



## Clinical trial results:

### Prophylactic Antipyretic Treatment in Children Receiving Booster Dose of Pneumococcal Vaccine GSK1024850A and DTPa-HBV-IPV/Hib Vaccine (Infanrix Hexa) and Assessment of Impact of Pneumococcal Vaccination on Nasopharyngeal Carriage

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2006-001481-17   |
| Trial protocol           | CZ               |
| Global end of trial date | 17 February 2009 |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v3 (current)  |
| This version publication date  | 22 July 2022  |
| First version publication date | 30 July 2015  |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Correction of full data set and alignment between registries. |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 107137 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00496015 |
| 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, 044 2089-904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact           | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, 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                       | 24 July 2009     |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 25 March 2008    |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 17 February 2009 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To determine the percentage reduction in febrile reactions [rectal temperature greater than or equal to ( $\geq$ ) 38.0 degrees celsius( $^{\circ}$ C) or oral/axillary/tympanic  $\geq$  37.5 $^{\circ}$ C] when prophylactic antipyretic treatment is administered compared to no prophylactic antipyretic treatment, after booster vaccination with GSK Biologicals' 10-valent pneumococcal conjugate vaccine and routine Diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated poliovirus and Haemophilus influenzae type b vaccine (DTPa-HBV-IPV/Hib) (Infanrix hexa) vaccination in children at 12-15 months of age.

Protection of trial subjects:

The vaccines were observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccine(s).

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 02 July 2007 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Czech Republic: 750 |
| Worldwide total number of subjects   | 750                 |
| EEA total number of subjects         | 750                 |

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)  | 750 |
| 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 was a multicenter study with the same centers as the primary vaccination study 10PN-PD-DIT-010 (107017) and all subjects enrolled in the primary vaccination study and received 10Pn-PD-DIT (Synflorix) vaccine were invited to participate in the study. In addition, an age-matched pneumococcal vaccine unprimed control group has been enrolled.

### 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            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | Synflorix I Group |

Arm description:

Subjects were vaccinated with 3 primary vaccination doses of Synflorix (10Pn) vaccine with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa along with prophylactic antipyretic treatment.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | 10-valent Streptococcus pneumoniae conjugate vaccine   |
| Investigational medicinal product code | GSK1024850A  |
| Other name                             | 10Pn, 10Pn-PD-DiT, GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine, Synflorix, GlaxoSmithKline (GSK) Biologicals' 1024850A vaccine |
| Pharmaceutical forms                   | Suspension for injection   |
| Routes of administration               | Intramuscular use  |

Dosage and administration details:

One booster dose at 12-15 months of age, into the right thigh or deltoid region.

|  |   |
|--|---|
| Investigational medicinal product name | Infanrix Hexa   |
| Investigational medicinal product code |   |
| Other name                             | DTPa-IPV-HBV/Hib, Infanrix Hexa GSK Biologicals' diphtheria-tetanus-acellular pertussis |
| Pharmaceutical forms                   | Powder and solvent for suspension for injection   |
| Routes of administration               | Intramuscular use   |

Dosage and administration details:

One booster dose at 12-15 months of age, into the left thigh or deltoid region.

|  |                |
|--|----------------|
| Investigational medicinal product name | PANADOL 125 mg |
| Investigational medicinal product code |                |
| Other name                             | Panadol 125    |
| Pharmaceutical forms                   | Suppository    |
| Routes of administration               | Rectal use     |

Dosage and administration details:

The prophylactic antipyretic treatment was administered as rectal suppositories according to the subject's body weight.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Synflorix II Group |
|------------------|--------------------|

**Arm description:**

Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | 10-valent Streptococcus pneumoniae conjugate vaccine   |
| Investigational medicinal product code | GSK1024850A  |
| Other name                             | 10Pn, 10Pn-PD-DiT, GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine, Synflorix, GlaxoSmithKline (GSK) Biologicals' 1024850A vaccine |
| Pharmaceutical forms                   | Suspension for injection   |
| Routes of administration               | Intramuscular use  |

**Dosage and administration details:**

One booster dose at 12-15 months of age, into the right thigh or deltoid region.

|  |   |
|--|---|
| Investigational medicinal product name | Infanrix Hexa   |
| Investigational medicinal product code |   |
| Other name                             | DTPa-IPV-HBV/Hib, Infanrix Hexa GSK Biologicals' diphtheria-tetanus-acellular pertussis |
| Pharmaceutical forms                   | Powder and solvent for suspension for injection   |
| Routes of administration               | Intramuscular use   |

**Dosage and administration details:**

One booster dose at 12-15 months of age, into the left thigh or deltoid region.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Synflorix PRE Group |
|------------------|---------------------|

**Arm description:**

Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study (before the implementation of the protocol amendment) at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.

|  |  |
|--|--|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | 10-valent Streptococcus pneumoniae conjugate vaccine   |
| Investigational medicinal product code | GSK1024850A  |
| Other name                             | 10Pn, 10Pn-PD-DiT, GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine, Synflorix, GlaxoSmithKline (GSK) Biologicals' 1024850A vaccine |
| Pharmaceutical forms                   | Suspension for injection   |
| Routes of administration               | Intramuscular use  |

**Dosage and administration details:**

One booster dose at 12-15 months of age, into the right thigh or deltoid region.

|  |   |
|--|---|
| Investigational medicinal product name | Infanrix Hexa   |
| Investigational medicinal product code |   |
| Other name                             | DTPa-IPV-HBV/Hib, Infanrix Hexa GSK Biologicals' diphtheria-tetanus-acellular pertussis |
| Pharmaceutical forms                   | Powder and solvent for suspension for injection   |
| Routes of administration               | Intramuscular use   |

**Dosage and administration details:**

One booster dose at 12-15 months of age, into the left thigh or deltoid region.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Synflorix POST Group |
|------------------|----------------------|

**Arm description:**

Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study (after the implementation of the protocol amendment) at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |  |
|--|--|
| Investigational medicinal product name | 10-valent Streptococcus pneumoniae conjugate vaccine   |
| Investigational medicinal product code | GSK1024850A  |
| Other name                             | 10Pn, 10Pn-PD-DiT, GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine, Synflorix, GlaxoSmithKline (GSK) Biologicals' 1024850A vaccine |
| Pharmaceutical forms                   | Suspension for injection   |
| Routes of administration               | Intramuscular use  |

Dosage and administration details:

One booster dose at 12-15 months of age, into the right thigh or deltoid region.

|  |   |
|--|---|
| Investigational medicinal product name | Infanrix Hexa   |
| Investigational medicinal product code |   |
| Other name                             | DTPa-IPV-HBV/Hib, Infanrix Hexa GSK Biologicals' diphtheria-tetanus-acellular pertussis |
| Pharmaceutical forms                   | Powder and solvent for suspension for injection   |
| Routes of administration               | Intramuscular use   |

Dosage and administration details:

One booster dose at 12-15 months of age, into the left thigh or deltoid region.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Mencevax + Infanrix Hexa Group |
|------------------|--------------------------------|

Arm description:

Age-matched pneumococcal vaccine unprimed group received a single dose of Mencevax vaccine co-administered with Infanrix hexa vaccine.

|  |                          |
|--|--------------------------|
| Arm type                               | Active comparator        |
| Investigational medicinal product name | Mencevax vaccine         |
| Investigational medicinal product code | GSK134612                |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intramuscular use        |

Dosage and administration details:

Single dose at 12-15 months of age, into the right thigh or deltoid region.

|  |   |
|--|---|
| Investigational medicinal product name | Infanrix hexa   |
| Investigational medicinal product code |   |
| Other name                             | DTPa-IPV-HBV/Hib, Infanrix Hexa GSK Biologicals' diphtheria-tetanus-acellular pertussis |
| Pharmaceutical forms                   | Powder and solvent for suspension for injection   |
| Routes of administration               | Intramuscular use   |

Dosage and administration details:

Single dose at 12-15 months of age, into the left thigh or deltoid region.

| <b>Number of subjects in period 1</b> | Synflorix I Group | Synflorix II Group | Synflorix PRE Group |
|---------------------------------------|-------------------|--------------------|---------------------|
| Started                               | 178               | 27                 | 172                 |
| Completed                             | 177               | 27                 | 172                 |
| Not completed                         | 1                 | 0                  | 0                   |
| Unspecified                           | 1                 | -                  | -                   |

| <b>Number of subjects in period 1</b> | Synflorix POST Group | Mencevax + Infanrix Hexa Group |
|---------------------------------------|----------------------|--------------------------------|
| Started                               | 37                   | 336                            |
| Completed                             | 36                   | 336                            |
| Not completed                         | 1                    | 0                              |

|             |   |   |
|-------------|---|---|
| Unspecified | 1 | - |
|-------------|---|---|

## Baseline characteristics

### Reporting groups

|  |                                |
|--|--------------------------------|
| Reporting group title  | Synflorix I Group              |
| Reporting group description:   |                                |
| Subjects were vaccinated with 3 primary vaccination doses of Synflorix (10Pn) vaccine with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa along with prophylactic antipyretic treatment.   |                                |
| Reporting group title  | Synflorix II Group             |
| Reporting group description:   |                                |
| Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.   |                                |
| Reporting group title  | Synflorix PRE Group            |
| Reporting group description:   |                                |
| Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study (before the implementation of the protocol amendment) at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment. |                                |
| Reporting group title  | Synflorix POST Group           |
| Reporting group description:   |                                |
| Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study (after the implementation of the protocol amendment) at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.  |                                |
| Reporting group title  | Mencevax + Infanrix Hexa Group |
| Reporting group description:   |                                |
| Age-matched pneumococcal vaccine unprimed group received a single dose of Mencevax vaccine co-administered with Infanrix hexa vaccine.   |                                |

| Reporting group values                             | Synflorix I Group | Synflorix II Group | Synflorix PRE Group |
|--|-------------------|--------------------|---------------------|
| Number of subjects                                 | 178               | 27                 | 172                 |
| 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)           | 178               | 27                 | 172                 |
| 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                                    | 12.6              | 13.2               | 12.7                |
| standard deviation                                 | ± 0.77            | ± 0.74             | ± 0.77              |

|                                       |    |    |    |
|---------------------------------------|----|----|----|
| Gender categorical<br>Units: Subjects |    |    |    |
| Female                                | 90 | 11 | 79 |
| Male                                  | 88 | 16 | 93 |

| Reporting group values                             | Synflorix POST Group | Mencevax + Infanrix Hexa Group | Total |
|--|----------------------|--------------------------------|-------|
| Number of subjects                                 | 37                   | 336                            | 750   |
| Age categorical<br>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)           | 37                   | 336                            | 750   |
| 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<br>Units: months                    |                      |                                |       |
| arithmetic mean                                    | 13.1                 | 13.1                           |       |
| standard deviation                                 | ± 1.15               | ± 1.1                          | -     |
| Gender categorical<br>Units: Subjects              |                      |                                |       |
| Female   | 18                   | 155                            | 353   |
| Male   | 19                   | 181                            | 397   |

### Subject analysis sets

|                            |                        |
|----------------------------|------------------------|
| Subject analysis set title | Pooled Synflorix Group |
| Subject analysis set type  | Sub-group analysis     |

Subject analysis set description:

For carriage analyses the Synforix I, Synforix II, Synflorix PRE Group and Synflorix POST Group were pooled.

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Pooled Synflorix PRE and POST Group |
| Subject analysis set type  | Sub-group analysis                  |

Subject analysis set description:

Pooled group with subjects from both, Synflorix PRE Group and Synflorix POST Group, that received in this study (before and after the implementation of the protocol amendment) a booster dose of Synforix vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.

| Reporting group values                             | Pooled Synflorix Group | Pooled Synflorix PRE and POST Group |  |
|--|------------------------|-------------------------------------|--|
| Number of subjects                                 | 414                    | 209                                 |  |
| Age categorical<br>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)           | 414                    | 209                                 |  |

|                           |        |        |  |
|---------------------------|--------|--------|--|
| Children (2-11 years)     | 0      | 0      |  |
| Adolescents (12-17 years) | 0      | 0      |  |
| Adults (18-64 years)      | 0      | 0      |  |
| From 65-84 years          | 0      | 0      |  |
| 85 years and over         | 0      | 0      |  |
| Age continuous            |        |        |  |
| Units: months             |        |        |  |
| arithmetic mean           | 12.73  | 12.8   |  |
| standard deviation        | ± 0.83 | ± 0.86 |  |
| Gender categorical        |        |        |  |
| Units: Subjects           |        |        |  |
| Female                    | 198    | 97     |  |
| Male                      | 216    | 112    |  |

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## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Synflorix I Group   |
| Reporting group description:<br>Subjects were vaccinated with 3 primary vaccination doses of Synflorix (10Pn) vaccine with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa along with prophylactic antipyretic treatment.   |   |
| Reporting group title  | Synflorix II Group  |
| Reporting group description:<br>Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.   |   |
| Reporting group title  | Synflorix PRE Group   |
| Reporting group description:<br>Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study (before the implementation of the protocol amendment) at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment. |   |
| Reporting group title  | Synflorix POST Group  |
| Reporting group description:<br>Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study (after the implementation of the protocol amendment) at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.  |   |
| Reporting group title  | Mencevax + Infanrix Hexa Group  |
| Reporting group description:<br>Age-matched pneumococcal vaccine unprimed group received a single dose of Mencevax vaccine co-administered with Infanrix hexa vaccine.   |   |
| Subject analysis set title   | Pooled Synflorix Group  |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>For carriage analyses the Synforix I, Synforix II, Synflorix PRE Group and Synflorix POST Group were pooled.  |   |
| Subject analysis set title   | Pooled Synflorix PRE and POST Group   |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Pooled group with subjects from both, Synflorix PRE Group and Synflorix POST Group, that received in this study (before and after the implementation of the protocol amendment) a booster dose of Synforix vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.  |   |
| <b>Primary: Number of subjects reported with core fever (rectal temperature) &gt;= the cut-off</b>   |   |
| End point title  | Number of subjects reported with core fever (rectal temperature) >= the cut-off |
| End point description:<br>The cut-off for core fever was 38.0°C.   |   |
| End point type   | Primary   |
| End point timeframe:<br>Within 4 days (Day 0-Day 3) after primary vaccine dose   |   |

| End point values                  | Synflorix I Group | Synflorix II Group | Synflorix PRE Group | Synflorix POST Group |
|-----------------------------------|-------------------|--------------------|---------------------|----------------------|
| Subject group type                | Reporting group   | Reporting group    | Reporting group     | Reporting group      |
| Number of subjects analysed       | 178               | 27                 | 172                 | 37                   |
| Units: Subjects                   |                   |                    |                     |                      |
| Fever $\geq 38.0^{\circ}\text{C}$ | 64                | 14                 | 100                 | 16                   |

| End point values                  | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|-----------------------------------|--------------------------------------|--|--|--|
| Subject group type                | Reporting group                      |  |  |  |
| Number of subjects analysed       | 336                                  |  |  |  |
| Units: Subjects                   |                                      |  |  |  |
| Fever $\geq 38.0^{\circ}\text{C}$ | 146                                  |  |  |  |

## Statistical analyses

| Statistical analysis title              | Difference between groups (core fever $\geq 38.0^{\circ}\text{C}$ ) |
|---|---|
| Comparison groups                       | Synflorix PRE Group v Synflorix I Group                             |
| Number of subjects included in analysis | 350   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority <sup>[1]</sup>  |
| Parameter estimate                      | Difference in percentages   |
| Point estimate                          | 22.18   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 11.78   |
| upper limit                             | 32.11   |

Notes:

[1] - Superiority was demonstrated if the lower limit (LL) computed standardized asymptotic 95 percent (%) CI was above 0%.

## Secondary: Number of subjects reported with core fever (rectal temperature) greater than (>) the cut-off

|  |   |
|--|---|
| End point title  | Number of subjects reported with core fever (rectal temperature) greater than (>) the cut-off |
| End point description:   |   |
| The cut-off value for core fever (rectal temperature) was $39.0^{\circ}\text{C}$ . |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Within 4 days (Day 0-Day 3) after primary vaccination dose                         |   |

| End point values                    | Synflorix I Group | Synflorix II Group | Synflorix PRE Group | Synflorix POST Group |
|-------------------------------------|-------------------|--------------------|---------------------|----------------------|
| Subject group type                  | Reporting group   | Reporting group    | Reporting group     | Reporting group      |
| Number of subjects analysed         | 178               | 27                 | 172                 | 37                   |
| Units: Subjects                     |                   |                    |                     |                      |
| Fever (rectal temperature) > 39.0°C | 4                 | 0                  | 14                  | 1                    |

| End point values                    | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|-------------------------------------|--------------------------------------|--|--|--|
| Subject group type                  | Reporting group                      |  |  |  |
| Number of subjects analysed         | 336                                  |  |  |  |
| Units: Subjects                     |                                      |  |  |  |
| Fever (rectal temperature) > 39.0°C | 16                                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reported with any and Grade 3 solicited local symptoms

|                 |   |
|-----------------|---|
| End point title | Number of subjects reported with any and Grade 3 solicited local symptoms |
|-----------------|---|

End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any was defined as any occurrence of the specified symptom regardless of intensity. Grade 3 pain was defined as cried when limb was moved/spontaneously painful. Grade 3 redness/swelling was defined as redness/swelling > 30 millimeters (mm) from injection site

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

End point timeframe:

During the 4-day (Days 0- Day 3) post-primary vaccination period

| End point values            | Synflorix I Group | Synflorix II Group | Synflorix PRE Group | Synflorix POST Group |
|-----------------------------|-------------------|--------------------|---------------------|----------------------|
| Subject group type          | Reporting group   | Reporting group    | Reporting group     | Reporting group      |
| Number of subjects analysed | 178               | 27                 | 172                 | 37                   |
| Units: Subjects             |                   |                    |                     |                      |
| Any Pain                    | 54                | 10                 | 79                  | 19                   |
| Grade 3 Pain                | 2                 | 2                  | 10                  | 3                    |
| Any Redness                 | 89                | 9                  | 74                  | 12                   |
| Grade 3 Redness             | 7                 | 1                  | 14                  | 1                    |
| Any Swelling                | 52                | 8                  | 50                  | 13                   |
| Grade 3 Swelling            | 2                 | 1                  | 9                   | 3                    |

|                             |                                      |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>     | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 336                                  |  |  |  |
| Units: Subjects             |                                      |  |  |  |
| Any Pain                    | 114                                  |  |  |  |
| Grade 3 Pain                | 4                                    |  |  |  |
| Any Redness                 | 146                                  |  |  |  |
| Grade 3 Redness             | 16                                   |  |  |  |
| Any Swelling                | 71                                   |  |  |  |
| Grade 3 Swelling            | 12                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reported with any, Grade 3 and related solicited general symptoms

|                 |  |
|-----------------|--|
| End point title | Number of subjects reported with any, Grade 3 and related solicited general symptoms |
|-----------------|--|

End point description:

Solicited general symptoms assessed were drowsiness, fever (rectal temperature  $\geq 38.5^{\circ}\text{C}$ ), irritability and loss of appetite. Any was defined as any occurrence of the specified symptom regardless of intensity and relation to vaccination. Grade 3 drowsiness was defined as drowsiness that prevented normal activity. Grade 3 fever was defined as rectal temperature  $>40.0^{\circ}\text{C}$ . Grade 3 irritability was defined as crying that could not be comforted/ prevented normal activity. Grade 3 loss of appetite was defined as not eating at all. Related was defined as solicited symptoms assessed by the investigator as causally related to the study vaccination.

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

End point timeframe:

During the 4-day (Day 0-Day 3) post-vaccination period

| <b>End point values</b>                                      | Synflorix I<br>Group | Synflorix II<br>Group | Synflorix PRE<br>Group | Synflorix POST<br>Group |
|--|----------------------|-----------------------|------------------------|-------------------------|
| Subject group type   | Reporting group      | Reporting group       | Reporting group        | Reporting group         |
| Number of subjects analysed                                  | 178                  | 27                    | 172                    | 37                      |
| Units: Subjects  |                      |                       |                        |                         |
| Any Drowsiness   | 91                   | 11                    | 84                     | 18                      |
| Grade 3 Drowsiness   | 0                    | 0                     | 1                      | 1                       |
| Related Drowsiness   | 84                   | 11                    | 79                     | 18                      |
| Any Fever (rectal temperature $\geq 38.0^{\circ}\text{C}$ )  | 64                   | 14                    | 100                    | 16                      |
| Grade 3 Fever (rectal temperature $> 40.0^{\circ}\text{C}$ ) | 1                    | 0                     | 1                      | 0                       |
| Related Fever (rectal temperature $> 40.0^{\circ}\text{C}$ ) | 62                   | 14                    | 99                     | 16                      |
| Any Irritability   | 86                   | 17                    | 105                    | 19                      |
| Grade 3 Irritability   | 1                    | 0                     | 2                      | 2                       |
| Related Irritability   | 80                   | 17                    | 98                     | 18                      |

|                          |    |   |    |    |
|--------------------------|----|---|----|----|
| Any Loss of appetite     | 47 | 8 | 46 | 10 |
| Grade 3 Loss of appetite | 0  | 0 | 4  | 1  |
| Related Loss of appetite | 42 | 7 | 41 | 10 |

| End point values                             | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                           | Reporting group                      |  |  |  |
| Number of subjects analysed                  | 336                                  |  |  |  |
| Units: Subjects                              |                                      |  |  |  |
| Any Drowsiness                               | 146                                  |  |  |  |
| Grade 3 Drowsiness                           | 2                                    |  |  |  |
| Related Drowsiness                           | 120                                  |  |  |  |
| Any Fever (rectal temperature $\geq$ 38.0°C) | 146                                  |  |  |  |
| Grade 3 Fever (rectal temperature > 40.0°C)  | 3                                    |  |  |  |
| Related Fever (rectal temperature > 40.0°C)  | 140                                  |  |  |  |
| Any Irritability                             | 147                                  |  |  |  |
| Grade 3 Irritability                         | 2                                    |  |  |  |
| Related Irritability                         | 129                                  |  |  |  |
| Any Loss of appetite                         | 88                                   |  |  |  |
| Grade 3 Loss of appetite                     | 3                                    |  |  |  |
| Related Loss of appetite                     | 71                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reported with unsolicited adverse events (AEs)

|                 |  |
|-----------------|--|
| End point title | Number of subjects reported with unsolicited adverse events (AEs) <sup>[2]</sup> |
|-----------------|--|

End point description:

The outcome measure was not reporting statistics for all the arms in the baseline period. Results were tabulated on baseline groups except for the Synforix PRE and Synforix POST groups, for which results were presented for the Pooled Synforix PRE and POST Group. An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to vaccination.

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

End point timeframe:

Within 31 days (Day 0-Day 30) after primary vaccine dose

Notes:

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

Justification: This endpoint is only reporting values for the Synforix I Group, Synforix II Group, Mencevax + Infanrix Hexa Group and the Pooled Synforix PRE and POST Group.

| End point values            | Synflorix I Group | Synflorix II Group | Mencevax +<br>Infanrix Hexa<br>Group | Pooled<br>Synflorix PRE<br>and POST<br>Group |
|-----------------------------|-------------------|--------------------|--------------------------------------|--|
| Subject group type          | Reporting group   | Reporting group    | Reporting group                      | Subject analysis set                         |
| Number of subjects analysed | 178               | 27                 | 336                                  | 209  |
| Units: Subjects             |                   |                    |                                      |  |
| Subject(s) with any AE(s)   | 22                | 3                  | 64                                   | 30   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reported with serious adverse events (SAEs)

|  |  |
|--|--|
| End point title  | Number of subjects reported with serious adverse events (SAEs) |
| End point description:<br>SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Throughout the entire study period (Month 0-Month 12)  |  |

| End point values            | Synflorix I Group | Synflorix II Group | Synflorix PRE Group | Synflorix POST Group |
|-----------------------------|-------------------|--------------------|---------------------|----------------------|
| Subject group type          | Reporting group   | Reporting group    | Reporting group     | Reporting group      |
| Number of subjects analysed | 178               | 27                 | 172                 | 37                   |
| Units: Subjects             |                   |                    |                     |                      |
| Subject(s) with any SAE(s)  | 13                | 5                  | 13                  | 4                    |

| End point values            | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 336                                  |  |  |  |
| Units: Subjects             |                                      |  |  |  |
| Subject(s) with any SAE(s)  | 30                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reported with AEs resulting in rash, new onset of chronic illness (NOCI), emergency room (ER) visits and non-routine physician office

## visits

|                 |  |
|-----------------|--|
| End point title | Number of subjects reported with AEs resulting in rash, new onset of chronic illness (NOCI), emergency room (ER) visits and non-routine physician office visits <sup>[3]</sup> |
|-----------------|--|

End point description:

Results were tabulated only on Mencevax + Infanrix Hexa Group, according to the outcome measure specification of the protocol.

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

End point timeframe:

Up to 6 months after vaccination with Mencevax

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group.

|  |                                |  |  |  |
|--|--------------------------------|--|--|--|
| <b>End point values</b>                          | Mencevax + Infanrix Hexa Group |  |  |  |
| Subject group type                               | Reporting group                |  |  |  |
| Number of subjects analysed                      | 336                            |  |  |  |
| Units: Subjects                                  |                                |  |  |  |
| Subject(s) with any rash(es)                     | 7                              |  |  |  |
| Subject(s) with any NOCI(s)                      | 1                              |  |  |  |
| Subject(s) with any ER visit(s)                  | 0                              |  |  |  |
| Subject(s) with any visit(s) at physician office | 53                             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with antibody concentrations against pneumococcal serotypes >= the cut-off

|                 |   |
|-----------------|---|
| End point title | Number of subjects with antibody concentrations against pneumococcal serotypes >= the cut-off |
|-----------------|---|

End point description:

Certain pneumococcal serotypes includes pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations were measured by 22F-inhibition Enzyme-Linked ImmunoSorbent Assay (ELISA). The seroprotection cut-off for the assay was >= 0.2 microgram per milliliter (µg/mL).

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

End point timeframe:

Prior to booster vaccination (PRE), 1 month (M1) and 12 months (M12) post-booster vaccination

| End point values                  | Synflorix I Group | Synflorix II Group | Synflorix PRE Group | Synflorix POST Group |
|-----------------------------------|-------------------|--------------------|---------------------|----------------------|
| Subject group type                | Reporting group   | Reporting group    | Reporting group     | Reporting group      |
| Number of subjects analysed       | 141               | 25                 | 168                 | 37                   |
| Units: Subjects                   |                   |                    |                     |                      |
| ANTI-1 PRE(N=132,25,163,37,284)   | 74                | 14                 | 115                 | 27                   |
| ANTI-1 M1(N=140,24,167,36,244)    | 140               | 24                 | 167                 | 36                   |
| ANTI-1 M12(N=138,25,167,36,263)   | 89                | 11                 | 122                 | 30                   |
| ANTI-4 PRE(N=139,25,160,35,289)   | 123               | 15                 | 147                 | 31                   |
| ANTI-4 M1(N=141,24,167,37,261)    | 141               | 24                 | 167                 | 37                   |
| ANTI-4 M12(N=139,25,168,36,288)   | 103               | 14                 | 147                 | 27                   |
| ANTI-5 PRE(N=131,25,156,37,277)   | 102               | 15                 | 142                 | 30                   |
| ANTI-5 M1(N=140,24,167,36,256)    | 140               | 23                 | 167                 | 36                   |
| ANTI-5 M12(N=139,25,168,36,281)   | 113               | 18                 | 159                 | 30                   |
| ANTI-6B PRE(N=139,25,164,37,282)  | 110               | 13                 | 143                 | 32                   |
| ANTI-6B M1(N=140,24,167,36,282)   | 134               | 21                 | 166                 | 35                   |
| ANTI-6B M12(N=139,25,168,36,289)  | 97                | 18                 | 148                 | 30                   |
| ANTI-7F PRE(N=136,24,159,35,281)  | 130               | 21                 | 156                 | 34                   |
| ANTI-7F M1(N=140,25,167,37,265)   | 140               | 25                 | 167                 | 37                   |
| ANTI-7F M12(N=139,25,168,36,283)  | 132               | 21                 | 165                 | 36                   |
| ANTI-9V PRE(N=127,24,154,35,279)  | 117               | 20                 | 152                 | 34                   |
| ANTI-9V M1(N=141,25,167,37,266)   | 141               | 24                 | 167                 | 37                   |
| ANTI-9V M12(N=139,25,168,36,285)  | 129               | 20                 | 166                 | 35                   |
| ANTI-14 PRE(N=136,25,164,37,274)  | 131               | 22                 | 159                 | 35                   |
| ANTI-14 M1(N=140,24,167,36,261)   | 140               | 24                 | 166                 | 36                   |
| ANTI-14 M12(N=139,25,168,36,277)  | 131               | 21                 | 166                 | 34                   |
| ANTI-18C PRE(N=135,25,163,35,275) | 118               | 14                 | 154                 | 29                   |
| ANTI-18C M1(N=141,25,167,37,269)  | 141               | 25                 | 167                 | 37                   |
| ANTI-18C M12(N=139,25,168,36,281) | 113               | 18                 | 157                 | 35                   |
| ANTI-19F PRE(N=137,25,165,37,278) | 128               | 21                 | 163                 | 36                   |
| ANTI-19F M1(N=141,25,167,37,269)  | 138               | 25                 | 165                 | 37                   |
| ANTI-19F M12(N=138,25,168,36,283) | 135               | 22                 | 165                 | 36                   |
| ANTI-23F PRE(N=136,25,155,35,275) | 103               | 14                 | 132                 | 30                   |
| ANTI-23F M1(N=140,24,167,37,259)  | 135               | 21                 | 163                 | 36                   |
| ANTI-23F M12(N=139,25,168,36,289) | 115               | 16                 | 154                 | 33                   |

| End point values                | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|---------------------------------|--------------------------------------|--|--|--|
| Subject group type              | Reporting group                      |  |  |  |
| Number of subjects analysed     | 289                                  |  |  |  |
| Units: Subjects                 |                                      |  |  |  |
| ANTI-1 PRE(N=132,25,163,37,284) | 6                                    |  |  |  |
| ANTI-1 M1(N=140,24,167,36,244)  | 5                                    |  |  |  |
| ANTI-1 M12(N=138,25,167,36,263) | 11                                   |  |  |  |
| ANTI-4 PRE(N=139,25,160,35,289) | 6                                    |  |  |  |
| ANTI-4 M1(N=141,24,167,37,261)  | 6                                    |  |  |  |
| ANTI-4 M12(N=139,25,168,36,288) | 20                                   |  |  |  |
| ANTI-5 PRE(N=131,25,156,37,277) | 6                                    |  |  |  |
| ANTI-5 M1(N=140,24,167,36,256)  | 10                                   |  |  |  |

|                                   |    |  |  |  |
|-----------------------------------|----|--|--|--|
| ANTI-5 M12(N=139,25,168,36,281)   | 31 |  |  |  |
| ANTI-6B PRE(N=139,25,164,37,282)  | 1  |  |  |  |
| ANTI-6B M1(N=140,24,167,36,282)   | 1  |  |  |  |
| ANTI-6B M12(N=139,25,168,36,289)  | 21 |  |  |  |
| ANTI-7F PRE(N=136,24,159,35,281)  | 5  |  |  |  |
| ANTI-7F M1(N=140,25,167,37,265)   | 9  |  |  |  |
| ANTI-7F M12(N=139,25,168,36,283)  | 20 |  |  |  |
| ANTI-9V PRE(N=127,24,154,35,279)  | 5  |  |  |  |
| ANTI-9V M1(N=141,25,167,37,266)   | 10 |  |  |  |
| ANTI-9V M12(N=139,25,168,36,285)  | 30 |  |  |  |
| ANTI-14 PRE(N=136,25,164,37,274)  | 25 |  |  |  |
| ANTI-14 M1(N=140,24,167,36,261)   | 29 |  |  |  |
| ANTI-14 M12(N=139,25,168,36,277)  | 63 |  |  |  |
| ANTI-18C PRE(N=135,25,163,35,275) | 8  |  |  |  |
| ANTI-18C M1(N=141,25,167,37,269)  | 9  |  |  |  |
| ANTI-18C M12(N=139,25,168,36,281) | 29 |  |  |  |
| ANTI-19F PRE(N=137,25,165,37,278) | 17 |  |  |  |
| ANTI-19F M1(N=141,25,167,37,269)  | 24 |  |  |  |
| ANTI-19F M12(N=138,25,168,36,283) | 90 |  |  |  |
| ANTI-23F PRE(N=136,25,155,35,275) | 2  |  |  |  |
| ANTI-23F M1(N=140,24,167,37,259)  | 4  |  |  |  |
| ANTI-23F M12(N=139,25,168,36,289) | 24 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Antibody concentrations against pneumococcal serotypes >= the cut-off

|   |   |
|---|---|
| End point title   | Antibody concentrations against pneumococcal serotypes >= the cut-off |
| End point description:  |   |
| Certain pneumococcal serotypes included pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). Anti-1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody concentrations were measured by 22F-inhibition Enzyme-Linked ImmunoSorbent Assay (ELISA). Seropositivity cut-off for the assay was >= 0.05 microgram per milliliter (µg/mL). |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Prior to booster vaccination (PRE), 1 month (M1) and 12 months (M12) post-booster vaccination   |   |

| End point values                         | Synflorix I Group   | Synflorix II Group  | Synflorix PRE Group | Synflorix POST Group |
|--|---------------------|---------------------|---------------------|----------------------|
| Subject group type                       | Reporting group     | Reporting group     | Reporting group     | Reporting group      |
| Number of subjects analysed              | 141                 | 25                  | 168                 | 37                   |
| Units: µg/mL                             |                     |                     |                     |                      |
| geometric mean (confidence interval 95%) |                     |                     |                     |                      |
| ANTI-1 PRE(N=132,25,163,37,284)          | 0.22 (0.19 to 0.25) | 0.18 (0.12 to 0.27) | 0.31 (0.27 to 0.35) | 0.26 (0.19 to 0.35)  |

|                                   |                     |                     |                     |                      |
|-----------------------------------|---------------------|---------------------|---------------------|----------------------|
| ANTI-1 M1(N=140,24,167,36,244)    | 1.67 (1.47 to 1.9)  | 1.64 (1.08 to 2.47) | 2.62 (2.3 to 2.99)  | 2.97 (2.21 to 3.99)  |
| ANTI-1 M12(N=138,25,167,36,263)   | 0.26 (0.22 to 0.31) | 0.18 (0.12 to 0.29) | 0.39 (0.34 to 0.45) | 0.41 (0.31 to 0.56)  |
| ANTI-4 PRE(N=139,25,160,35,289)   | 0.4 (0.35 to 0.45)  | 0.24 (0.17 to 0.35) | 0.6 (0.52 to 0.69)  | 0.45 (0.35 to 0.58)  |
| ANTI-4 M1(N=141,24,167,37,261)    | 3.01 (2.69 to 3.36) | 2.84 (1.98 to 4.08) | 4.21 (3.72 to 4.76) | 3.95 (2.97 to 5.26)  |
| ANTI-4 M12(N=139,25,168,36,288)   | 0.34 (0.29 to 0.39) | 0.21 (0.13 to 0.33) | 0.5 (0.43 to 0.56)  | 0.55 (0.39 to 0.78)  |
| ANTI-5 PRE(N=131,25,156,37,277)   | 0.36 (0.32 to 0.42) | 0.31 (0.18 to 0.52) | 0.59 (0.52 to 0.68) | 0.53 (0.36 to 0.78)  |
| ANTI-5 M1(N=140,24,167,36,256)    | 2.3 (2.04 to 2.6)   | 2 (1.31 to 3.06)    | 3.68 (3.26 to 4.15) | 3.03 (2.16 to 4.26)  |
| ANTI-5 M12(N=139,25,168,36,281)   | 0.42 (0.36 to 0.48) | 0.35 (0.23 to 0.52) | 0.72 (0.63 to 0.83) | 0.58 (0.42 to 0.81)  |
| ANTI-6B PRE(N=139,25,164,37,282)  | 0.35 (0.3 to 0.41)  | 0.18 (0.1 to 0.32)  | 0.55 (0.48 to 0.63) | 0.5 (0.35 to 0.72)   |
| ANTI-6B M1(N=140,24,167,36,282)   | 1.35 (1.12 to 1.61) | 0.89 (0.46 to 1.72) | 2.45 (2.17 to 2.77) | 2.25 (1.51 to 3.33)  |
| ANTI-6B M12(N=139,25,168,36,289)  | 0.4 (0.32 to 0.5)   | 0.36 (0.19 to 0.66) | 0.56 (0.47 to 0.68) | 0.54 (0.37 to 0.81)  |
| ANTI-7F PRE(N=136,24,159,35,281)  | 0.74 (0.65 to 0.84) | 0.55 (0.4 to 0.76)  | 1.05 (0.93 to 1.18) | 0.87 (0.66 to 1.13)  |
| ANTI-7F M1(N=140,25,167,37,265)   | 2.9 (2.59 to 3.25)  | 2.37 (1.86 to 3.03) | 4.13 (3.69 to 4.63) | 4.38 (3.35 to 5.72)  |
| ANTI-7F M12(N=139,25,168,36,283)  | 0.68 (0.6 to 0.78)  | 0.45 (0.32 to 0.63) | 0.91 (0.82 to 1.02) | 0.96 (0.74 to 1.24)  |
| ANTI-9V PRE(N=127,24,154,35,279)  | 0.61 (0.53 to 0.7)  | 0.59 (0.33 to 1.05) | 1 (0.88 to 1.13)    | 0.99 (0.78 to 1.26)  |
| ANTI-9V M1(N=141,25,167,37,266)   | 2.86 (2.52 to 3.23) | 2.57 (1.73 to 3.81) | 4.39 (3.91 to 4.94) | 4.35 (3.3 to 5.73)   |
| ANTI-9V M12(N=139,25,168,36,285)  | 0.67 (0.56 to 0.8)  | 0.55 (0.33 to 0.92) | 0.97 (0.85 to 1.12) | 0.86 (0.64 to 1.17)  |
| ANTI-14 PRE(N=136,25,164,37,274)  | 0.82 (0.69 to 0.96) | 0.52 (0.36 to 0.74) | 1.57 (1.32 to 1.86) | 1.27 (0.86 to 1.88)  |
| ANTI-14 M1(N=140,24,167,36,261)   | 4.58 (4.05 to 5.18) | 4.37 (3.01 to 6.33) | 5.95 (5.28 to 6.71) | 5.86 (4.35 to 7.89)  |
| ANTI-14 M12(N=139,25,168,36,277)  | 0.89 (0.73 to 1.09) | 0.94 (0.48 to 1.84) | 1.54 (1.3 to 1.81)  | 1.25 (0.9 to 1.76)   |
| ANTI-18C PRE(N=135,25,163,35,275) | 0.47 (0.41 to 0.54) | 0.29 (0.2 to 0.43)  | 0.78 (0.69 to 0.89) | 0.54 (0.39 to 0.76)  |
| ANTI-18C M1(N=141,25,167,37,269)  | 4.96 (4.4 to 5.6)   | 3.46 (2.35 to 5.09) | 7 (6.28 to 7.79)    | 6.13 (4.85 to 7.75)  |
| ANTI-18C M12(N=139,25,168,36,281) | 0.56 (0.47 to 0.66) | 0.44 (0.27 to 0.72) | 1.05 (0.92 to 1.21) | 0.92 (0.69 to 1.21)  |
| ANTI-19F PRE(N=137,25,165,37,278) | 0.98 (0.81 to 1.19) | 0.63 (0.39 to 1.02) | 1.48 (1.27 to 1.73) | 1.4 (1 to 1.97)      |
| ANTI-19F M1(N=141,25,167,37,269)  | 6 (5.08 to 7.08)    | 4.84 (3.47 to 6.77) | 7.55 (6.48 to 8.79) | 8.77 (6.68 to 11.53) |
| ANTI-19F M12(N=138,25,168,36,283) | 1.46 (1.18 to 1.82) | 0.82 (0.56 to 1.2)  | 1.8 (1.52 to 2.13)  | 2.04 (1.41 to 2.94)  |
| ANTI-23F PRE(N=136,25,155,35,275) | 0.38 (0.31 to 0.46) | 0.3 (0.16 to 0.58)  | 0.54 (0.45 to 0.64) | 0.45 (0.31 to 0.65)  |
| ANTI-23F M1(N=140,24,167,37,259)  | 1.99 (1.67 to 2.38) | 1.33 (0.64 to 2.78) | 2.92 (2.5 to 3.4)   | 3.86 (2.52 to 5.91)  |
| ANTI-23F M12(N=139,25,168,36,289) | 0.46 (0.38 to 0.56) | 0.29 (0.16 to 0.52) | 0.8 (0.67 to 0.95)  | 0.98 (0.69 to 1.39)  |

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                     | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
| Subject group type                          | Reporting group                      |  |  |  |
| Number of subjects analysed                 | 289                                  |  |  |  |
| Units: µg/mL                                |                                      |  |  |  |
| geometric mean (confidence interval<br>95%) |                                      |  |  |  |
| ANTI-1 PRE(N=132,25,163,37,284)             | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-1 M1(N=140,24,167,36,244)              | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-1 M12(N=138,25,167,36,263)             | 0.04 (0.04 to<br>0.04)               |  |  |  |
| ANTI-4 PRE(N=139,25,160,35,289)             | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-4 M1(N=141,24,167,37,261)              | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-4 M12(N=139,25,168,36,288)             | 0.04 (0.03 to<br>0.04)               |  |  |  |
| ANTI-5 PRE(N=131,25,156,37,277)             | 0.04 (0.03 to<br>0.04)               |  |  |  |
| ANTI-5 M1(N=140,24,167,36,256)              | 0.04 (0.03 to<br>0.04)               |  |  |  |
| ANTI-5 M12(N=139,25,168,36,281)             | 0.06 (0.05 to<br>0.06)               |  |  |  |
| ANTI-6B PRE(N=139,25,164,37,282)            | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-6B M1(N=140,24,167,36,282)             | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-6B M12(N=139,25,168,36,289)            | 0.04 (0.04 to<br>0.04)               |  |  |  |
| ANTI-7F PRE(N=136,24,159,35,281)            | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-7F M1(N=140,25,167,37,265)             | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-7F M12(N=139,25,168,36,283)            | 0.04 (0.04 to<br>0.04)               |  |  |  |
| ANTI-9V PRE(N=127,24,154,35,279)            | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-9V M1(N=141,25,167,37,266)             | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-9V M12(N=139,25,168,36,285)            | 0.04 (0.04 to<br>0.05)               |  |  |  |
| ANTI-14 PRE(N=136,25,164,37,274)            | 0.04 (0.04 to<br>0.05)               |  |  |  |
| ANTI-14 M1(N=140,24,167,36,261)             | 0.05 (0.04 to<br>0.05)               |  |  |  |
| ANTI-14 M12(N=139,25,168,36,277)            | 0.11 (0.09 to<br>0.13)               |  |  |  |
| ANTI-18C PRE(N=135,25,163,35,275)           | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-18C M1(N=141,25,167,37,269)            | 0.03 (0.03 to<br>0.03)               |  |  |  |
| ANTI-18C M12(N=139,25,168,36,281)           | 0.04 (0.04 to<br>0.05)               |  |  |  |
| ANTI-19F PRE(N=137,25,165,37,278)           | 0.03 (0.03 to<br>0.04)               |  |  |  |
| ANTI-19F M1(N=141,25,167,37,269)            | 0.05 (0.04 to<br>0.05)               |  |  |  |
| ANTI-19F M12(N=138,25,168,36,283)           | 0.12 (0.1 to<br>0.14)                |  |  |  |

|                                   |                     |  |  |  |
|-----------------------------------|---------------------|--|--|--|
| ANTI-23F PRE(N=136,25,155,35,275) | 0.03 (0.03 to 0.03) |  |  |  |
| ANTI-23F M1(N=140,24,167,37,259)  | 0.03 (0.03 to 0.03) |  |  |  |
| ANTI-23F M12(N=139,25,168,36,289) | 0.04 (0.03 to 0.04) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Opsonophagocytic activity (OPA) titers against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F

|                 |   |
|-----------------|---|
| End point title | Opsonophagocytic activity (OPA) titers against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F |
|-----------------|---|

End point description:

OPA titers against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (Opsono-1, -4, -5, -6B, -7F, -9V, -14, -18C, -19F and -23F) were calculated, expressed as geometric mean titers (GMTs) and tabulated. The seropositivity cut-off for the assay was  $\geq 8$ .

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

End point timeframe:

Prior to booster vaccination (PRE), 1 month (M1) and 12 months (M12) post-booster vaccination

| End point values                         | Synflorix I Group         | Synflorix II Group      | Synflorix PRE Group     | Synflorix POST Group    |
|--|---------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                       | Reporting group           | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed              | 131                       | 25                      | 161                     | 35                      |
| Units: Titers                            |                           |                         |                         |                         |
| geometric mean (confidence interval 95%) |                           |                         |                         |                         |
| OPSONO-1 PRE(N=125,25,152,31,26)         | 6.1 (5 to 7.4)            | 5.6 (4 to 8)            | 8.1 (6.6 to 10)         | 6 (4.2 to 8.5)          |
| OPSONO-1 M1(N=130,23,156,34,39)          | 144.6 (109.6 to 190.6)    | 193.4 (95.8 to 390.8)   | 417 (330.6 to 526.2)    | 325 (178.8 to 590.7)    |
| OPSONO-1 M12(N=129,21,153,34,126)        | 12.8 (10 to 16.5)         | 12.5 (6.8 to 23.2)      | 23.1 (18.2 to 29.2)     | 20.5 (13.1 to 32.3)     |
| OPSONO-4 PRE(N=121,22,148,31,31)         | 23.8 (16.5 to 34.2)       | 8.8 (5.2 to 14.9)       | 44.9 (33.2 to 60.8)     | 29.7 (14.3 to 61.6)     |
| OPSONO-4 M1(N=130,22,158,32,23)          | 1547.9 (1357.9 to 1764.4) | 971.6 (615.8 to 1532.7) | 2297 (2005.8 to 2630.4) | 1303.2 (918.6 to 1849)  |
| OPSONO-4 M12(N=125,21,152,33,119)        | 19.9 (13.9 to 28.6)       | 14.9 (6.4 to 34.8)      | 51.2 (36.2 to 72.4)     | 72.5 (33.7 to 156.1)    |
| OPSONO-5 PRE(N=121,24,146,31,26)         | 8.5 (7 to 10.4)           | 10.4 (6.2 to 17.4)      | 16.6 (13.2 to 20.9)     | 15.1 (8.8 to 25.9)      |
| OPSONO-5 M1(N=130,23,156,34,45)          | 134.3 (109.8 to 164.2)    | 105 (55.9 to 196.9)     | 289.3 (243.5 to 343.7)  | 227.7 (130.7 to 396.6)  |
| OPSONO-5 M12(N=124,21,154,32,135)        | 10.3 (8.3 to 12.9)        | 10.5 (5.9 to 18.7)      | 23.7 (18.9 to 29.8)     | 15.4 (10.2 to 23.2)     |
| OPSONO-6B PRE(N=126,22,154,31,25)        | 32.5 (21.6 to 48.9)       | 15.9 (6 to 42.1)        | 45.2 (32.9 to 62.2)     | 49.7 (23 to 107.3)      |
| OPSONO-6B M1(N=130,22,157,34,29)         | 496.7 (351.4 to 702.2)    | 148.3 (46.5 to 472.5)   | 985.7 (807.1 to 1203.9) | 718.3 (445.7 to 1157.5) |

|  |                           |                          |                           |                           |
|--|---------------------------|--------------------------|---------------------------|---------------------------|
| OPSONO-6B<br>M12(N=123,22,145,31,113)  | 46.9 (29.6 to 74.2)       | 97.7 (27.7 to 345.1)     | 53.9 (36.1 to 80.4)       | 29.4 (13.2 to 65.2)       |
| OPSONO-7F PRE(N=115,22,148,32,23)      | 413.6 (266.1 to 642.9)    | 221.4 (65.7 to 745.9)    | 584.7 (426.1 to 802.3)    | 258.4 (119.9 to 556.7)    |
| OPSONO-7F M1(N=130,23,158,34,28)       | 4025.8 (3457.3 to 4687.9) | 1749 (1144.2 to 2673.4)  | 4674.7 (4102.2 to 5327)   | 2212.2 (1569.1 to 3118.7) |
| OPSONO-7F<br>M12(N=130,25,159,34,118)  | 1503.3 (1209.1 to 1869.2) | 1606.4 (1101.4 to 2343)  | 1285.7 (1050.8 to 1573)   | 1738.3 (1330.6 to 2271)   |
| OPSONO-9V PRE(N=119,21,147,31,23)      | 420.7 (342.7 to 516.5)    | 472.9 (255.6 to 874.7)   | 407.7 (340.3 to 488.4)    | 365.7 (240.6 to 555.8)    |
| OPSONO-9V M1(N=129,23,157,34,31)       | 2234.8 (1905.7 to 2620.7) | 752.9 (476.9 to 1188.8)  | 2403.7 (2092.3 to 2761.4) | 1155.5 (733.4 to 1820.4)  |
| OPSONO-9V<br>M12(N=131,25,161,35,124)  | 791.6 (647.4 to 967.9)    | 552.2 (337.1 to 904.6)   | 906.7 (757.6 to 1085.2)   | 716.8 (481 to 1068.2)     |
| OPSONO-14 PRE(N=118,21,152,29,12)      | 189.7 (141.7 to 254)      | 150.2 (81.5 to 276.8)    | 293.2 (235.3 to 365.5)    | 227.4 (115.1 to 449.4)    |
| OPSONO-14 M1(N=130,22,154,34,19)       | 1581.7 (1381.1 to 1811.4) | 1515 (911.2 to 2519)     | 1865.2 (1633.4 to 2129.9) | 1964.5 (1359.9 to 2837.9) |
| OPSONO-14 M12(N=117,15,147,32,98)      | 434.5 (353 to 534.8)      | 438.4 (137.7 to 1396)    | 447.5 (376 to 532.6)      | 558 (425 to 732.5)        |
| OPSONO-18C<br>PRE(N=124,23,148,24,38)  | 6.1 (5.2 to 7.2)          | 6 (3.7 to 9.7)           | 11.7 (9.2 to 15.1)        | 9.5 (4.9 to 18.5)         |
| OPSONO-18C M1(N=128,22,154,34,42)      | 652.9 (553.5 to 770.1)    | 269.7 (128.9 to 564.3)   | 737.8 (633.6 to 859.1)    | 537.6 (370.9 to 779.3)    |
| OPSONO-18C<br>M12(N=121,23,154,28,124) | 11.9 (8.9 to 16.1)        | 24.7 (9 to 67.5)         | 27.7 (21.3 to 36)         | 23.5 (11 to 50.3)         |
| OPSONO-19F PRE(N=121,24,149,32,39)     | 21.2 (16.1 to 28)         | 17.4 (10.5 to 28.7)      | 35.1 (28 to 44)           | 36.4 (22 to 60.3)         |
| OPSONO-19F M1(N=130,23,156,34,42)      | 629.4 (496.6 to 797.7)    | 372.9 (180.1 to 772.5)   | 1062.2 (871.8 to 1294.3)  | 1198.8 (807.1 to 1780.5)  |
| OPSONO-19F<br>M12(N=130,25,155,35,132) | 64.3 (47.6 to 86.7)       | 39.4 (17.3 to 89.5)      | 101.3 (80.7 to 127)       | 121.3 (67.5 to 218.1)     |
| OPSONO-23F PRE(N=122,20,149,31,25)     | 288.7 (192.1 to 434)      | 310.1 (85.9 to 1119.4)   | 408 (288.6 to 576.6)      | 305.3 (135 to 690.5)      |
| OPSONO-23F M1(N=130,23,157,34,28)      | 2335.7 (2016.2 to 2705.7) | 1223.1 (910.6 to 1642.8) | 3154 (2658 to 3742.4)     | 1808.7 (1381.1 to 2368.7) |
| OPSONO-23F<br>M12(N=122,20,152,33,124) | 386.4 (250 to 597.2)      | 433.8 (110.1 to 1709.8)  | 857.5 (634 to 1159.7)     | 670.2 (331.9 to 1353.3)   |

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 135                                  |  |  |  |
| Units: Titers                            |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| OPSONO-1 PRE(N=125,25,152,31,26)         | 4.9 (3.7 to 6.5)                     |  |  |  |
| OPSONO-1 M1(N=130,23,156,34,39)          | 5.1 (4.1 to 6.4)                     |  |  |  |
| OPSONO-1 M12(N=129,21,153,34,126)        | 4.7 (4.3 to 5.1)                     |  |  |  |
| OPSONO-4 PRE(N=121,22,148,31,31)         | 5.9 (3.4 to 10.2)                    |  |  |  |

|                                     |                        |  |  |  |
|-------------------------------------|------------------------|--|--|--|
| OPSONO-4 M1(N=130,22,158,32,23)     | 7.8 (3.6 to 16.8)      |  |  |  |
| OPSONO-4 M12(N=125,21,152,33,119)   | 6.8 (5 to 9.3)         |  |  |  |
| OPSONO-5 PRE(N=121,24,146,31,26)    | 4.2 (3.8 to 4.7)       |  |  |  |
| OPSONO-5 M1(N=130,23,156,34,45)     | 4.3 (3.8 to 4.8)       |  |  |  |
| OPSONO-5 M12(N=124,21,154,32,135)   | 4 (4 to 4)             |  |  |  |
| OPSONO-6B PRE(N=126,22,154,31,25)   | 9.9 (3.5 to 27.7)      |  |  |  |
| OPSONO-6B M1(N=130,22,157,34,29)    | 20.9 (6.6 to 65.9)     |  |  |  |
| OPSONO-6B M12(N=123,22,145,31,113)  | 19.1 (12 to 30.5)      |  |  |  |
| OPSONO-7F PRE(N=115,22,148,32,23)   | 90 (23.2 to 349.8)     |  |  |  |
| OPSONO-7F M1(N=130,23,158,34,28)    | 267.3 (89.1 to 801.2)  |  |  |  |
| OPSONO-7F M12(N=130,25,159,34,118)  | 681.1 (499.7 to 928.3) |  |  |  |
| OPSONO-9V PRE(N=119,21,147,31,23)   | 69.2 (22.9 to 208.9)   |  |  |  |
| OPSONO-9V M1(N=129,23,157,34,31)    | 87.4 (45.2 to 169)     |  |  |  |
| OPSONO-9V M12(N=131,25,161,35,124)  | 127.2 (86.8 to 186.2)  |  |  |  |
| OPSONO-14 PRE(N=118,21,152,29,12)   | 11.5 (3.3 to 40.1)     |  |  |  |
| OPSONO-14 M1(N=130,22,154,34,19)    | 158 (59.4 to 420.2)    |  |  |  |
| OPSONO-14 M12(N=117,15,147,32,98)   | 287.8 (203.2 to 407.6) |  |  |  |
| OPSONO-18C PRE(N=124,23,148,24,38)  | 4.5 (3.5 to 5.8)       |  |  |  |
| OPSONO-18C M1(N=128,22,154,34,42)   | 4 (4 to 4)             |  |  |  |
| OPSONO-18C M12(N=121,23,154,28,124) | 4.6 (4 to 5.3)         |  |  |  |
| OPSONO-19F PRE(N=121,24,149,32,39)  | 5.3 (3.7 to 7.7)       |  |  |  |
| OPSONO-19F M1(N=130,23,156,34,42)   | 4.5 (3.7 to 5.6)       |  |  |  |
| OPSONO-19F M12(N=130,25,155,35,132) | 6.4 (5.1 to 8.1)       |  |  |  |
| OPSONO-23F PRE(N=122,20,149,31,25)  | 20.2 (7.2 to 56.2)     |  |  |  |
| OPSONO-23F M1(N=130,23,157,34,28)   | 261.8 (97.9 to 700.5)  |  |  |  |
| OPSONO-23F M12(N=122,20,152,33,124) | 147.1 (86.7 to 249.9)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Concentrations of antibodies against protein D (Anti-PD)

|   |  |
|---|--|
| End point title   | Concentrations of antibodies against protein D (Anti-PD) |
| End point description:<br>The seropositivity cut-off for the assay was $\geq 100$ Enzyme-Linked ImmunoSorbent Assay (ELISA) units per milliliter (EL.U/mL). |  |
| End point type  | Secondary  |

End point timeframe:

Prior to booster vaccination (PRE), 1 month (M1) and 12 months (M12) post-booster vaccination

| End point values                         | Synflorix I Group       | Synflorix II Group        | Synflorix PRE Group       | Synflorix POST Group      |
|--|-------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type                       | Reporting group         | Reporting group           | Reporting group           | Reporting group           |
| Number of subjects analysed              | 140                     | 25                        | 167                       | 37                        |
| Units: EL.U/mL                           |                         |                           |                           |                           |
| geometric mean (confidence interval 95%) |                         |                           |                           |                           |
| Anti-PD-PRE (N=135,25,158,37,260)        | 365.1 (302.1 to 441.1)  | 356.5 (247 to 514.4)      | 685.5 (585.4 to 802.9)    | 584.3 (393.1 to 868.4)    |
| Anti-PD-M1 (N=140,24,166,36,258)         | 1654 (1399.9 to 1954.4) | 1813.5 (1111.5 to 2958.9) | 3134.2 (2765.4 to 3552.1) | 2612.3 (1804.4 to 3782.1) |
| Anti-PD-M12 (N=138,25,167,36,270)        | 468.1 (381.8 to 573.8)  | 418 (259.9 to 672.3)      | 834.6 (720 to 967.5)      | 713.4 (476.9 to 1067.4)   |

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 270                                  |  |  |  |
| Units: EL.U/mL                           |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-PD-PRE (N=135,25,158,37,260)        | 65.6 (60.9 to 70.8)                  |  |  |  |
| Anti-PD-M1 (N=140,24,166,36,258)         | 64.6 (59.9 to 69.5)                  |  |  |  |
| Anti-PD-M12 (N=138,25,167,36,270)        | 74.4 (67.8 to 81.6)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Antibody concentrations against pneumococcal serotypes 6A and 19A (anti-6A and 19A)

|                 |   |
|-----------------|---|
| End point title | Antibody concentrations against pneumococcal serotypes 6A and 19A (anti-6A and 19A) |
|-----------------|---|

End point description:

Anti-6A and 19A antibody concentrations were measured by 22F-inhibition ELISA.

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

End point timeframe:

Prior to booster vaccination (PRE), 1 month (M1) and 12 months (M12) post-booster vaccination

| End point values                         | Synflorix I Group   | Synflorix II Group  | Synflorix PRE Group | Synflorix POST Group |
|--|---------------------|---------------------|---------------------|----------------------|
| Subject group type                       | Reporting group     | Reporting group     | Reporting group     | Reporting group      |
| Number of subjects analysed              | 139                 | 25                  | 168                 | 37                   |
| Units: µg/mL                             |                     |                     |                     |                      |
| geometric mean (confidence interval 95%) |                     |                     |                     |                      |
| Anti-6A-PRE N(=136,25,161,37,278)        | 0.12 (0.1 to 0.15)  | 0.08 (0.05 to 0.12) | 0.21 (0.18 to 0.26) | 0.19 (0.12 to 0.29)  |
| Anti-6A-M1 (N=138,25,166,36,288)         | 0.4 (0.31 to 0.51)  | 0.29 (0.15 to 0.55) | 0.86 (0.69 to 1.07) | 0.75 (0.43 to 1.3)   |
| Anti-6A-M12 (N=139,25,167,36,279)        | 0.14 (0.11 to 0.18) | 0.1 (0.07 to 0.16)  | 0.24 (0.2 to 0.3)   | 0.2 (0.13 to 0.29)   |
| Anti-19A-PRE (n=138,25,165,36,277)       | 0.15 (0.13 to 0.18) | 0.12 (0.07 to 0.19) | 0.23 (0.19 to 0.27) | 0.2 (0.14 to 0.29)   |
| Anti-19A-M1 (N=138,25,166,37,276)        | 0.84 (0.67 to 1.05) | 0.56 (0.29 to 1.09) | 1.34 (1.09 to 1.66) | 1.54 (0.98 to 2.43)  |
| Anti-19A-M12 (N=139,25,168,36,284)       | 0.22 (0.17 to 0.28) | 0.13 (0.08 to 0.22) | 0.36 (0.3 to 0.44)  | 0.41 (0.26 to 0.65)  |

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 288                                  |  |  |  |
| Units: µg/mL                             |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-6A-PRE N(=136,25,161,37,278)        | 0.03 (0.03 to 0.03)                  |  |  |  |
| Anti-6A-M1 (N=138,25,166,36,288)         | 0.03 (0.03 to 0.03)                  |  |  |  |
| Anti-6A-M12 (N=139,25,167,36,279)        | 0.04 (0.03 to 0.04)                  |  |  |  |
| Anti-19A-PRE (n=138,25,165,36,277)       | 0.03 (0.03 to 0.04)                  |  |  |  |
| Anti-19A-M1 (N=138,25,166,37,276)        | 0.04 (0.03 to 0.04)                  |  |  |  |
| Anti-19A-M12 (N=139,25,168,36,284)       | 0.06 (0.05 to 0.07)                  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Opsonophagocytic activity (OPA) titers against pneumococcal cross-reactive serotypes 6A and 19A

|                 |   |
|-----------------|---|
| End point title | Opsonophagocytic activity (OPA) titers against pneumococcal cross-reactive serotypes 6A and 19A |
|-----------------|---|

End point description:

OPA titers against pneumococcal serotypes 6A and 19A (Opsono-6A and 19A) were calculated, expressed as geometric mean titers (GMTs) and tabulated. The seropositivity cut-off for the assay was  $\geq 8$ .

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Prior to booster vaccination (PRE), 1 month (M1) and 12 months (M12) post-booster vaccination |           |

| End point values                         | Synflorix I Group    | Synflorix II Group    | Synflorix PRE Group    | Synflorix POST Group   |
|--|----------------------|-----------------------|------------------------|------------------------|
| Subject group type                       | Reporting group      | Reporting group       | Reporting group        | Reporting group        |
| Number of subjects analysed              | 129                  | 22                    | 153                    | 33                     |
| Units: Titers                            |                      |                       |                        |                        |
| geometric mean (confidence interval 95%) |                      |                       |                        |                        |
| OPSONO-6A-PRE (N=116,19,139,20,24)       | 72.4 (48.3 to 108.4) | 35.6 (12.2 to 104.1)  | 65.4 (45.7 to 93.7)    | 66 (25.7 to 169.5)     |
| OPSONO-6A-M1 (N=124,21,149,31,16)        | 251.5 (180.2 to 351) | 105.1 (40.6 to 271.8) | 401.7 (319.5 to 505.2) | 403.7 (253.5 to 642.9) |
| OPSONO-6A-M12 (N=111,17,131,29,115)      | 59.4 (38.8 to 91)    | 23 (8.4 to 62.6)      | 52.1 (35.6 to 76.3)    | 37.2 (17.5 to 79)      |
| OPSONO-19A-PRE (N=118,21,141,28,36)      | 5 (4.3 to 5.7)       | 4.9 (3.2 to 7.3)      | 4.8 (4.3 to 5.4)       | 5 (3.6 to 6.9)         |
| OPSONO-19A-M1 (N=129,18,151,31,45)       | 39.2 (26.4 to 58.2)  | 39.7 (11.5 to 137.4)  | 89.7 (61.2 to 131.6)   | 99.6 (40.8 to 243.1)   |
| OPSONO-19A-M12 (N=127,22,153,33,131)     | 7 (5.5 to 8.8)       | 4.8 (3.6 to 6.5)      | 8.9 (7.1 to 11.1)      | 9.5 (5.6 to 16.1)      |

| End point values                         | Mencevax + Infanrix Hexa Group |  |  |  |
|--|--------------------------------|--|--|--|
| Subject group type                       | Reporting group                |  |  |  |
| Number of subjects analysed              | 131                            |  |  |  |
| Units: Titers                            |                                |  |  |  |
| geometric mean (confidence interval 95%) |                                |  |  |  |
| OPSONO-6A-PRE (N=116,19,139,20,24)       | 9.7 (4.7 to 20)                |  |  |  |
| OPSONO-6A-M1 (N=124,21,149,31,16)        | 16.1 (5 to 52)                 |  |  |  |
| OPSONO-6A-M12 (N=111,17,131,29,115)      | 17.1 (11.7 to 24.9)            |  |  |  |
| OPSONO-19A-PRE (N=118,21,141,28,36)      | 4 (4 to 4)                     |  |  |  |
| OPSONO-19A-M1 (N=129,18,151,31,45)       | 4 (4 to 4)                     |  |  |  |
| OPSONO-19A-M12 (N=127,22,153,33,131)     | 4.7 (4.2 to 5.2)               |  |  |  |

## Statistical analyses

**Secondary: Number of subjects with serum bactericidal antibodies, using baby rabbit complement for assay (rSBA) titres  $\geq$  the cut-off values**

|                 |  |
|-----------------|--|
| End point title | Number of subjects with serum bactericidal antibodies, using baby rabbit complement for assay (rSBA) titres $\geq$ the cut-off values <sup>[4]</sup> |
|-----------------|--|

## End point description:

The cut-off values assessed were 1:8 and 1:128 for meningococcal polysaccharides A , C, W-135 and Y serum bactericidal antibodies, using baby rabbit complement for assay (rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY). Results were only tabulated for subjects who received a vaccine including the respective antigens (Mencevax + Infanrix Hexa Group).

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

## End point timeframe:

Prior to vaccination (PRE), 1 month (M1) and 12 months (M12) post-vaccination

## Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group.

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 301                                  |  |  |  |
| Units: Subjects                          |                                      |  |  |  |
| rSBA-MenA,Pre, $\geq$ 1:8 [N=244]        | 69                                   |  |  |  |
| rSBA-MenA, Pre, $\geq$ 1:128 [N=244]     | 44                                   |  |  |  |
| rSBA-MenA, M1, $\geq$ 1:8 [N=299]        | 298                                  |  |  |  |
| rSBA-MenA, M1, $\geq$ 1:128 [N=299]      | 298                                  |  |  |  |
| rSBA-MenA, M12, $\geq$ 1:8 [N=136]       | 136                                  |  |  |  |
| rSBA-MenA, M12, $\geq$ 1:128 [N=136]     | 134                                  |  |  |  |
| rSBA-MenC,Pre, $\geq$ 1:8 [N=295]        | 50                                   |  |  |  |
| rSBA-MenC, Pre, $\geq$ 1:128 [N=295]     | 17                                   |  |  |  |
| rSBA-MenC, M1, $\geq$ 1:8 [N=301]        | 300                                  |  |  |  |
| rSBA-MenC, M1, $\geq$ 1:128 [N=301]      | 294                                  |  |  |  |
| rSBA-MenC, M12, $\geq$ 1:8 [N=161]       | 154                                  |  |  |  |
| rSBA-MenC, M12, $\geq$ 1:128 [N=161]     | 105                                  |  |  |  |
| rSBA-MenW-135,Pre, $\geq$ 1:8 [N=287]    | 114                                  |  |  |  |
| rSBA-MenW-135, Pre, $\geq$ 1:128 [N=287] | 59                                   |  |  |  |
| rSBA-MenW-135, M1, $\geq$ 1:8 [N=301]    | 301                                  |  |  |  |
| rSBA-MenW-135, M1, $\geq$ 1:128 [N=301]  | 301                                  |  |  |  |
| rSBA-MenW-135, M12, $\geq$ 1:8 [N=139]   | 138                                  |  |  |  |
| rSBA-MenW-135, M12, $\geq$ 1:128 [N=139] | 129                                  |  |  |  |
| rSBA-MenY,Pre, $\geq$ 1:8 [N=297]        | 167                                  |  |  |  |
| rSBA-MenY, Pre, $\geq$ 1:128 [N=297]     | 93                                   |  |  |  |
| rSBA-MenY, M1, $\geq$ 1:8 [N=301]        | 300                                  |  |  |  |
| rSBA-MenY, M1, $\geq$ 1:128 [N=301]      | 300                                  |  |  |  |
| rSBA-MenY, M12, $\geq$ 1:8 [N=138]       | 137                                  |  |  |  |
| rSBA-MenY, M12, $\geq$ 1:128 [N=138]     | 127                                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titers in the Mencevax + Infanrix Hexa Group

|                 |   |
|-----------------|---|
| End point title | rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY titers in the Mencevax + Infanrix Hexa Group <sup>[5]</sup> |
|-----------------|---|

End point description:

Results were only tabulated for subjects who received a vaccine including the respective antigens (Mencevax + Infanrix Hexa Group).

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

End point timeframe:

Prior to vaccination (PRE), 1 month (M1) and 12 months (M12) post vaccination

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group.

| End point values                         | Mencevax + Infanrix Hexa Group |  |  |  |
|--|--------------------------------|--|--|--|
| Subject group type                       | Reporting group                |  |  |  |
| Number of subjects analysed              | 301                            |  |  |  |
| Units: Titers                            |                                |  |  |  |
| geometric mean (confidence interval 95%) |                                |  |  |  |
| rSBA-MenA,Pre [N=244]                    | 11.5 (9.2 to 14.3)             |  |  |  |
| rSBA-MenA, M1 [N=299]                    | 2151.3 (1927.4 to 2401.2)      |  |  |  |
| rSBA-MenA, M12 [N=136]                   | 677.6 (579.9 to 791.8)         |  |  |  |
| rSBA-MenC,Pre [N=295]                    | 6.9 (6 to 8)                   |  |  |  |
| rSBA-MenC, M1 [N=301]                    | 811.2 (728 to 904)             |  |  |  |
| rSBA-MenC, M12 [N=161]                   | 191.1 (153.5 to 238)           |  |  |  |
| rSBA-MenW-135,Pre [N=287]                | 16.3 (13.2 to 20.1)            |  |  |  |
| rSBA-MenW-135, M1 [N=301]                | 5393.6 (4888.2 to 5951.1)      |  |  |  |
| rSBA-MenW-135, M12 [N=139]               | 573.1 (479.3 to 685.3)         |  |  |  |
| rSBA-MenY,Pre [N=297]                    | 30.2 (24.2 to 37.7)            |  |  |  |
| rSBA-MenY, M1 [N=301]                    | 2863.7 (2537.8 to 3231.4)      |  |  |  |

|                        |                        |  |  |  |
|------------------------|------------------------|--|--|--|
| rSBA-MenY, M12 [N=138] | 665.2 (547.9 to 807.7) |  |  |  |
|------------------------|------------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with anti-polysaccharide N (anti-PS) concentrations $\geq$ the cut-off value

|                 |  |
|-----------------|--|
| End point title | Number of subjects with anti-polysaccharide N (anti-PS) concentrations $\geq$ the cut-off value <sup>[6]</sup> |
|-----------------|--|

End point description:

Anti-PS assessed were anti-PS meningitidis serogroup A (anti-PSA), C (anti-PSC), W (anti-PSW-135) and Y (anti-PSY). The cut-offs for anti-PS concentrations were 0.3 µg/mL and 2.0 µg/mL, tabulated for subjects who received a vaccine including the respective antigens (Mencevax + Infanrix Hexa Group).

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

End point timeframe:

Prior to vaccination (PRE), 1 month (M1) and 12 months (M12) post vaccination

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group.

| End point values                         | Mencevax + Infanrix Hexa Group |  |  |  |
|--|--------------------------------|--|--|--|
| Subject group type                       | Reporting group                |  |  |  |
| Number of subjects analysed              | 278                            |  |  |  |
| Units: Subjects                          |                                |  |  |  |
| ANTI-PSA PRE(N=246) $\geq$ 0.3 µg/mL     | 12                             |  |  |  |
| ANTI-PSA PRE(N=246) $\geq$ 2.0 µg/mL     | 1                              |  |  |  |
| ANTI-PSA M1(N=272) $\geq$ 0.3 µg/mL      | 271                            |  |  |  |
| ANTI-PSA M1(N=272) $\geq$ 2.0 µg/mL      | 271                            |  |  |  |
| ANTI-PSA M12(N=153) $\geq$ 0.3 µg/mL     | 133                            |  |  |  |
| ANTI-PSA M12(N=153) $\geq$ 2.0 µg/mL     | 47                             |  |  |  |
| ANTI-PSC PRE(N=269) $\geq$ 0.3 µg/mL     | 3                              |  |  |  |
| ANTI-PSC PRE(N=269) $\geq$ 2.0 µg/mL     | 0                              |  |  |  |
| ANTI-PSC M1(N=278) $\geq$ 0.3 µg/mL      | 278                            |  |  |  |
| ANTI-PSC M1(N=278) $\geq$ 2.0 µg/mL      | 277                            |  |  |  |
| ANTI-PSC M12(N=157) $\geq$ 0.3 µg/mL     | 94                             |  |  |  |
| ANTI-PSC M12(N=157) $\geq$ 2.0 µg/mL     | 9                              |  |  |  |
| ANTI-PSW-135 PRE(N=236) $\geq$ 0.3 µg/mL | 1                              |  |  |  |
| ANTI-PSW-135 PRE(N=236) $\geq$ 2.0 µg/mL | 0                              |  |  |  |
| ANTI-PSW-135 M1(N=259) $\geq$ 0.3 µg/mL  | 258                            |  |  |  |
| ANTI-PSW-135 M1(N=259) $\geq$ 2.0 µg/mL  | 234                            |  |  |  |
| ANTI-PSW-135 M12(N=132) $\geq$ 0.3 µg/mL | 117                            |  |  |  |
| ANTI-PSW-135 M12(N=132) $\geq$ 2.0 µg/mL | 45                             |  |  |  |
| ANTI-PSY PRE(N=261) $\geq$ 0.3 µg/mL     | 3                              |  |  |  |
| ANTI-PSY PRE(N=261) $\geq$ 2.0 µg/mL     | 0                              |  |  |  |
| ANTI-PSY M1(N=263) $\geq$ 0.3 µg/mL      | 261                            |  |  |  |

|                               |     |  |  |  |
|-------------------------------|-----|--|--|--|
| ANTI-PSY M1(N=263)≥2.0 µg/mL  | 249 |  |  |  |
| ANTI-PSY M12(N=135)≥0.3 µg/mL | 131 |  |  |  |
| ANTI-PSY M12(N=135)≥2.0 µg/mL | 59  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean antibody concentration (GMCs) for anti-polysaccharide N (anti-PS) antibody concentrations

|                 |   |
|-----------------|---|
| End point title | Geometric mean antibody concentration (GMCs) for anti-polysaccharide N (anti-PS) antibody concentrations <sup>[7]</sup> |
|-----------------|---|

End point description:

Anti-PS assessed were Anti-PSA, anti-PSC, anti-PSW-135 and anti-PSY. Results were only tabulated for subjects who received a vaccine including the respective antigens (Mencevax + Infanrix Hexa Group).

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

End point timeframe:

Prior to vaccination (PRE), 1 month (M1) and 12 months (M12) post vaccination

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group.

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 278                                  |  |  |  |
| Units: µg/mL                             |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-PSA, Pre [N=246]                    | 0.16 (0.15 to 0.17)                  |  |  |  |
| Anti-PSA, M1 [N=272]                     | 36.28 (32.8 to 40.15)                |  |  |  |
| Anti-PSA, M12 [N=153]                    | 0.99 (0.82 to 1.19)                  |  |  |  |
| Anti-PSC, Pre [N=269]                    | 0.15 (0.15 to 0.16)                  |  |  |  |
| Anti-PSC, M1 [N=278]                     | 14.12 (13 to 15.32)                  |  |  |  |
| Anti-PSC, M12 [N=157]                    | 0.42 (0.36 to 0.49)                  |  |  |  |
| Anti-PSW-135, Pre [N=236]                | 0.15 (0.15 to 0.15)                  |  |  |  |
| Anti-PSW-135, M1 [N=259]                 | 6.11 (5.45 to 6.86)                  |  |  |  |
| Anti-PSW-135, M12 [N=132]                | 1.21 (0.98 to 1.48)                  |  |  |  |
| Anti-PSY, Pre [N=261]                    | 0.15 (0.15 to 0.16)                  |  |  |  |
| Anti-PSY, M1 [N=263]                     | 8.03 (7.17 to 8.99)                  |  |  |  |
| Anti-PSY, M12 [N=135]                    | 1.81 (1.5 to 2.19)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-tetanus toxoids (anti-T) antibody concentrations in the Mencevax + Infanrix Hexa Group

|                 |  |
|-----------------|--|
| End point title | Anti-tetanus toxoids (anti-T) antibody concentrations in the Mencevax + Infanrix Hexa Group <sup>[8]</sup> |
|-----------------|--|

End point description:

The seroprotection cut-off for the assay was  $\geq 0.1$  international units per milliliter (IU/mL).

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

End point timeframe:

Prior to vaccination (Pre)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group.

| End point values                         | Mencevax + Infanrix Hexa Group |  |  |  |
|--|--------------------------------|--|--|--|
| Subject group type                       | Reporting group                |  |  |  |
| Number of subjects analysed              | 266                            |  |  |  |
| Units: IU/mL                             |                                |  |  |  |
| geometric mean (confidence interval 95%) |                                |  |  |  |
| Anti-T, Pre [266]                        | 0.512 (0.456 to 0.575)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-hepatitis B surface antigen (anti-HBs) antibody concentrations in the Mencevax + Infanrix Hexa Group

|                 |  |
|-----------------|--|
| End point title | Anti-hepatitis B surface antigen (anti-HBs) antibody concentrations in the Mencevax + Infanrix Hexa Group <sup>[9]</sup> |
|-----------------|--|

End point description:

The seroprotection cut-off for the assay was  $\geq 10$  mIU/mL. Results were only tabulated for subjects who received a vaccine including the respective antigens (Mencevax + Infanrix Hexa Group).

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

End point timeframe:

Prior to vaccination (Pre)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group.

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 2                                    |  |  |  |
| Units: mIU/mL                            |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-HBs, Pre [2]                        | 1336.1 (52.3<br>to 34160.2)          |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Concentrations of antibodies against diphtheria and tetanus toxoids (anti-D and T)

|  |  |
|--|--|
| End point title  | Concentrations of antibodies against diphtheria and tetanus toxoids (anti-D and T) |
| End point description:<br>The seroprotection cut-off for the assay was $\geq 0.1$ IU/mL. |  |
| End point type   | Secondary  |
| End point timeframe:<br>1 month post-vaccination (M1)                                    |  |

| End point values                         | Synflorix I<br>Group        | Synflorix II<br>Group     | Synflorix PRE<br>Group     | Synflorix POST<br>Group   |
|--|-----------------------------|---------------------------|----------------------------|---------------------------|
| Subject group type                       | Reporting group             | Reporting group           | Reporting group            | Reporting group           |
| Number of subjects analysed              | 140                         | 24                        | 167                        | 37                        |
| Units: IU/mL                             |                             |                           |                            |                           |
| geometric mean (confidence interval 95%) |                             |                           |                            |                           |
| Anti-D, M1 (N=140,24,166,37,245)         | 10.112 (9.042<br>to 11.309) | 9.839 (7.475<br>to 12.95) | 12.285 (11.18<br>to 13.5)  | 11 (8.786 to<br>13.77)    |
| Anti-T, M1 (N=139,24,167,37,245)         | 7.382 (6.639<br>to 8.208)   | 8.684 (6.37 to<br>11.839) | 9.583 (8.927<br>to 10.287) | 8.196 (6.829<br>to 9.837) |

| End point values            | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 245                                  |  |  |  |
| Units: IU/mL                |                                      |  |  |  |

|  |                          |  |  |  |
|--|--------------------------|--|--|--|
| geometric mean (confidence interval 95%) |                          |  |  |  |
| Anti-D, M1 (N=140,24,166,37,245)         | 7.291 (6.592 to 8.064)   |  |  |  |
| Anti-T, M1 (N=139,24,167,37,245)         | 11.79 (10.684 to 13.011) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations

|                        |   |
|------------------------|---|
| End point title        | Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations |
| End point description: | The seropositivity cut-off for the assay was $\geq 5$ ELISA units per milliliter (EL.U/mL).                                       |
| End point type         | Secondary   |
| End point timeframe:   | 1 month post-vaccination (M1)   |

| End point values                         | Synflorix I Group      | Synflorix II Group     | Synflorix PRE Group    | Synflorix POST Group   |
|--|------------------------|------------------------|------------------------|------------------------|
| Subject group type                       | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed              | 140                    | 24                     | 167                    | 37                     |
| Units: EL.U/mL                           |                        |                        |                        |                        |
| geometric mean (confidence interval 95%) |                        |                        |                        |                        |
| Anti-PT, M1 (N=138,24,166,36,248)        | 83.3 (73.8 to 94)      | 81.6 (62.2 to 106.9)   | 82 (73.4 to 91.7)      | 76.7 (62.2 to 94.4)    |
| Anti-FHA, M1 (N=140,24,167,37,251)       | 467.9 (422.4 to 518.3) | 431.1 (318.8 to 582.9) | 453.8 (412.6 to 499.1) | 400.4 (321.8 to 498.2) |
| Anti-PRN, M1 (N=140,24,167,36,246)       | 222.8 (193.9 to 256)   | 153.4 (97.5 to 241.2)  | 254.9 (225.8 to 287.8) | 220.4 (168.7 to 288)   |

| End point values                         | Mencevax + Infanrix Hexa Group |  |  |  |
|--|--------------------------------|--|--|--|
| Subject group type                       | Reporting group                |  |  |  |
| Number of subjects analysed              | 251                            |  |  |  |
| Units: EL.U/mL                           |                                |  |  |  |
| geometric mean (confidence interval 95%) |                                |  |  |  |
| Anti-PT, M1 (N=138,24,166,36,248)        | 163.1 (143 to 185.9)           |  |  |  |
| Anti-FHA, M1 (N=140,24,167,37,251)       | 580.8 (532.2 to 633.8)         |  |  |  |

|                                    |                        |  |  |  |
|------------------------------------|------------------------|--|--|--|
| Anti-PRN, M1 (N=140,24,167,36,246) | 350.7 (316.8 to 388.3) |  |  |  |
|------------------------------------|------------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Anti-hepatitis B surface antigen (anti-HBs) antibody concentrations

|  |   |
|--|---|
| End point title  | Anti-hepatitis B surface antigen (anti-HBs) antibody concentrations |
| End point description:<br>The seroprotection cut-off for the assay was $\geq 10$ mIU/mL. Dummy LL (0.0) and UL (99999.9) are entered when number of subjects analysed = 1. |   |
| End point type   | Secondary   |
| End point timeframe:<br>1 month post-vaccination (M1)  |   |

| End point values                         | Synflorix I Group         | Synflorix II Group       | Synflorix PRE Group   | Synflorix POST Group      |
|--|---------------------------|--------------------------|-----------------------|---------------------------|
| Subject group type                       | Reporting group           | Reporting group          | Reporting group       | Reporting group           |
| Number of subjects analysed              | 105                       | 16                       | 130                   | 26                        |
| Units: mIU/mL                            |                           |                          |                       |                           |
| geometric mean (confidence interval 95%) |                           |                          |                       |                           |
| Anti-HBs, M1                             | 1883.9 (1332.9 to 2662.7) | 1460.6 (816.4 to 2613.2) | 2133 (1615 to 2817.1) | 1818.5 (1142.8 to 2893.6) |

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 1                                    |  |  |  |
| Units: mIU/mL                            |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-HBs, M1                             | 20610 (0 to 99999.9)                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Anti-polyribosyl-ribitol phosphate (anti-PRP) antibody concentrations**

|                 |   |
|-----------------|---|
| End point title | Anti-polyribosyl-ribitol phosphate (anti-PRP) antibody concentrations |
|-----------------|---|

End point description:

The seroprotection cut-off for the assay was  $\geq 0.15$   $\mu\text{g/mL}$ .

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

End point timeframe:

1 month post-vaccination (M1)

| End point values                         | Synflorix I Group         | Synflorix II Group       | Synflorix PRE Group       | Synflorix POST Group      |
|--|---------------------------|--------------------------|---------------------------|---------------------------|
| Subject group type                       | Reporting group           | Reporting group          | Reporting group           | Reporting group           |
| Number of subjects analysed              | 141                       | 24                       | 167                       | 36                        |
| Units: $\mu\text{g/mL}$                  |                           |                          |                           |                           |
| geometric mean (confidence interval 95%) |                           |                          |                           |                           |
| Anti-PRP, M1                             | 23.066 (18.806 to 28.291) | 26.006 (15.56 to 43.463) | 27.373 (22.915 to 32.697) | 22.011 (16.288 to 29.745) |

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 269                                  |  |  |  |
| Units: $\mu\text{g/mL}$                  |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-PRP, M1                             | 20.985 (17.966 to 24.511)            |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Anti-poliovirus (Anti-Polio) types 1, 2 and 3 titers**

|                 |  |
|-----------------|--|
| End point title | Anti-poliovirus (Anti-Polio) types 1, 2 and 3 titers |
|-----------------|--|

End point description:

The seroprotection cut-off for the assay was  $\geq 8$ . Dummy LL (0.0) and UL (99999.9) are entered when number of subjects analysed = 1.

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

End point timeframe:

1 month post-vaccination (M1)

| End point values                         | Synflorix I Group         | Synflorix II Group      | Synflorix PRE Group       | Synflorix POST Group      |
|--|---------------------------|-------------------------|---------------------------|---------------------------|
| Subject group type                       | Reporting group           | Reporting group         | Reporting group           | Reporting group           |
| Number of subjects analysed              | 93                        | 12                      | 114                       | 23                        |
| Units: Titers                            |                           |                         |                           |                           |
| geometric mean (confidence interval 95%) |                           |                         |                           |                           |
| Anti-Polio 1, M1 (N=93,12,114,23,1)      | 1193 (993.8 to 1432.2)    | 1534.2 (952 to 2472.5)  | 1058.7 (870.2 to 1288)    | 1208.6 (764.2 to 1911.2)  |
| Anti-Polio 2, M1 (N=93,12,113,22,1)      | 1354.1 (1115.8 to 1643.3) | 2047.9 (1246 to 3365.9) | 1413.2 (1174.3 to 1700.7) | 2215.8 (1544.4 to 3178.9) |
| Anti-Polio 3, M1 (N=92,12,114,23,1)      | 2354.2 (1946.1 to 2847.9) | 2233.3 (1300.9 to 3834) | 2647.5 (2221.5 to 3155.3) | 3576.5 (2617.3 to 4887.2) |

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 1                                    |  |  |  |
| Units: Titers                            |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-Polio 1, M1 (N=93,12,114,23,1)      | 4096 (0 to 99999.9)                  |  |  |  |
| Anti-Polio 2, M1 (N=93,12,113,22,1)      | 8192 (0 to 99999.9)                  |  |  |  |
| Anti-Polio 3, M1 (N=92,12,114,23,1)      | 8192 (0 to 99999.9)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Anti-hepatitis B surface antigen (Anti-HBs) antibody concentrations

|                 |   |
|-----------------|---|
| End point title | Anti-hepatitis B surface antigen (Anti-HBs) antibody concentrations |
|-----------------|---|

End point description:

The seroprotection cut-off for the assay was  $\geq 10$  mIU/mL.

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

End point timeframe:

12 month post-vaccination (M12)

| End point values                         | Synflorix I Group      | Synflorix II Group    | Synflorix PRE Group    | Synflorix POST Group  |
|--|------------------------|-----------------------|------------------------|-----------------------|
| Subject group type                       | Reporting group        | Reporting group       | Reporting group        | Reporting group       |
| Number of subjects analysed              | 107                    | 16                    | 133                    | 20                    |
| Units: mIU/mL                            |                        |                       |                        |                       |
| geometric mean (confidence interval 95%) |                        |                       |                        |                       |
| Anti-HBs, M12                            | 219.3 (164.8 to 291.7) | 147.3 (62.6 to 346.9) | 231.2 (179.7 to 297.6) | 139.2 (74.3 to 260.9) |

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 19                                   |  |  |  |
| Units: mIU/mL                            |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-HBs, M12                            | 535.1 (277.8 to 1030.6)              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-poliovirus (Anti-Polio) type 1, 2 and 3 titers

|  |   |
|--|---|
| End point title  | Anti-poliovirus (Anti-Polio) type 1, 2 and 3 titers |
| End point description:<br>The seroprotection cut-off for the assay was $\geq 8$ . Dummy lower limit (LL) (0.0) and upper limit UL (99999.9) were entered when number of subjects analysed = 1. |   |
| End point type   | Secondary   |
| End point timeframe:<br>12 month post-vaccination (M12)  |   |

| End point values                         | Synflorix I Group      | Synflorix II Group    | Synflorix PRE Group    | Synflorix POST Group  |
|--|------------------------|-----------------------|------------------------|-----------------------|
| Subject group type                       | Reporting group        | Reporting group       | Reporting group        | Reporting group       |
| Number of subjects analysed              | 97                     | 13                    | 122                    | 14                    |
| Units: Titers                            |                        |                       |                        |                       |
| geometric mean (confidence interval 95%) |                        |                       |                        |                       |
| Anti-Polio 1, M12 (N=97,13,122,14,9)     | 208.2 (164.7 to 263.2) | 150.4 (87.2 to 259.3) | 234.5 (189.5 to 290.3) | 220.8 (92.3 to 528.2) |
| Anti-Polio 2, M12 (N=96,13,122,14,9)     | 311.2 (241.5 to 401)   | 212.4 (100.5 to 449)  | 310.6 (256 to 376.9)   | 400 (218.6 to 732.1)  |
| Anti-Polio 3, M12 (N=97,13,122,14,9)     | 431.3 (332.4 to 559.5) | 301 (125.8 to 720.4)  | 506.3 (406.3 to 630.7) | 672.2 (330 to 1369.4) |

| End point values                         | Mencevax +<br>Infanrix Hexa<br>Group |  |  |  |
|--|--------------------------------------|--|--|--|
| Subject group type                       | Reporting group                      |  |  |  |
| Number of subjects analysed              | 9                                    |  |  |  |
| Units: Titers                            |                                      |  |  |  |
| geometric mean (confidence interval 95%) |                                      |  |  |  |
| Anti-Polio 1, M12 (N=97,13,122,14,9)     | 335.4 (146.4 to 768.2)               |  |  |  |
| Anti-Polio 2, M12 (N=96,13,122,14,9)     | 322.7 (172.9 to 602.3)               |  |  |  |
| Anti-Polio 3, M12 (N=97,13,122,14,9)     | 203.3 (63.7 to 649.2)                |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of nasopharyngeal swabs with S.pneumoniae (vaccine serotypes)

|                 |  |
|-----------------|--|
| End point title | Number of nasopharyngeal swabs with S.pneumoniae (vaccine serotypes) <sup>[10]</sup> |
|-----------------|--|

End point description:

Results were tabulated on Pooled Synflorix Group and on Mencevax + Infanrix Hexa Group.

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

End point timeframe:

Prior to vaccination (Pre), 1 month post-vaccination (M1), 3 months post-vaccination (M3), 7 months post-vaccination (M7), 12 months post-vaccination (M12) and across all time points (Overall)

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group and Pooled Synflorix Group.

| End point values            | Mencevax +<br>Infanrix Hexa<br>Group | Pooled<br>Synflorix Group |  |  |
|-----------------------------|--------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                      | Subject analysis set      |  |  |
| Number of subjects analysed | 336                                  | 414                       |  |  |
| Units: Swabs                |                                      |                           |  |  |
| Pre (N=330,407)             | 53                                   | 43                        |  |  |
| M1 (N=332,408)              | 47                                   | 45                        |  |  |
| M3 (N=332,408)              | 55                                   | 49                        |  |  |
| M7 (N=334,406)              | 50                                   | 42                        |  |  |
| M12 (N=334,409)             | 43                                   | 34                        |  |  |
| Overall (N=336,414)         | 115                                  | 111                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of nasopharyngeal swabs with S.pneumoniae (cross-reactive serotypes)

|                 |   |
|-----------------|---|
| End point title | Number of nasopharyngeal swabs with S.pneumoniae (cross-reactive serotypes) <sup>[11]</sup> |
|-----------------|---|

End point description:

Results were tabulated on Pooled Synflorix Group and on Mencevax + Infanrix Hexa Group.

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

End point timeframe:

Prior to vaccination (Pre), 1 month post-vaccination (M1), 3 months post-vaccination (M3), 7 months post-vaccination (M7), 12 months post-vaccination (M12) and across all time points (Overall)

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group and Pooled Synflorix Group.

| End point values            | Mencevax +<br>Infanrix Hexa<br>Group | Pooled<br>Synflorix Group |  |  |
|-----------------------------|--------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                      | Subject analysis set      |  |  |
| Number of subjects analysed | 336                                  | 414                       |  |  |
| Units: Swabs                |                                      |                           |  |  |
| Pre (N=330,407)             | 13                                   | 15                        |  |  |
| M1 (N=332,408)              | 19                                   | 22                        |  |  |
| M3 (N=332,408)              | 21                                   | 27                        |  |  |
| M7 (N=334,406)              | 19                                   | 21                        |  |  |
| M12 (N=334,409)             | 19                                   | 18                        |  |  |
| Overall (N=336,414)         | 55                                   | 59                        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of nasopharyngeal swabs with S.pneumoniae (non-vaccine and non-cross-reactive serotypes)

|                 |   |
|-----------------|---|
| End point title | Number of nasopharyngeal swabs with S.pneumoniae (non-vaccine and non-cross-reactive serotypes) <sup>[12]</sup> |
|-----------------|---|

End point description:

Results were tabulated on Mencevax + Infanrix Hexa Group and on Pooled Synflorix Group.

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

End point timeframe:

Prior to vaccination (Pre), 1 month post-vaccination (M1), 3 months post-vaccination (M3), 7 months post-vaccination (M7), 12 months post-vaccination (M12) and across all time points (Overall)

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group and Pooled Synflorix Group.

| End point values            | Mencevax +<br>Infanrix Hexa<br>Group | Pooled<br>Synflorix Group |  |  |
|-----------------------------|--------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                      | Subject analysis set      |  |  |
| Number of subjects analysed | 336                                  | 414                       |  |  |
| Units: Swabs                |                                      |                           |  |  |
| Pre (N=330,407)             | 26                                   | 27                        |  |  |
| M1 (N=332,408)              | 30                                   | 42                        |  |  |
| M3 (N=332,408)              | 32                                   | 45                        |  |  |
| M7 (N=334,406)              | 29                                   | 42                        |  |  |
| M12 (N=334,409)             | 22                                   | 39                        |  |  |
| Overall (N=336,414)         | 82                                   | 111                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of nasopharyngeal swabs with H. influenzae

|                 |   |
|-----------------|---|
| End point title | Number of nasopharyngeal swabs with H. influenzae <sup>[13]</sup> |
|-----------------|---|

End point description:

Results were tabulated on Mencevax + Infanrix Hexa Group and on Pooled Synflorix Group.

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

End point timeframe:

Prior to vaccination (Pre), 1 month post-vaccination (M1), 3 months post-vaccination (M3), 7 months post-vaccination (M7), 12 months post-vaccination (M12) and across all time points (Overall)

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group and Pooled Synflorix Group.

| End point values            | Mencevax +<br>Infanrix Hexa<br>Group | Pooled<br>Synflorix Group |  |  |
|-----------------------------|--------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                      | Subject analysis set      |  |  |
| Number of subjects analysed | 336                                  | 414                       |  |  |
| Units: Swabs                |                                      |                           |  |  |
| Pre (N=312,397)             | 41                                   | 48                        |  |  |
| M1 (N=318,402)              | 39                                   | 56                        |  |  |
| M3 (N=328,403)              | 34                                   | 62                        |  |  |
| M7 (N=332,403)              | 49                                   | 64                        |  |  |
| M12 (N=333,406)             | 57                                   | 46                        |  |  |

|                     |     |     |  |  |
|---------------------|-----|-----|--|--|
| Overall (N=336,414) | 124 | 160 |  |  |
|---------------------|-----|-----|--|--|

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of nasopharyngeal swabs with *S. pneumoniae* and *H. influenzae*

|                 |   |
|-----------------|---|
| End point title | Number of nasopharyngeal swabs with <i>S. pneumoniae</i> and <i>H. influenzae</i> <sup>[14]</sup> |
|-----------------|---|

End point description:

Results were tabulated on Mencevax + Infanrix Hexa Group and on Pooled Synflorix Group.

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

End point timeframe:

Prior to vaccination (Pre), 1 month post-vaccination (M1), 3 months post-vaccination (M3), 7 months post-vaccination (M7), 12 months post-vaccination (M12) and across all time points (Overall)

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group and Pooled Synflorix Group.

| End point values            | Mencevax + Infanrix Hexa Group | Pooled Synflorix Group |  |  |
|-----------------------------|--------------------------------|------------------------|--|--|
| Subject group type          | Reporting group                | Subject analysis set   |  |  |
| Number of subjects analysed | 336                            | 414                    |  |  |
| Units: Swabs                |                                |                        |  |  |
| Pre (N=312,397)             | 19                             | 21                     |  |  |
| M1 (N=318,402)              | 20                             | 30                     |  |  |
| M3 (N=328,403)              | 17                             | 31                     |  |  |
| M7 (N=332,403)              | 22                             | 28                     |  |  |
| M12 (N=333,406)             | 22                             | 19                     |  |  |
| Overall (N=336,414)         | 61                             | 86                     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with new acquisition associated to *S. pneumoniae* detected in nasopharyngeal swabs

|                 |   |
|-----------------|---|
| End point title | Number of subjects with new acquisition associated to <i>S. pneumoniae</i> detected in nasopharyngeal swabs <sup>[15]</sup> |
|-----------------|---|

End point description:

Results were tabulated on Mencevax + Infanrix Hexa Group and on Pooled Synflorix Group.

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

End point timeframe:

1 month post-vaccination (M1), 3 months post-vaccination (M3), 7 months post-vaccination (M7), 12 months post-vaccination (M12) and across all time points (Overall)

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group and Pooled Synflorix Group.

| End point values            | Mencevax +<br>Infanrix Hexa<br>Group | Pooled<br>Synflorix Group |  |  |
|-----------------------------|--------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                      | Subject analysis set      |  |  |
| Number of subjects analysed | 336                                  | 414                       |  |  |
| Units: Subjects             |                                      |                           |  |  |
| M1 (N=332,408)              | 43                                   | 56                        |  |  |
| M3 (N=332,408)              | 63                                   | 76                        |  |  |
| M7 (N=334,406)              | 70                                   | 73                        |  |  |
| M12 (N=334,409)             | 65                                   | 70                        |  |  |
| Overall (N=336,414)         | 161                                  | 195                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with new acquisition associated to H. influenzae detected in nasopharyngeal swabs

|                 |  |
|-----------------|--|
| End point title | Number of subjects with new acquisition associated to H. influenzae detected in nasopharyngeal swabs <sup>[16]</sup> |
|-----------------|--|

End point description:

Results were tabulated on Mencevax + Infanrix Hexa Group and on Pooled Synflorix Group.

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

End point timeframe:

1 month post-vaccination (M1), 3 months post-vaccination (M3), 7 months post-vaccination (M7), 12 months post-vaccination (M12) and across all time points (Overall)

Notes:

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

Justification: This endpoint is only reporting values for the Mencevax + Infanrix Hexa Group and Pooled Synflorix Group.

| End point values            | Mencevax +<br>Infanrix Hexa<br>Group | Pooled<br>Synflorix Group |  |  |
|-----------------------------|--------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                      | Subject analysis set      |  |  |
| Number of subjects analysed | 336                                  | 414                       |  |  |
| Units: Subjects             |                                      |                           |  |  |
| M1 (N=318,402)              | 21                                   | 32                        |  |  |
| M3 (N=328,403)              | 22                                   | 40                        |  |  |
| M7 (N=332,403)              | 37                                   | 42                        |  |  |
| M12 (N=333,406)             | 39                                   | 35                        |  |  |
| Overall (N=336,414)         | 104                                  | 129                       |  |  |

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Solicited and unsolicited symptoms: during the 31-day (Day 0-Day 30) follow-up periods after vaccination. SAEs: Entire study period (Month 0- Month 12).

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

### Dictionary used

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

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

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Synflorix I Group |
|-----------------------|-------------------|

Reporting group description:

Subjects were vaccinated with 3 primary vaccination doses of Synflorix vaccine with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa along with prophylactic antipyretic treatment.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Synflorix II Group |
|-----------------------|--------------------|

Reporting group description:

Subjects were vaccinated with 3 primary vaccination doses of Synflorix vaccine with prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Synflorix PRE Group |
|-----------------------|---------------------|

Reporting group description:

Subjects were vaccinated with 3 primary vaccination doses of Synflorix vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Synflorix POST Group |
|-----------------------|----------------------|

Reporting group description:

Subjects were vaccinated with 3 primary vaccination doses of 10Pn vaccine without prophylactic administration of paracetamol in study 10PN-PD-DIT-010 (107017), and received in this study at 12-15 months of age a booster dose of 10Pn vaccine, co-administered with Infanrix hexa without prophylactic antipyretic treatment.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Mencevax + Infanrix Hexa Group |
|-----------------------|--------------------------------|

Reporting group description:

Age-matched pneumococcal vaccine unprimed group receiving a single dose of Mencevax co-administered with Infanrix hexa vaccine.

| Serious adverse events                            | Synflorix I Group | Synflorix II Group | Synflorix PRE Group |
|---|-------------------|--------------------|---------------------|
| Total subjects affected by serious adverse events |                   |                    |                     |
| subjects affected / exposed                       | 13 / 178 (7.30%)  | 5 / 27 (18.52%)    | 13 / 172 (7.56%)    |
| number of deaths (all causes)                     | 0                 | 0                  | 0                   |
| number of deaths resulting from adverse events    | 0                 | 0                  | 0                   |
| Injury, poisoning and procedural complications    |                   |                    |                     |
| Concussion  |                   |                    |                     |
| alternative assessment type: Non-systematic       |                   |                    |                     |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 178 (0.56%) | 0 / 27 (0.00%) | 2 / 172 (1.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Fall  |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 2 / 178 (1.12%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Foreign body trauma                             |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 1 / 178 (0.56%) | 1 / 27 (3.70%) | 1 / 172 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Accidental exposure                             |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (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           |
| Head injury                                     |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 1 / 172 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Thermal burn                                    |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 1 / 172 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Caustic injury                                  |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 1 / 172 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

|  |                 |                |                 |
|--|-----------------|----------------|-----------------|
| Pharyngeal injury                                    |                 |                |                 |
| alternative assessment type: Non-systematic          |                 |                |                 |
| subjects affected / exposed                          | 0 / 178 (0.00%) | 1 / 27 (3.70%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Poisoning  |                 |                |                 |
| alternative assessment type: Non-systematic          |                 |                |                 |
| subjects affected / exposed                          | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (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           |
| Skull fracture                                       |                 |                |                 |
| alternative assessment type: Non-systematic          |                 |                |                 |
| subjects affected / exposed                          | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Congenital, familial and genetic disorders           |                 |                |                 |
| Arteriovenous malformation                           |                 |                |                 |
| alternative assessment type: Non-systematic          |                 |                |                 |
| subjects affected / exposed                          | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| Nervous system disorders                             |                 |                |                 |
| Febrile convulsion                                   |                 |                |                 |
| alternative assessment type: Non-systematic          |                 |                |                 |
| subjects affected / exposed                          | 1 / 178 (0.56%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |
| General disorders and administration site conditions |                 |                |                 |
| Pyrexia  |                 |                |                 |
| alternative assessment type: Non-systematic          |                 |                |                 |
| subjects affected / exposed                          | 1 / 178 (0.56%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Blood and lymphatic system disorders            |                 |                |                 |
| Lymphadenopathy                                 |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Reproductive system and breast disorders        |                 |                |                 |
| Testicular retraction                           |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 1 / 172 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                 |                |                 |
| Dyspepsia                                       |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 1 / 178 (0.56%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                |                 |
| Adenoidal hypertrophy                           |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 1 / 178 (0.56%) | 1 / 27 (3.70%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Tonsillar disorder                              |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 1 / 27 (3.70%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                |                 |
| Dermal cyst                                     |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Infections and infestations                     |                 |                |                 |
| Gastroenteritis                                 |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 1 / 178 (0.56%) | 1 / 27 (3.70%) | 2 / 172 (1.16%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Laryngitis                                      |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 2 / 178 (1.12%) | 1 / 27 (3.70%) | 1 / 172 (0.58%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Bronchopneumonia                                |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 2 / 172 (1.16%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastroenteritis rotavirus                       |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 1 / 178 (0.56%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Viral infection                                 |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 1 / 27 (3.70%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Bronchitis                                      |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (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           |
| Tonsillitis                                     |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (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           |
| Nasopharyngitis                                 |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 1 / 178 (0.56%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pyelonephritis                                  |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Otitis media                                    |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 1 / 178 (0.56%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pharyngitis                                     |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (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           |
| Pyelonephritis acute                            |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (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           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Salmonellosis                                   |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 1 / 27 (3.70%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Urinary tract infection                         |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (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           |
| Vulvitis  |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 0 / 172 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                |                 |
| Dehydration                                     |                 |                |                 |
| alternative assessment type: Non-systematic     |                 |                |                 |
| subjects affected / exposed                     | 0 / 178 (0.00%) | 0 / 27 (0.00%) | 1 / 172 (0.58%) |
| 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                            | Synflorix POST Group | Mencevax + Infanrix Hexa Group |  |
|---|----------------------|--------------------------------|--|
| Total subjects affected by serious adverse events |                      |                                |  |
| subjects affected / exposed                       | 4 / 37 (10.81%)      | 30 / 336 (8.93%)               |  |
| number of deaths (all causes)                     | 0                    | 0                              |  |
| number of deaths resulting from adverse events    | 0                    | 0                              |  |
| Injury, poisoning and procedural complications    |                      |                                |  |
| Concussion  |                      |                                |  |
| alternative assessment type: Non-systematic       |                      |                                |  |
| subjects affected / exposed                       | 0 / 37 (0.00%)       | 3 / 336 (0.89%)                |  |
| occurrences causally related to treatment / all   | 0 / 0                | 0 / 3                          |  |
| deaths causally related to treatment / all        | 0 / 0                | 0 / 0                          |  |
| Fall  |                      |                                |  |

|   |                |                 |  |  |
|---|----------------|-----------------|--|--|
| alternative assessment type: Non-systematic     |                |                 |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 2 / 336 (0.60%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |  |
| Foreign body trauma                             |                |                 |  |  |
| alternative assessment type: Non-systematic     |                |                 |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |  |
| Accidental exposure                             |                |                 |  |  |
| alternative assessment type: Non-systematic     |                |                 |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%) | 1 / 336 (0.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |  |
| Head injury                                     |                |                 |  |  |
| alternative assessment type: Non-systematic     |                |                 |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |  |
| Thermal burn                                    |                |                 |  |  |
| alternative assessment type: Non-systematic     |                |                 |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |  |
| Caustic injury                                  |                |                 |  |  |
| alternative assessment type: Non-systematic     |                |                 |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |  |
| Pharyngeal injury                               |                |                 |  |  |
| alternative assessment type: Non-systematic     |                |                 |  |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Poisoning  |                |                 |  |
| alternative assessment type: Non-systematic          |                |                 |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Skull fracture                                       |                |                 |  |
| alternative assessment type: Non-systematic          |                |                 |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Congenital, familial and genetic disorders           |                |                 |  |
| Arteriovenous malformation                           |                |                 |  |
| alternative assessment type: Non-systematic          |                |                 |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Nervous system disorders                             |                |                 |  |
| Febrile convulsion                                   |                |                 |  |
| alternative assessment type: Non-systematic          |                |                 |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) | 2 / 336 (0.60%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| General disorders and administration site conditions |                |                 |  |
| Pyrexia  |                |                 |  |
| alternative assessment type: Non-systematic          |                |                 |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Blood and lymphatic system disorders                 |                |                 |  |
| Lymphadenopathy                                      |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Reproductive system and breast disorders        |                |                 |  |
| Testicular retraction                           |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Dyspepsia                                       |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Adenoidal hypertrophy                           |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Tonsillar disorder                              |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                |                 |  |
| Dermal cyst                                     |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|   |  |   |  |  |
|---|--|---|--|--|
| Infections and infestations<br>Gastroenteritis<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br><br>1 / 37 (2.70%)<br>0 / 1<br>0 / 0 | <br><br>4 / 336 (1.19%)<br>0 / 4<br>0 / 0 |  |  |
| Laryngitis<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                     | <br><br>0 / 37 (0.00%)<br>0 / 0<br>0 / 0 | <br><br>4 / 336 (1.19%)<br>0 / 4<br>0 / 0 |  |  |
| Bronchopneumonia<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                               | <br><br>0 / 37 (0.00%)<br>0 / 0<br>0 / 0 | <br><br>2 / 336 (0.60%)<br>0 / 2<br>0 / 0 |  |  |
| Gastroenteritis rotavirus<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                      | <br><br>1 / 37 (2.70%)<br>0 / 1<br>0 / 0 | <br><br>3 / 336 (0.89%)<br>0 / 3<br>0 / 0 |  |  |
| Viral infection<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | <br><br>0 / 37 (0.00%)<br>0 / 0<br>0 / 0 | <br><br>4 / 336 (1.19%)<br>0 / 4<br>0 / 0 |  |  |
| Bronchitis<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                     | <br><br>0 / 37 (0.00%)<br>0 / 0<br>0 / 0 | <br><br>4 / 336 (1.19%)<br>0 / 4<br>0 / 0 |  |  |
| Tonsillitis<br>alternative assessment type: Non-systematic  |  |   |  |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 37 (2.70%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nasopharyngitis                                 |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pyelonephritis                                  |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 2 / 336 (0.60%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Otitis media                                    |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pharyngitis                                     |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pyelonephritis acute                            |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Salmonellosis                                   |                |                 |  |
| alternative assessment type: Non-systematic     |                |                 |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| Urinary tract infection<br>alternative assessment type: Non-systematic |                |                 |  |
| subjects affected / exposed  | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all                        | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all                             | 0 / 0          | 0 / 0           |  |
| Vulvitis<br>alternative assessment type: Non-systematic                |                |                 |  |
| subjects affected / exposed  | 0 / 37 (0.00%) | 1 / 336 (0.30%) |  |
| occurrences causally related to treatment / all                        | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all                             | 0 / 0          | 0 / 0           |  |
| Metabolism and nutrition disorders                                     |                |                 |  |
| Dehydration<br>alternative assessment type: Non-systematic             |                |                 |  |
| subjects affected / exposed  | 0 / 37 (0.00%) | 0 / 336 (0.00%) |  |
| occurrences causally related to treatment / all                        | 0 / 0          | 0 / 0           |  |
| deaths causally related to treatment / all                             | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                         | Synflorix I Group  | Synflorix II Group | Synflorix PRE Group |
|---|--------------------|--------------------|---------------------|
| Total subjects affected by non-serious adverse events     |                    |                    |                     |
| subjects affected / exposed                               | 153 / 178 (85.96%) | 23 / 27 (85.19%)   | 154 / 172 (89.53%)  |
| General disorders and administration site conditions      |                    |                    |                     |
| Pain  |                    |                    |                     |
| subjects affected / exposed                               | 54 / 178 (30.34%)  | 10 / 27 (37.04%)   | 79 / 172 (45.93%)   |
| occurrences (all)   | 54                 | 10                 | 79                  |
| Redness   |                    |                    |                     |
| subjects affected / exposed                               | 89 / 178 (50.00%)  | 9 / 27 (33.33%)    | 74 / 172 (43.02%)   |
| occurrences (all)   | 89                 | 9                  | 74                  |
| Swelling  |                    |                    |                     |
| subjects affected / exposed                               | 52 / 178 (29.21%)  | 8 / 27 (29.63%)    | 50 / 172 (29.07%)   |
| occurrences (all)   | 52                 | 8                  | 50                  |
| Drowsiness<br>alternative assessment type: Non-systematic |                    |                    |                     |

|   |                         |                        |                           |
|---|-------------------------|------------------------|---------------------------|
| subjects affected / exposed<br>occurrences (all)  | 91 / 178 (51.12%)<br>91 | 11 / 27 (40.74%)<br>11 | 84 / 172 (48.84%)<br>84   |
| Irritability<br>subjects affected / exposed<br>occurrences (all)  | 86 / 178 (48.31%)<br>86 | 17 / 27 (62.96%)<br>17 | 105 / 172 (61.05%)<br>105 |
| Loss of appetite<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                               | 47 / 178 (26.40%)<br>47 | 8 / 27 (29.63%)<br>8   | 46 / 172 (26.74%)<br>46   |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 64 / 178 (35.96%)<br>64 | 14 / 27 (51.85%)<br>14 | 100 / 172 (58.14%)<br>100 |
| Infections and infestations<br>Nasopharyngitis<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 2 / 178 (1.12%)<br>2    | 3 / 27 (11.11%)<br>3   | 4 / 172 (2.33%)<br>4      |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 178 (1.69%)<br>3    | 0 / 27 (0.00%)<br>0    | 2 / 172 (1.16%)<br>2      |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)   | 2 / 178 (1.12%)<br>2    | 0 / 27 (0.00%)<br>0    | 0 / 172 (0.00%)<br>0      |

| <b>Non-serious adverse events</b>  | Synflorix POST Group   | Mencevax + Infanrix Hexa Group |  |
|--|------------------------|--------------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                             | 35 / 37 (94.59%)       | 290 / 336 (86.31%)             |  |
| General disorders and administration site conditions<br>Pain<br>subjects affected / exposed<br>occurrences (all) | 19 / 37 (51.35%)<br>19 | 114 / 336 (33.93%)<br>114      |  |
| Redness<br>subjects affected / exposed<br>occurrences (all)  | 12 / 37 (32.43%)<br>12 | 146 / 336 (43.45%)<br>146      |  |
| Swelling   |                        |                                |  |

|   |                  |                    |  |
|---|------------------|--------------------|--|
| subjects affected / exposed                 | 13 / 37 (35.14%) | 71 / 336 (21.13%)  |  |
| occurrences (all)                           | 13               | 71                 |  |
| Drowsiness                                  |                  |                    |  |
| alternative assessment type: Non-systematic |                  |                    |  |
| subjects affected / exposed                 | 18 / 37 (48.65%) | 146 / 336 (43.45%) |  |
| occurrences (all)                           | 18               | 146                |  |
| Irritability                                |                  |                    |  |
| subjects affected / exposed                 | 19 / 37 (51.35%) | 147 / 336 (43.75%) |  |
| occurrences (all)                           | 19               | 147                |  |
| Loss of appetite                            |                  |                    |  |
| alternative assessment type: Non-systematic |                  |                    |  |
| subjects affected / exposed                 | 10 / 37 (27.03%) | 88 / 336 (26.19%)  |  |
| occurrences (all)                           | 10               | 88                 |  |
| Pyrexia                                     |                  |                    |  |
| subjects affected / exposed                 | 16 / 37 (43.24%) | 146 / 336 (43.45%) |  |
| occurrences (all)                           | 16               | 147                |  |
| Infections and infestations                 |                  |                    |  |
| Nasopharyngitis                             |                  |                    |  |
| alternative assessment type: Non-systematic |                  |                    |  |
| subjects affected / exposed                 | 1 / 37 (2.70%)   | 3 / 336 (0.89%)    |  |
| occurrences (all)                           | 1                | 3                  |  |
| Bronchitis                                  |                  |                    |  |
| subjects affected / exposed                 | 2 / 37 (5.41%)   | 12 / 336 (3.57%)   |  |
| occurrences (all)                           | 2                | 12                 |  |
| Viral infection                             |                  |                    |  |
| subjects affected / exposed                 | 2 / 37 (5.41%)   | 5 / 336 (1.49%)    |  |
| occurrences (all)                           | 2                | 5                  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 18 April 2007 | <p>The amendment was written in response to comments given by the Czech Republic Authorities.</p> <p>In addition the following changes have been included :</p> <ul style="list-style-type: none"><li>• Change in Central Study Coordinator.</li><li>• The microbiological procedures to assess the occurrence of other bacteriological pathogens have been described in more detail.</li><li>• To avoid confusion regarding the administration of DTPa-HBV-IPV/Hib vaccine, this section has been rewritten.</li><li>• Clarification of attribution of subject and treatment numbers to the subjects in the unprimed group.</li><li>• Estimation of sample size of unprimed group has been clarified.</li><li>• Analysis of carriage has been updated in accordance with the microbiological procedures used to assess the occurrence of other bacteriological pathogens.</li><li>• Update of literature references.</li></ul>  |
| 19 July 2007  | <p>As groups were defined as primed and unprimed with regard to pneumococcal vaccination it seemed obvious that the unprimed group was supposed not to have been vaccinated with any pneumococcal vaccine before enrolment. To ensure that the subjects that had previously received a pneumococcal vaccine would not be enrolled or that subjects that received a pneumococcal vaccine during the study would be eliminated, this criterium was added.</p> <ul style="list-style-type: none"><li>• Serology testing with regard to pneumococcal antibodies for the unprimed group was considered scientifically relevant to set a baseline for the interpretation of the carriage results of the primed group. In addition serology testing with regard to antibodies against the co-administered vaccine was added for both groups.</li><li>• As GSK Biologicals is considering an extension study, the possibility to participate in a long-term follow-up study should be addressed at the concluding visit of this study.</li><li>• For the unprimed group the power to detect group difference in carriage of <i>S. pneumoniae</i> and <i>H. influenzae</i> was adjusted to better reflect what was already observed in POET (study Undeca-Pn-010 [347414/010])</li><li>• Update of literature references.</li></ul> |

|                   |  |
|-------------------|--|
| 24 September 2007 | <p>The results of the primary vaccination study 10PN-PD-DIT-010 have shown that paracetamol (acetaminophen) given as a prophylactic treatment at the time of vaccination significantly reduced the incidence of febrile reactions following vaccination with GSK Biologicals. 10-valent pneumococcal conjugate vaccine coadministered with DTPa-HBV-IPV/Hib (Infanrix hexa) vaccine at 3, 4 and 5 months of age and GSK Biologicals. oral live attenuated HRV (Rotarix) vaccine at 3 and 4 months of age [41.6% of subjects experienced fever <math>\geq 38^{\circ}\text{C}</math> (rectal temperature) in the antipyretic group versus 66.1% of subjects in the non-antipyretic group].</p> <p>In addition, the study also showed that the use of prophylactic paracetamol seemed to interfere with the primary immune response. The reason for a decrease in the immune response may relate to a reduction of the inflammatory signals that attract the dendritic cells to the injection sites, such that fewer and/or less activated dendritic cells reach the draining lymph nodes, resulting in a reduced B cell stimulation and lower antibody concentrations.</p> <p>In addition, it cannot be excluded that the induction of memory cells (T cells and B cells) is also affected by the prophylactic administration of paracetamol, which may prevent children from developing an adequate booster immune response. Therefore, the prophylactic administration of paracetamol during the booster phase will be stopped.</p> <p>Approximately 50% of the subjects were already enrolled and vaccinated according to the protocol (with or without prophylactic administration of paracetamol). The immune responses of all vaccinated children will be carefully monitored and the need for additional doses will be evaluated after the booster dose. Additional doses of vaccines will be made available, when necessary.</p> |
| 18 January 2008   | <ul style="list-style-type: none"> <li>• Details about the planned interim analysis.</li> <li>• Planning of a second interim analysis.</li> <li>• Correction in the EudraCT number.</li> </ul> <p>In addition, strikethrough text related to previous amendments has been removed. Furthermore, all bold italic text related to previous amendments has been changed into normal text. Those additional changes are documented below following the changes for which this fourth amendment has been developed.</p>   |
| 03 February 2009  | <p>The study protocol has been amended for the following reason:</p> <ul style="list-style-type: none"> <li>- The availability of the results of the microbiological assessments on nasopharyngeal carriage up to Visit 3 has been delayed. Therefore there is a need to cancel second interim analysis on carriage based on the time point V3 and to involve additional other laboratories designated by GSK Biologicals to speed up the microbiological work.</li> <li>• The fact that microbial assessments can be performed not only at the regional laboratory in the Czech Republic, but also at a laboratory designated by GSK Biologicals, was added.</li> <li>• The planned second interim analysis will not be performed anymore.</li> </ul>   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported