0.47 to 0.67) | 0.48 (0.4 to 0.58) | | |
| Anti-4 [post-booster] (N=106;109) | 7.53 (6.44 to 8.8) | 7.43 (6.33 to 8.71) | | |
| Anti-5 [pre-booster] (N=101;100) | 0.77 (0.65 to 0.9) | 0.54 (0.46 to 0.62) | | |
| Anti-5 [post-booster] (N=106;108) | 7.91 (6.91 to 9.06) | 7.16 (6.25 to 8.2) | | |
| Anti-6B [pre-booster] (N=101;99) | 0.34 (0.29 to 0.4) | 0.32 (0.25 to 0.41) | | |
| Anti-6B [post-booster] (N=106;109) | 3.3 (2.85 to 3.81) | 3.12 (2.59 to 3.76) | | |
| Anti-7F [pre-booster] (N=102;102) | 0.88 (0.75 to 1.04) | 0.93 (0.8 to 1.08) | | |
| Anti-7F [post-booster] (N=106;109) | 9.02 (7.77 to 10.47) | 9.25 (8.04 to 10.64) | | |
| Anti-9V [pre-booster] (N=103;99) | 0.9 (0.77 to 1.06) | 0.72 (0.62 to 0.84) | | |
| Anti-9V [post-booster] (N=107;109) | 9.36 (8.15 to 10.75) | 10.42 (8.94 to 12.14) | | |
| Anti-14 [pre-booster] (N=103;97) | 1.05 (0.85 to 1.31) | 0.93 (0.76 to 1.14) | | |
| Anti-14 [post-booster] (N=106;106) | 13.03 (10.95 to 15.5) | 13.28 (11.06 to 15.95) | | |
| Anti-18C [pre-booster] (N=107;105) | 0.83 (0.69 to 1.01) | 0.78 (0.66 to 0.94) | | |
| Anti-18C [post-booster] (N=106;108) | 19.8 (17.02 to 23.03) | 24.19 (20.66 to 28.33) | | |
| Anti-19F [pre-booster] (N=101;100) | 1.11 (0.87 to 1.41) | 0.97 (0.82 to 1.14) | | |
| Anti-19F [post-booster] (N=106;108) | 19.68 (17.22 to 22.51) | 20.55 (17.62 to 23.98) | | |
| Anti-23F [pre-booster] (N=106;103) | 0.65 (0.5 to 0.83) | 0.47 (0.38 to 0.59) | | |
| Anti-23F [post-booster] (N=107;109) | 7.19 (5.94 to 8.71) | 6.83 (5.77 to 8.07) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against cross-reactive pneumococcal serotypes

| | |
|---|--|
| End point title | Concentrations of antibodies against cross-reactive pneumococcal serotypes |
| End point description: Cross-reactive pneumococcal serotypes assessed were serotypes 6A and 19A. Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). The antibody concentrations against the cross-reactive pneumococcal serotypes 6A and 19A were determined by 22F-inhibition Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 0.05 µg/mL. | |
| End point type | Secondary |
| End point timeframe: Before and one month after booster vaccination (at Month 0 and Month 1) | |

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 110 | 109 | | |
| Units: µg/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-6A [pre-booster] (N=107;108) | 0.23 (0.18 to 0.28) | 0.21 (0.16 to 0.26) | | |
| Anti-6A [post-booster] (N=106;108) | 2.13 (1.7 to 2.66) | 1.99 (1.6 to 2.49) | | |
| Anti-19A [pre-booster] (N=110;106) | 0.18 (0.14 to 0.22) | 0.2 (0.15 to 0.25) | | |
| Anti-19A [post-booster] (N=106;109) | 2.13 (1.65 to 2.76) | 2.96 (2.26 to 3.87) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against protein D (PD)

| | |
|--|---|
| End point title | Concentrations of antibodies against protein D (PD) |
| End point description: Anti-PD antibodies were determined using an ELISA assay. Concentration of specific PD antibodies was determined, using a standard reference serum. The cut-off of the assay is 100 ELISA units per millilitre (EU/mL). | |
| End point type | Secondary |
| End point timeframe: Before and one month after booster vaccination (at Month 0 and Month 1) | |

| End point values | Synflorix Clinical- Commercial + Infanrix- IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix- IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 113 | 115 | | |
| Units: EU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-PD [pre-booster] (N=113;115) | 794.9 (686.3 to 920.7) | 618.4 (527.8 to 724.6) | | |
| Anti-PD [post-booster] (N=107;111) | 3631.3 (3149.2 to 4187.2) | 3115.9 (2634.7 to 3685.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against diphtheria and tetanus

| | |
|--|---|
| End point title | Concentrations of antibodies against diphtheria and tetanus |
| End point description: | |
| Concentrations were expressed as geometric mean concentrations (GMCs) in International units per millilitre (IU/mL). The cut-off of the assay was 0.1 IU/mL. | |
| End point type | Secondary |
| End point timeframe: | |
| Before and one month after booster vaccination (at Month 0 and Month 1) | |

| End point values | Synflorix Clinical- Commercial + Infanrix- IPV/Hib Group | Synflorix Commercial- Commercial + Infanrix- IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 55 | | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-diphtheria [pre-booster] (N=41;47) | 0.31 (0.25 to 0.39) | 0.29 (0.23 to 0.37) | | |
| Anti-diphtheria [post-booster] (N=52;55) | 8.17 (6.72 to 9.94) | 10.89 (9.16 to 12.94) | | |
| Anti-tetanus [pre-booster] (N=42;46) | 0.52 (0.43 to 0.62) | 0.46 (0.37 to 0.58) | | |
| Anti-tetanus [post-booster] (N=52;55) | 14.35 (12.41 to 16.6) | 14.73 (12.75 to 17.01) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)

| | |
|--|--|
| End point title | Concentrations of antibodies against pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) |
| End point description: Concentrations were expressed as geometric mean concentrations (GMCs) in ELISA units per millilitre (EU/mL). The cut-off of the assay was 5 EU/mL. | |
| End point type | Secondary |
| End point timeframe: Before and one month after booster vaccination (at Month 0 and Month 1) | |

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 55 | | |
| Units: EU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-PT [pre-booster] (N=40;43) | 5.8 (4.5 to 7.3) | 6.8 (4.9 to 9.3) | | |
| Anti-PT [post-booster] (N=52;55) | 80.8 (65.6 to 99.4) | 86 (67.9 to 108.9) | | |
| Anti-FHA [pre-booster] (N=39;44) | 19.3 (14.8 to 25.2) | 29.6 (21.5 to 40.7) | | |
| Anti-FHA [post-booster] (N=52;54) | 358.3 (290.5 to 442) | 484.3 (418.9 to 559.9) | | |
| Anti-PRN [pre-booster] (N=41;45) | 15 (10.7 to 20.9) | 15.4 (11.3 to 21) | | |
| Anti-PRN [post-booster] (N=52;55) | 314.3 (229.6 to 430.2) | 509.5 (387 to 670.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against polyribosyl-ribitol phosphate (PRP)

| | |
|-----------------|--|
| End point title | Concentrations of antibodies against polyribosyl-ribitol phosphate (PRP) |
|-----------------|--|

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per millilitre (µg/mL). The cut-off of the assay was 0.15 µg/mL.

End point type Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 53 | 55 | | |
| Units: µg/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-PRP [pre-booster] (N=51;55) | 0.66 (0.48 to 0.9) | 0.84 (0.64 to 1.12) | | |
| Anti-PRP [post-booster] (N=53;55) | 58.26 (43.71 to 77.66) | 49.36 (37.4 to 65.15) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Titers of antibodies against poliovirus types 1, 2 and 3

End point title Titers of antibodies against poliovirus types 1, 2 and 3

End point description:

Titers were expressed as geometric mean titers (GMTs). The cut-off of the assay was 8.

End point type Secondary

End point timeframe:

Before and one month after booster vaccination (at Month 0 and Month 1)

| End point values | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 27 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-polio 1 [pre-booster] (N=28;25) | 44.2 (25.3 to 77.1) | 32.8 (19.1 to 56.3) | | |
| Anti-polio 1 [post-booster] (N=25;27) | 982.2 (688 to 1402.3) | 985.2 (627.9 to 1546) | | |

| | | | | |
|---------------------------------------|--------------------------|---------------------------|--|--|
| Anti-polio 2 [pre-booster] (N=28;25) | 38 (25.7 to 56.4) | 34.9 (18.8 to 64.7) | | |
| Anti-polio 2 [post-booster] (N=25;27) | 1144.1 (773.7 to 1691.7) | 823.4 (553.5 to 1224.8) | | |
| Anti-polio 3 [pre-booster] (N=28;25) | 41 (24.2 to 69.7) | 43.3 (24 to 78) | | |
| Anti-polio 3 [post-booster] (N=25;26) | 1350.8 (857.4 to 2128.2) | 1527.4 (1016.6 to 2294.7) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs: Within 4 days (Days 0-3) after booster vaccination. SAEs: During the entire study period, from the booster vaccination, at Month 0, up to the study end, at Month 1. Unsolicited AEs: Within 31 days (Days 0-30) after booster vaccination.

Adverse event reporting additional description:

The occurrence of reported AEs (all/related) was not available and is encoded as equal to the number of subjects affected. Systematically assessed Other Adverse Events are reported only for those participants who completed their symptoms sheet.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group |
|-----------------------|--|

Reporting group description:

Children primed with 3 doses of commercial lot of Synflorix co-administered with Rotarix and Infanrix-hexa in the primary phase of the study (NCT00808444) and boosted with commercial lot of Synflorix co-administered with Infanrix-IPV/Hib. The Synflorix vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

| | |
|-----------------------|--|
| Reporting group title | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group |
|-----------------------|--|

Reporting group description:

Children primed with 3 doses of clinical lot of Synflorix + Rotarix co-administered with Infanrix-hexa in the primary phase of the study (NCT00808444) and boosted with commercial lot of Synflorix co-administered with Infanrix-IPV/Hib. The Synflorix vaccine (clinical and commercial lots) was administered intramuscularly in the right deltoid or anterolateral thigh and the Infanrix-IPV/Hib vaccine was administered intramuscularly in the left deltoid or anterolateral thigh.

| Serious adverse events | Synflorix Commercial-Commercial + Infanrix-IPV/Hib Group | Synflorix Clinical-Commercial + Infanrix-IPV/Hib Group | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 120 (3.33%) | 0 / 118 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Laceration | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 118 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 118 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 118 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 120 (1.67%) | 0 / 118 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 118 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Synflorix Commercial- Commercial + Infanrix-IPV/Hib Group | Synflorix Clinical- Commercial + Infanrix-IPV/Hib Group | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 108 / 120 (90.00%) | 98 / 118 (83.05%) | |
| General disorders and administration site conditions | | | |
| Pain | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed ^[1] | 70 / 117 (59.83%) | 61 / 117 (52.14%) | |
| occurrences (all) | 70 | 61 | |
| Redness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed ^[2] | 61 / 117 (52.14%) | 66 / 117 (56.41%) | |
| occurrences (all) | 61 | 66 | |
| Swelling | | | |
| alternative assessment type: | | | |

| | | | |
|---|-------------------|-------------------|--|
| Systematic | | | |
| subjects affected / exposed ^[3] | 49 / 117 (41.88%) | 45 / 117 (38.46%) | |
| occurrences (all) | 49 | 45 | |
| Drowsiness | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed ^[4] | 49 / 117 (41.88%) | 38 / 117 (32.48%) | |
| occurrences (all) | 49 | 38 | |
| Fever | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed ^[5] | 75 / 117 (64.10%) | 56 / 117 (47.86%) | |
| occurrences (all) | 75 | 56 | |
| Irritability | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed ^[6] | 67 / 117 (57.26%) | 51 / 117 (43.59%) | |
| occurrences (all) | 67 | 51 | |
| Loss of appetite | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed ^[7] | 49 / 117 (41.88%) | 42 / 117 (35.90%) | |
| occurrences (all) | 49 | 42 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 7 / 118 (5.93%) | |
| occurrences (all) | 5 | 7 | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | 4 / 118 (3.39%) | |
| occurrences (all) | 6 | 4 | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

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