



## Clinical trial results:

**A phase IIIb, randomized, open, multicentre study to evaluate the immunogenicity and safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 AS04 vaccine co-administered with GlaxoSmithKline Biologicals' combined reduced-antigen diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine (Boostrix® Polio) in healthy female subjects aged 10–18 years.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2006-003807-38 |
| Trial protocol           | DE FR ES       |
| Global end of trial date | 25 July 2008   |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 27 April 2016    |
| First version publication date | 22 November 2014 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 108464 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00426361 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                        |
|------------------------------|--------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | GlaxoSmithKline Biologicals                                                                            |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium,                                                              |
| Public contact               | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact           | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089904466, GSKClinicalSupportHD@gsk.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 25 July 2008 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 25 July 2008 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

- To demonstrate non-inferiority of the dTpa-IPV immune response at Month 1 when dTpa-IPV is co-administered with HPV-16/18 L1 AS04 vaccine at Month 0 compared to when dTpa-IPV is administered alone at Month 0.

Protection of trial subjects:

As with all injectable vaccines, appropriate medical treatment was always readily available in case of anaphylactic reactions following the administration of the vaccine.

For this reason, the vaccinee remained under medical supervision for 30 minutes after vaccination.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 13 February 2007 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Spain: 262   |
| Country: Number of subjects enrolled | France: 183  |
| Country: Number of subjects enrolled | Germany: 306 |
| Worldwide total number of subjects   | 751          |
| EEA total number of subjects         | 751          |

Notes:

### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 751 |
| Adults (18-64 years)                      | 0   |

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

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 751 |
| Number of subjects completed | 751 |

### 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>             | Cervarix Group |

Arm description:

Subjects who received GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 0, 1 and 6.

|                                        |                                                          |
|----------------------------------------|----------------------------------------------------------|
| Arm type                               | Experimental                                             |
| Investigational medicinal product name | GSK Biologicals' HPV-16/18 L1 AS04 vaccine (Cervarix TM) |
| Investigational medicinal product code | Cervarix TM                                              |
| Other name                             |                                                          |
| Pharmaceutical forms                   | Injection                                                |
| Routes of administration               | Intramuscular and intravenous use                        |

Dosage and administration details:

Three doses of vaccine administered intramuscularly, with the second and third dose give one month and six months after the first dose respectively

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Cervarix + Boostrix Polio Group |
|------------------|---------------------------------|

Arm description:

Subjects who received GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 0, 1 and 6 with co-administration of Boostrix™ Polio at Month 0.

|                                        |                                   |
|----------------------------------------|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Boostrix ® Polio                  |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Injection                         |
| Routes of administration               | Intramuscular and intravenous use |

Dosage and administration details:

One dose of vaccine administered intramuscularly

|                                        |                                                          |
|----------------------------------------|----------------------------------------------------------|
| Investigational medicinal product name | GSK Biologicals' HPV-16/18 L1 AS04 vaccine (Cervarix TM) |
| Investigational medicinal product code | Cervarix TM                                              |
| Other name                             |                                                          |
| Pharmaceutical forms                   | Injection                                                |
| Routes of administration               | Intramuscular and intravenous use                        |

Dosage and administration details:

Three doses of vaccine administered intramuscularly, with the second and third dose give one month

and six months after the first dose respectively

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Boostrix Polio Cervarix Group |
|------------------|-------------------------------|

Arm description:

Subjects who received Boostrix™ Polio at Month 0 and GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 1, 2 and 7.

|                                        |                                                          |
|----------------------------------------|----------------------------------------------------------|
| Arm type                               | Experimental                                             |
| Investigational medicinal product name | GSK Biologicals' HPV-16/18 L1 AS04 vaccine (Cervarix TM) |
| Investigational medicinal product code | Cervarix TM                                              |
| Other name                             |                                                          |
| Pharmaceutical forms                   | Injection                                                |
| Routes of administration               | Intramuscular and intravenous use                        |

Dosage and administration details:

Three doses of vaccine administered intramuscularly, with the second and third dose give one month and six months after the first dose respectively

|                                        |                                   |
|----------------------------------------|-----------------------------------|
| Investigational medicinal product name | Boostrix ® Polio                  |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Injection                         |
| Routes of administration               | Intramuscular and intravenous use |

Dosage and administration details:

One dose of vaccine administered intramuscularly

| <b>Number of subjects in period 1</b> | Cervarix Group | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |
|---------------------------------------|----------------|---------------------------------|-------------------------------|
| Started                               | 248            | 255                             | 248                           |
| Completed                             | 244            | 250                             | 243                           |
| Not completed                         | 4              | 5                               | 5                             |
| Consent withdrawn by subject          | 1              | 3                               | -                             |
| Lost to follow-up                     | 3              | 2                               | 5                             |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                      |                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title                                                                                                                                                                | Cervarix Group                  |
| Reporting group description:<br>Subjects who received GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 0, 1 and 6.                                                      |                                 |
| Reporting group title                                                                                                                                                                | Cervarix + Boostrix Polio Group |
| Reporting group description:<br>Subjects who received GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 0, 1 and 6 with co-administration of Boostrix™ Polio at Month 0. |                                 |
| Reporting group title                                                                                                                                                                | Boostrix Polio Cervarix Group   |
| Reporting group description:<br>Subjects who received Boostrix™ Polio at Month 0 and GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 1, 2 and 7.                       |                                 |

| Reporting group values                             | Cervarix Group | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |
|----------------------------------------------------|----------------|---------------------------------|-------------------------------|
| Number of subjects                                 | 248            | 255                             | 248                           |
| Age categorical<br>Units: Subjects                 |                |                                 |                               |
| In utero                                           |                |                                 |                               |
| Preterm newborn infants (gestational age < 37 wks) |                |                                 |                               |
| Newborns (0-27 days)                               |                |                                 |                               |
| Infants and toddlers (28 days-23 months)           |                |                                 |                               |
| Children (2-11 years)                              |                |                                 |                               |
| Adolescents (12-17 years)                          |                |                                 |                               |
| Adults (18-64 years)                               |                |                                 |                               |
| From 65-84 years                                   |                |                                 |                               |
| 85 years and over                                  |                |                                 |                               |
| Age continuous<br>Units: years                     |                |                                 |                               |
| median                                             | 13.9           | 14                              | 13.9                          |
| standard deviation                                 | ± 2.59         | ± 2.43                          | ± 2.47                        |
| Gender categorical<br>Units: Subjects              |                |                                 |                               |
| Female                                             | 248            | 255                             | 248                           |
| Male                                               | 0              | 0                               | 0                             |

| Reporting group values                             | Total |  |  |
|----------------------------------------------------|-------|--|--|
| Number of subjects                                 | 751   |  |  |
| Age categorical<br>Units: Subjects                 |       |  |  |
| In utero                                           | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                               | 0     |  |  |
| Infants and toddlers (28 days-23 months)           | 0     |  |  |
| Children (2-11 years)                              | 0     |  |  |

|                           |     |  |  |
|---------------------------|-----|--|--|
| Adolescents (12-17 years) | 0   |  |  |
| Adults (18-64 years)      | 0   |  |  |
| From 65-84 years          | 0   |  |  |
| 85 years and over         | 0   |  |  |
| Age continuous            |     |  |  |
| Units: years              |     |  |  |
| median                    |     |  |  |
| standard deviation        | -   |  |  |
| Gender categorical        |     |  |  |
| Units: Subjects           |     |  |  |
| Female                    | 751 |  |  |
| Male                      | 0   |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                      |                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title                                                                                                                                                                | Cervarix Group                  |
| Reporting group description:<br>Subjects who received GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 0, 1 and 6.                                                      |                                 |
| Reporting group title                                                                                                                                                                | Cervarix + Boostrix Polio Group |
| Reporting group description:<br>Subjects who received GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 0, 1 and 6 with co-administration of Boostrix™ Polio at Month 0. |                                 |
| Reporting group title                                                                                                                                                                | Boostrix Polio Cervarix Group   |
| Reporting group description:<br>Subjects who received Boostrix™ Polio at Month 0 and GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 1, 2 and 7.                       |                                 |

### Primary: Number of subjects seroprotected against diphtheria and tetanus

|                                                                                                                                                                                                                             |                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                             | Number of subjects seroprotected against diphtheria and tetanus <sup>[1][2]</sup> |
| End point description:<br>Seroprotection against diphtheria and tetanus is defined as anti-diphtheria and anti-tetanus antibody titres greater than or equal to 0.1 International Units per Milliliter ( $\geq 0.1$ IU/mL). |                                                                                   |
| End point type                                                                                                                                                                                                              | Primary                                                                           |
| End point timeframe:<br>One month after vaccination with Boostrix Polio                                                                                                                                                     |                                                                                   |
| Notes:                                                                                                                                                                                                                      |                                                                                   |

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

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

[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: Only subjects who had received DTPa vaccination were included in the analysis.

| End point values            | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |  |
|-----------------------------|---------------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group                 | Reporting group               |  |  |
| Number of subjects analysed | 240                             | 233                           |  |  |
| Units: Subjects             |                                 |                               |  |  |
| Diphtheria                  | 238                             | 233                           |  |  |
| Tetanus                     | 240                             | 233                           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Titers of anti-pertussis toxoid (anti-PT), anti-pertactin toxoid (anti-PRN) and anti-filamentous hemagglutinin (anti-FHA) antibodies

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Titers of anti-pertussis toxoid (anti-PT), anti-pertactin toxoid |
|-----------------|------------------------------------------------------------------|

## End point description:

Titers are given as geometric mean titers (GMTs) calculated on all subjects and expressed as Enzyme-linked Immunosorbent Assay Units per Milliliter (EL.U/mL).

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

## End point timeframe:

One month after vaccination with Boostrix Polio

## Notes:

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

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

[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: Only subjects who had received DTPa vaccination were included in the analysis.

| End point values                         | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |  |
|------------------------------------------|---------------------------------|-------------------------------|--|--|
| Subject group type                       | Reporting group                 | Reporting group               |  |  |
| Number of subjects analysed              | 240                             | 233                           |  |  |
| Units: EL.U/mL                           |                                 |                               |  |  |
| geometric mean (confidence interval 95%) |                                 |                               |  |  |
| Anti-PT (n=238, 229)                     | 84.2 (73.6 to 96.4)             | 75.4 (65.6 to 86.8)           |  |  |
| Anti-FHA (n=240, 233)                    | 611.7 (553.6 to 675.9)          | 615.2 (552.3 to 685.2)        |  |  |
| Anti-PRN (n=239, 233)                    | 426.2 (368.1 to 493.4)          | 360 (299.3 to 433.1)          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects seroprotected against Poliovirus type 1 (Polio 1), Polio 2 and Polio 3

|                 |                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects seroprotected against Poliovirus type 1 (Polio 1), Polio 2 and Polio 3 <sup>[5][6]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------|

## End point description:

Seroprotection against polio 1, 2 and 3 is defined as anti-polio 1, 2 and 3 antibody titers greater than or equal to 8 Effective Dose 50% ( $\geq 8$  ED<sub>50</sub>).

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

## End point timeframe:

One month after vaccination with Boostrix Polio

## Notes:

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

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

[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: Only subjects who had received DTPa vaccination were included in the analysis.

| End point values            | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |  |
|-----------------------------|---------------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group                 | Reporting group               |  |  |
| Number of subjects analysed | 240                             | 232                           |  |  |
| Units: Subjects             |                                 |                               |  |  |
| Polio 1 (n=240, 231)        | 239                             | 231                           |  |  |
| Polio 2 (n=240, 232)        | 240                             | 232                           |  |  |
| Polio 3 (n=239, 232)        | 239                             | 232                           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Seroconverted for Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-HPV-18 Antibodies after completing the Cervarix vaccination course

|                 |                                                                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects Seroconverted for Anti-human Papilloma Virus 16 (Anti-HPV-16) and Anti-HPV-18 Antibodies after completing the Cervarix vaccination course |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Seroconversion is defined as the appearance of antibodies with titers greater than or equal to the predefined cut-off value in the serum of subject seronegative before vaccination. Cut-off values assessed include 8 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL) for anti-HPV-16 antibodies and 7 EL.U/mL for anti-HPV-18 antibodies.

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

End point timeframe:

One month post Cervarix Dose 3 (Month 7/8)

| End point values              | Cervarix Group  | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |
|-------------------------------|-----------------|---------------------------------|-------------------------------|--|
| Subject group type            | Reporting group | Reporting group                 | Reporting group               |  |
| Number of subjects analysed   | 198             | 204                             | 204                           |  |
| Units: Subjects               |                 |                                 |                               |  |
| Anti-HPV-16 (n=198, 202, 204) | 198             | 201                             | 204                           |  |
| Anti-HPV-18 (n=191, 204, 203) | 191             | 203                             | 203                           |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects Seroconverted for Anti-HPV-16 and Anti-HPV-18 Antibodies after incomplete Cervarix vaccination course

|                 |                                                                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects Seroconverted for Anti-HPV-16 and Anti-HPV-18 Antibodies after incomplete Cervarix vaccination course <sup>[7]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Seroconversion is defined as the appearance of antibodies with titers greater than or equal to the predefined cut-off value in the serum of subject seronegative before vaccination. Cut-off values assessed include 8 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL) for anti-HPV-16 antibodies and 7 EL.U/mL for anti-HPV-18 antibodies.

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

End point timeframe:

One month post Dose 1

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: Only subjects who had received HPV vaccination were included in the analysis.

| End point values            | Cervarix Group  | Cervarix + Boostrix Polio Group |  |  |
|-----------------------------|-----------------|---------------------------------|--|--|
| Subject group type          | Reporting group | Reporting group                 |  |  |
| Number of subjects analysed | 198             | 204                             |  |  |
| Units: Subjects             |                 |                                 |  |  |
| Anti-HPV-16 (n=198, 202)    | 198             | 201                             |  |  |
| Anti-HPV-18 (n=191, 204)    | 191             | 203                             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Titers of anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibodies After Completing the Cervarix Vaccination Course

|                 |                                                                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Titers of anti-human Papilloma virus 16 (anti-HPV-16) and anti-human Papilloma virus 18 (anti-HPV-18) antibodies After Completing the Cervarix Vaccination Course |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Titers are given as Geometric Mean Titers (GMTs) expressed as Enzyme-linked Immunosorbent Assay Units Per Milliliter (EL.U/mL).

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

End point timeframe:

One month post Cervarix Dose 3 (Month 7/8)]

| End point values                         | Cervarix Group              | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group   |  |
|------------------------------------------|-----------------------------|---------------------------------|---------------------------------|--|
| Subject group type                       | Reporting group             | Reporting group                 | Reporting group                 |  |
| Number of subjects analysed              | 213                         | 222                             | 218                             |  |
| Units: EL.U/mL                           |                             |                                 |                                 |  |
| geometric mean (confidence interval 95%) |                             |                                 |                                 |  |
| Anti-HPV-16 (n= 213, 222, 218)           | 18363.6<br>(16243 to 20761) | 15370.2<br>(13350.9 to 17694.8) | 14089.5<br>(12460.9 to 15930.9) |  |

|                                |                           |                         |                         |  |
|--------------------------------|---------------------------|-------------------------|-------------------------|--|
| Anti-HPV-18 (n= 210, 218, 216) | 7032.8 (6220.7 to 7950.9) | 6630.4 (5768 to 7621.6) | 5135 (4537.3 to 5811.5) |  |
|--------------------------------|---------------------------|-------------------------|-------------------------|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Titers of anti-diphtheria and anti-tetanus antibodies

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Titers of anti-diphtheria and anti-tetanus antibodies <sup>[8]</sup> |
|-----------------|----------------------------------------------------------------------|

End point description:

Titers are given as Geometric Mean Titers (GMTs) and expressed as IU/mL.

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

End point timeframe:

One month after vaccination with Boostrix-Polio

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: Only subjects who had received DTPa vaccination were included in the analysis.

| End point values                         | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |  |
|------------------------------------------|---------------------------------|-------------------------------|--|--|
| Subject group type                       | Reporting group                 | Reporting group               |  |  |
| Number of subjects analysed              | 240                             | 233                           |  |  |
| Units: IU/mL                             |                                 |                               |  |  |
| geometric mean (confidence interval 95%) |                                 |                               |  |  |
| Anti-diphtheria                          | 5.085 (4.551 to 5.681)          | 5.466 (4.896 to 6.103)        |  |  |
| Anti-tetanus                             | 8.552 (7.889 to 9.272)          | 9.039 (8.321 to 9.818)        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with anti-diphtheria and anti-tetanus antibody titers above 1.0 International Units per Milliliter (IU/mL)

|                 |                                                                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with anti-diphtheria and anti-tetanus antibody titers above 1.0 International Units per Milliliter (IU/mL) <sup>[9]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Anti-diphtheria and anti-tetanus antibodies cut-off value assessed include 1.0 IU/mL.

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

End point timeframe:

One month after vaccination with Boostrix Polio

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: Only subjects who had received DTPa vaccination were included in the analysis.

| End point values            | Cervarix +<br>Boostrix Polio<br>Group | Boostrix Polio<br>Cervarix Group |  |  |
|-----------------------------|---------------------------------------|----------------------------------|--|--|
| Subject group type          | Reporting group                       | Reporting group                  |  |  |
| Number of subjects analysed | 240                                   | 233                              |  |  |
| Units: Subjects             |                                       |                                  |  |  |
| Anti-diphtheria             | 231                                   | 226                              |  |  |
| Anti-tetanus                | 239                                   | 233                              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Anti-poliovirus type 1 (anti-polio 1), anti-polio 2 and anti-polio 3 antibody titers

|                 |                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------|
| End point title | Anti-poliovirus type 1 (anti-polio 1), anti-polio 2 and anti-polio 3 antibody titers <sup>[10]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------|

End point description:

Titers are given as Geometric Mean Titers (GMTs). The titer is a serum dilution giving 50 percent reduction of signal compared to control without serum.

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

End point timeframe:

One month after vaccination with Boostrix Polio

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: Only subjects who had received DTPa vaccination were included in the analysis.

| End point values                         | Cervarix +<br>Boostrix Polio<br>Group | Boostrix Polio<br>Cervarix Group |  |  |
|------------------------------------------|---------------------------------------|----------------------------------|--|--|
| Subject group type                       | Reporting group                       | Reporting group                  |  |  |
| Number of subjects analysed              | 240                                   | 232                              |  |  |
| Units: Titer                             |                                       |                                  |  |  |
| geometric mean (confidence interval 95%) |                                       |                                  |  |  |
| Anti-polio 1 (n=240, 231)                | 2045.1 (1714.7 to 2439.2)             | 2390.5 (2021.4 to 2826.9)        |  |  |
| Anti-polio 2 (n=240, 232)                | 2151.1 (1806.5 to 2561.6)             | 2158.1 (1821.3 to 2557.1)        |  |  |
| Anti-polio 3 (n=239, 232)                | 2777.2 (2376.5 to 3245.4)             | 2732.5 (2318 to 3221.2)          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with booster response to diphtheria and tetanus

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Number of subjects with booster response to diphtheria and tetanus <sup>[11]</sup> |
|-----------------|------------------------------------------------------------------------------------|

End point description:

Booster responses to diphtheria and tetanus were defined as: - For initially seronegative subjects (pre-vaccination titer below cut-off value of 0.1 International Units per Milliliter): antibody titers at least four times the cut-off (post-vaccination titer greater than or equal to 0.4 IU/mL), and - For initially seropositive subjects (pre-vaccination titer greater than or equal to 0.1 IU/mL): an increase in antibody titers of at least four times the pre-vaccination titer.

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

End point timeframe:

One month after vaccination with Boostrix Polio

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: Only subjects who had received DTPa vaccination were included in the analysis.

| End point values            | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |  |
|-----------------------------|---------------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group                 | Reporting group               |  |  |
| Number of subjects analysed | 240                             | 232                           |  |  |
| Units: Subjects             |                                 |                               |  |  |
| Diphtheria                  | 160                             | 159                           |  |  |
| Tetanus                     | 167                             | 161                           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with booster response to pertussis toxoid (PT), pertactin toxoid (PRN) and filamentous hemagglutinin (FHA)

|                 |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with booster response to pertussis toxoid (PT), pertactin toxoid (PRN) and filamentous hemagglutinin (FHA) <sup>[12]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Booster response to PT, FHA and PRN were defined as: - For initially seronegative subjects [pre-vaccination titer below cut-off value of 5 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL)]: antibody titers at least 4 times the cut-off, - For initially seropositive subjects with pre-vaccination titer above 5 EL.U/mL and < 20 EL.U/mL: an increase in antibody titers of at least 4 times the pre-vaccination titer, - For initially seropositive subjects with pre-vaccination titer above 20 EL.U/mL: an increase in antibody titers of at least 2 times the pre-vaccination titer.

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

End point timeframe:

One month after vaccination with Boostrix Polio

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: Only subjects who had received DTPa vaccination were included in the analysis.

| End point values            | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |  |
|-----------------------------|---------------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group                 | Reporting group               |  |  |
| Number of subjects analysed | 238                             | 230                           |  |  |
| Units: Subjects             |                                 |                               |  |  |
| PT (n=236, 228)             | 199                             | 182                           |  |  |
| FHA (n=235, 226)            | 210                             | 205                           |  |  |
| PRN (n=238, 230)            | 222                             | 207                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting solicited symptoms

|                                                                                                                                                                                                                                                                   |                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| End point title                                                                                                                                                                                                                                                   | Number of subjects reporting solicited symptoms |
| End point description:                                                                                                                                                                                                                                            |                                                 |
| Solicited local symptoms assessed include pain, redness and swelling at the injection site. Solicited general symptoms assessed include arthralgia, fatigue, fever (above 37.5 degree Celsius), gastrointestinal symptoms, headache, myalgia, rash and urticaria. |                                                 |
| End point type                                                                                                                                                                                                                                                    | Secondary                                       |
| End point timeframe:                                                                                                                                                                                                                                              |                                                 |
| During the 7-day period (Day 0-6) following each vaccination                                                                                                                                                                                                      |                                                 |

| End point values            | Cervarix Group  | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |
|-----------------------------|-----------------|---------------------------------|-------------------------------|--|
| Subject group type          | Reporting group | Reporting group                 | Reporting group               |  |
| Number of subjects analysed | 246             | 253                             | 247                           |  |
| Units: Subjects             |                 |                                 |                               |  |
| Pain                        | 225             | 237                             | 233                           |  |
| Redness                     | 110             | 128                             | 140                           |  |
| Swelling                    | 124             | 125                             | 123                           |  |
| Arthralgia                  | 58              | 71                              | 77                            |  |
| Fatigue                     | 109             | 135                             | 121                           |  |
| Fever                       | 30              | 46                              | 37                            |  |
| Gastrointestinal symptoms   | 51              | 63                              | 61                            |  |
| Headache                    | 111             | 138                             | 122                           |  |
| Myalgia                     | 107             | 144                             | 127                           |  |
| Rash                        | 20              | 27                              | 17                            |  |
| Urticaria                   | 12              | 11                              | 15                            |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of subjects reporting unsolicited adverse events**

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

End point description:

Unsolicited adverse event = Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms was reported as an unsolicited adverse event.

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

End point timeframe:

During the 30-day period (Day 0-29) following vaccination

| End point values            | Cervarix Group  | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |
|-----------------------------|-----------------|---------------------------------|-------------------------------|--|
| Subject group type          | Reporting group | Reporting group                 | Reporting group               |  |
| Number of subjects analysed | 248             | 255                             | 248                           |  |
| Units: Subjects             |                 |                                 |                               |  |
| unsolicited adverse events  | 85              | 74                              | 99                            |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of Subjects Reporting Unsolicited Adverse Events as New Onset Chronic Diseases (NOCDs) and Other Medically Significant Adverse Events (MSAEs)**

|                 |                                                                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects Reporting Unsolicited Adverse Events as New Onset Chronic Diseases (NOCDs) and Other Medically Significant Adverse Events (MSAEs) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

NOCDs assessed include e.g. autoimmune disorders, asthma, type I diabetes. MSAEs assessed include AEs prompting emergency room or physician visits that are not related to common diseases or SAEs that are not related to common diseases.

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

End point timeframe:

During the active phase of the study (up to Month 7/8) and during the safety follow-up (up to Month 12/13)

| End point values                           | Cervarix Group  | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |
|--------------------------------------------|-----------------|---------------------------------|-------------------------------|--|
| Subject group type                         | Reporting group | Reporting group                 | Reporting group               |  |
| Number of subjects analysed                | 248             | 255                             | 248                           |  |
| Units: Subjects                            |                 |                                 |                               |  |
| NOCDs [Active phase] (n=248, 255, 248)     | 5               | 9                               | 9                             |  |
| NOCDs [Safety follow-up] (n=244, 250, 243) | 0               | 0                               | 0                             |  |
| MSAEs [Active phase] (n=248, 255, 248)     | 35              | 27                              | 49                            |  |

|                                            |   |   |   |  |
|--------------------------------------------|---|---|---|--|
| MSAEs [Safety follow-up] (n=244, 250, 243) | 7 | 3 | 5 |  |
|--------------------------------------------|---|---|---|--|

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

During the active phase of the study (up to Month 7/8) and during the safety follow-up (up to Month 12/13)

| End point values                   | Cervarix Group  | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |  |
|------------------------------------|-----------------|---------------------------------|-------------------------------|--|
| Subject group type                 | Reporting group | Reporting group                 | Reporting group               |  |
| Number of subjects analysed        | 248             | 255                             | 248                           |  |
| Units: Subjects                    |                 |                                 |                               |  |
| Active phase (n=248, 255, 248)     | 2               | 4                               | 2                             |  |
| Safety follow-up (n=244, 250, 243) | 1               | 0                               | 1                             |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During the 7 day follow-up period after any vaccination for other (non-serious) adverse events. During the entire study period (12 months for Cervarix and Cervarix + Boostrix groups and 13 months for Cervarix Boostrix group) for serious adverse events.

Adverse event reporting additional description:

For other (non-serious) adverse events collected by systematic assessment, the number of subjects at risk corresponds to the number of subjects from the Total Vaccinated Cohort with a documented dose.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Cervarix Group |
|-----------------------|----------------|

Reporting group description:

Subjects who received GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 0, 1 and 6.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Cervarix + Boostrix Polio Group |
|-----------------------|---------------------------------|

Reporting group description:

Subjects who received GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 0, 1 and 6 with co-administration of Boostrix™ Polio at Month 0.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Boostrix Polio Cervarix Group |
|-----------------------|-------------------------------|

Reporting group description:

Subjects who received Boostrix™ Polio at Month 0 and GSK Biologicals HPV 16/18 vaccine 580299 (Cervarix™) at Month 1, 2 and 7.

| Serious adverse events                            | Cervarix Group  | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |
|---------------------------------------------------|-----------------|---------------------------------|-------------------------------|
| Total subjects affected by serious adverse events |                 |                                 |                               |
| subjects affected / exposed                       | 3 / 248 (1.21%) | 4 / 255 (1.57%)                 | 3 / 248 (1.21%)               |
| number of deaths (all causes)                     | 0               | 0                               | 0                             |
| number of deaths resulting from adverse events    | 0               | 0                               | 0                             |
| Injury, poisoning and procedural complications    |                 |                                 |                               |
| Muscle rupture                                    |                 |                                 |                               |
| subjects affected / exposed                       | 0 / 248 (0.00%) | 1 / 255 (0.39%)                 | 0 / 248 (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                         |
| Nervous system disorders                          |                 |                                 |                               |
| Presyncope                                        |                 |                                 |                               |
| subjects affected / exposed                       | 0 / 248 (0.00%) | 0 / 255 (0.00%)                 | 1 / 248 (0.40%)               |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 0                           | 0 / 1                         |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0                           | 0 / 0                         |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Pregnancy, puerperium and perinatal conditions  |                 |                 |                 |
| Imminent abortion                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 248 (0.00%) | 1 / 255 (0.39%) | 0 / 248 (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           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Ovarian cyst                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 248 (0.00%) | 0 / 255 (0.00%) | 1 / 248 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ovarian cyst ruptured                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 248 (0.40%) | 0 / 255 (0.00%) | 0 / 248 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Suicide attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 248 (0.40%) | 0 / 255 (0.00%) | 0 / 248 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Scoliosis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 248 (0.00%) | 1 / 255 (0.39%) | 0 / 248 (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           |
| Infections and infestations                     |                 |                 |                 |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 248 (0.00%) | 1 / 255 (0.39%) | 0 / 248 (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           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 248 (0.40%) | 0 / 255 (0.00%) | 0 / 248 (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           |
| Tonsillitis streptococcal                       |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 248 (0.00%) | 0 / 255 (0.00%) | 1 / 248 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Cervarix Group     | Cervarix + Boostrix Polio Group | Boostrix Polio Cervarix Group |
|-------------------------------------------------------|--------------------|---------------------------------|-------------------------------|
| Total subjects affected by non-serious adverse events |                    |                                 |                               |
| subjects affected / exposed                           | 225 / 248 (90.73%) | 237 / 255 (92.94%)              | 233 / 248 (93.95%)            |
| Nervous system disorders                              |                    |                                 |                               |
| Headache (unsolicited AE)                             |                    |                                 |                               |
| subjects affected / exposed                           | 4 / 248 (1.61%)    | 6 / 255 (2.35%)                 | 14 / 248 (5.65%)              |
| occurrences (all)                                     | 4                  | 6                               | 14                            |
| General disorders and administration site conditions  |                    |                                 |                               |
| Pain                                                  |                    |                                 |                               |
| alternative assessment type: Systematic               |                    |                                 |                               |
| subjects affected / exposed <sup>[1]</sup>            | 225 / 246 (91.46%) | 237 / 253 (93.68%)              | 233 / 247 (94.33%)            |
| occurrences (all)                                     | 225                | 237                             | 233                           |
| Redness                                               |                    |                                 |                               |
| alternative assessment type: Systematic               |                    |                                 |                               |
| subjects affected / exposed <sup>[2]</sup>            | 110 / 246 (44.72%) | 128 / 253 (50.59%)              | 140 / 247 (56.68%)            |
| occurrences (all)                                     | 110                | 128                             | 140                           |
| Swelling                                              |                    |                                 |                               |
| alternative assessment type: Systematic               |                    |                                 |                               |
| subjects affected / exposed <sup>[3]</sup>            | 124 / 246 (50.41%) | 125 / 253 (49.41%)              | 123 / 247 (49.80%)            |
| occurrences (all)                                     | 124                | 125                             | 123                           |
| Arthralgia                                            |                    |                                 |                               |
| alternative assessment type: Systematic               |                    |                                 |                               |
| subjects affected / exposed <sup>[4]</sup>            | 58 / 246 (23.58%)  | 71 / 253 (28.06%)               | 77 / 247 (31.17%)             |
| occurrences (all)                                     | 58                 | 71                              | 77                            |
| Fatigue                                               |                    |                                 |                               |
| alternative assessment type: Systematic               |                    |                                 |                               |
| subjects affected / exposed <sup>[5]</sup>            | 109 / 246 (44.31%) | 135 / 253 (53.36%)              | 121 / 247 (48.99%)            |
| occurrences (all)                                     | 109                | 135                             | 121                           |
| Fever (above 37.5 degree Celsius)                     |                    |                                 |                               |

|                                                                                                                                                             |                           |                           |                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------|---------------------------|
| alternative assessment type:<br>Systematic<br>subjects affected / exposed <sup>[6]</sup><br>occurrences (all)                                               | 30 / 246 (12.20%)<br>30   | 46 / 253 (18.18%)<br>46   | 37 / 247 (14.98%)<br>37   |
| Gastrointestinal symptoms<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed <sup>[7]</sup><br>occurrences (all)                  | 51 / 246 (20.73%)<br>51   | 63 / 253 (24.90%)<br>63   | 61 / 247 (24.70%)<br>61   |
| Headache (solicited general<br>symptom AE)<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed <sup>[8]</sup><br>occurrences (all) | 111 / 246 (45.12%)<br>111 | 138 / 253 (54.55%)<br>138 | 122 / 247 (49.39%)<br>122 |
| Myalgia<br>subjects affected / exposed <sup>[9]</sup><br>occurrences (all)                                                                                  | 107 / 246 (43.50%)<br>107 | 144 / 253 (56.92%)<br>144 | 127 / 247 (51.42%)<br>127 |
| Rash<br>subjects affected / exposed <sup>[10]</sup><br>occurrences (all)                                                                                    | 20 / 246 (8.13%)<br>20    | 27 / 253 (10.67%)<br>27   | 17 / 247 (6.88%)<br>17    |
| Urticaria<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed <sup>[11]</sup><br>occurrences (all)                                 | 12 / 246 (4.88%)<br>12    | 11 / 253 (4.35%)<br>11    | 15 / 247 (6.07%)<br>15    |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                                        | 14 / 248 (5.65%)<br>14    | 4 / 255 (1.57%)<br>4      | 10 / 248 (4.03%)<br>10    |

Notes:

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

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects

exposed for the reporting group. These numbers are expected to be equal.

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

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

Justification: The analysis was performed on subjects with symptom sheets completed.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported