



## Clinical trial results:

A phase III, open, randomized, multicentre, multicountry study to compare the reactogenicity and evaluate the safety and immunogenicity of GSK Bio's combined hepatitis A / hepatitis B vaccine (at least 720 EL.U of hepatitis A antigen and 20 µg of hepatitis B surface antigen per dose of 1 ml) administered according to a 0, 6 month schedule by intramuscular injection versus Twinrix™ Junior (at least 360 EL.U of hepatitis A antigen and 10 µg of hepatitis B surface antigen per dose of 0.5 ml) administered according to a 0, 1, 6 month schedule by intramuscular injection in healthy children between 1 to 11 years old.

## Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2015-001515-12   |
| Trial protocol           | Outside EU/EEA   |
| Global end of trial date | 25 February 2008 |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 13 May 2016  |
| First version publication date | 26 July 2015 |

## Trial information

### Trial identification

|                       |                                |
|-----------------------|--------------------------------|
| Sponsor protocol code | 208127/120,/132,/133,/134,/137 |
|-----------------------|--------------------------------|

### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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 Disclosure Advisor, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact           | Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |

Notes:

## Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 10 December 2004 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 25 February 2008 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

For the primary study:

To demonstrate that the combined hepatitis A / hepatitis B (720/20) vaccine is not more reactogenic than Twinrix™ Junior.

For the long term follow up (LTFU):

To evaluate anti-HAV and anti-HBs antibody persistence at Year 2, Year 3, Year 4 and Year 5 after the first vaccine dose of the primary vaccination course (a two-dose schedule of Twinrix Adult 720/20 vaccine or a three-dose schedule of Twinrix Junior 360/10 vaccine).

To evaluate the immune memory in the subjects who became seronegative for anti-HAV antibodies (i.e. anti-HAV antibody concentrations < 15 mIU/ml) or had anti-HBs antibody concentrations < 10 mIU/ml at the long-term blood sampling time-point (i.e. Year 2, 3, 4 or 5) and who received the challenge dose (administered 6 to 12 months after the Year 5 time-point).

Protection of trial subjects:

All subjects were supervised for 30 min after vaccination/product administration with appropriate medical treatment readily available. Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products. Subjects were followed-up for 30 days after the last vaccination/product administration.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 10 September 2001 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety, Efficacy  |
| Long term follow-up duration                              | 5 Years           |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Australia: 229 |
| Country: Number of subjects enrolled | Belgium: 61    |
| Country: Number of subjects enrolled | Spain: 110     |
| Country: Number of subjects enrolled | Sweden: 110    |
| Worldwide total number of subjects   | 510            |
| EEA total number of subjects         | 281            |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 100 |
| Children (2-11 years)                     | 410 |
| 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: -

### 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               | Year 1                  |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

|                              |               |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes           |
| <b>Arm title</b>             | Twinrix Adult |

Arm description:

Subjects received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Twinrix™ Adult    |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

Intramuscular injection in the left deltoid, 2 doses, Adult formulation in primary study.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Twinrix Junior |
|------------------|----------------|

Arm description:

Subjects received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | Twinrix™ Junior   |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

Intramuscular injection in the left deltoid, 3 doses, junior formulation in primary study.

| <b>Number of subjects in period 1</b> | Twinrix Adult | Twinrix Junior |
|---------------------------------------|---------------|----------------|
| Started                               | 254           | 256            |
| Completed                             | 249           | 250            |
| Not completed                         | 5             | 6              |
| Consent withdrawn by subject          | 4             | 1              |
| Migrated/moved from study area        | -             | 2              |

|                    |   |   |
|--------------------|---|---|
| Lost to follow-up  | - | 2 |
| Protocol deviation | 1 | 1 |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Year 2 - Year 5         |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

## Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Twinrix Adult Y2-Y5 |

Arm description:

Subjects previously received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Twinrix™ Adult    |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

Intramuscular injection in the left deltoid, 2 doses, Adult formulation in primary study.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Twinrix Junior Y2-Y5 |
|------------------|----------------------|

Arm description:

Subjects previously received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | Twinrix™ Junior   |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

Intramuscular injection in the left deltoid, 3 doses, junior formulation in primary study.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Twinrix Adult Y2-Y5 | Twinrix Junior Y2-Y5 |
|-----------------------------------------------------|---------------------|----------------------|
| Started                                             | 139                 | 137                  |
| Completed                                           | 139                 | 137                  |

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects returned for the follow-up phase.

## Baseline characteristics

### Reporting groups

|                                                                                               |                |
|-----------------------------------------------------------------------------------------------|----------------|
| Reporting group title                                                                         | Twinrix Adult  |
| Reporting group description:                                                                  |                |
| Subjects received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).  |                |
| Reporting group title                                                                         | Twinrix Junior |
| Reporting group description:                                                                  |                |
| Subjects received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation). |                |

| Reporting group values                                | Twinrix Adult | Twinrix Junior | Total |
|-------------------------------------------------------|---------------|----------------|-------|
| Number of subjects                                    | 254           | 256            | 510   |
| Age categorical<br>Units: Subjects                    |               |                |       |
| In utero                                              |               |                | 0     |
| Preterm newborn infants<br>(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<br>Units: years                        |               |                |       |
| median                                                | 6.2           | 5.8            |       |
| standard deviation                                    | ± 3.11        | ± 3.17         | -     |
| Gender categorical<br>Units: Subjects                 |               |                |       |
| Female                                                | 112           | 117            | 229   |
| Male                                                  | 142           | 139            | 281   |

## End points

### End points reporting groups

|                                                                                                                                          |                      |
|------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Reporting group title                                                                                                                    | Twinrix Adult        |
| Reporting group description:<br>Subjects received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).             |                      |
| Reporting group title                                                                                                                    | Twinrix Junior       |
| Reporting group description:<br>Subjects received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).            |                      |
| Reporting group title                                                                                                                    | Twinrix Adult Y2-Y5  |
| Reporting group description:<br>Subjects previously received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).  |                      |
| Reporting group title                                                                                                                    | Twinrix Junior Y2-Y5 |
| Reporting group description:<br>Subjects previously received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation). |                      |

### Primary: Anti-hepatitis A (HAV) antibody concentrations

|                                                                                                                                                                                                                                                                                                         |                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                         | Anti-hepatitis A (HAV) antibody concentrations <sup>[1]</sup> |
| End point description:<br>Geometric mean concentration for anti-HAV antibodies expressed as Milli-International Units per milliliter (mIU/mL)                                                                                                                                                           |                                                               |
| End point type                                                                                                                                                                                                                                                                                          | Primary                                                       |
| End point timeframe:<br>Year 2 (Month 24), Year 3 (Month 36), Year 4 (Month 48) and Year 5 (Month 60)                                                                                                                                                                                                   |                                                               |
| Notes:<br>[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.<br>Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed. |                                                               |

| End point values                         | Twinrix Adult Y2-Y5     | Twinrix Junior Y2-Y5      |  |  |
|------------------------------------------|-------------------------|---------------------------|--|--|
| Subject group type                       | Reporting group         | Reporting group           |  |  |
| Number of subjects analysed              | 129                     | 119                       |  |  |
| Units: mIU/mL                            |                         |                           |  |  |
| geometric mean (confidence interval 95%) |                         |                           |  |  |
| At year 2 (n=107; 94)                    | 1122.2 (937.7 to 1343)  | 1377.8 (1114 to 1704.2)   |  |  |
| At year 3 (n=129; 119)                   | 737.5 (845.8 to 1178.9) | 1347.1 (1145.1 to 1584.8) |  |  |
| At year 4 (n=115; 105)                   | 576.8 (623.6 to 872.3)  | 915.9 (774 to 1084)       |  |  |
| At year 5 (n=103; 101)                   | 998.6 (473.6 to 702.5)  | 698.4 (585.1 to 833.7)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Anti-hepatitis B (HBs) antibody concentrations

|                                                                                                                                                |                                                               |
|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| End point title                                                                                                                                | Anti-hepatitis B (HBs) antibody concentrations <sup>[2]</sup> |
| End point description:<br>Geometric mean concentration for anti-HBs antibodies expressed as Milli-International Units per milliliter (mIU/mL). |                                                               |
| End point type                                                                                                                                 | Primary                                                       |
| End point timeframe:<br>Year 2 (Month 24), Year 3 (Month 36), Year 4 (Month 48) and Year 5 (Month 60)                                          |                                                               |

Notes:

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

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

| End point values                         | Twinrix Adult<br>Y2-Y5 | Twinrix Junior<br>Y2-Y5 |  |  |
|------------------------------------------|------------------------|-------------------------|--|--|
| Subject group type                       | Reporting group        | Reporting group         |  |  |
| Number of subjects analysed              | 129                    | 119                     |  |  |
| Units: mIU/mL                            |                        |                         |  |  |
| geometric mean (confidence interval 95%) |                        |                         |  |  |
| At year 2 (n=107; 94)                    | 479.9 (356.6 to 646)   | 830.6 (609.5 to 1131.9) |  |  |
| At year 3 (n=129; 119)                   | 325.1 (244.7 to 431.8) | 695.1 (516.5 to 935.5)  |  |  |
| At year 4 (n=115; 105)                   | 270.2 (201 to 363.3)   | 519.7 (378.5 to 713.6)  |  |  |
| At year 5 (n=102; 100)                   | 150.2 (110.5 to 204.3) | 283.7 (208.6 to 386)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Anti-HAV antibody concentrations in subjects receiving the additional vaccine dose.

|                                                                                                                                                                                                                                                     |                                                                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                     | Anti-HAV antibody concentrations in subjects receiving the additional vaccine dose. <sup>[3]</sup> |
| End point description:<br>Any subjects becoming seronegative for anti-HAV antibodies (i.e. titres < 15 mIU/ml) at any long term time point, were to receive an additional vaccine dose administered between 6 to 12 months after Year 5 time point. |                                                                                                    |
| End point type                                                                                                                                                                                                                                      | Primary                                                                                            |
| End point timeframe:<br>Before and one month after additional vaccination                                                                                                                                                                           |                                                                                                    |

Notes:

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

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

| End point values                         | Twinrix Adult<br>Y2-Y5 | Twinrix Junior<br>Y2-Y5 |  |  |
|------------------------------------------|------------------------|-------------------------|--|--|
| Subject group type                       | Reporting group        | Reporting group         |  |  |
| Number of subjects analysed              | 0 <sup>[4]</sup>       | 0 <sup>[5]</sup>        |  |  |
| Units: mIU/mL                            |                        |                         |  |  |
| geometric mean (confidence interval 95%) | ( to )                 | ( to )                  |  |  |

Notes:

[4] - No subjects became seronegative for anti-HAV antibodies.

[5] - No subjects became seronegative for anti-HAV antibodies.

## Statistical analyses

No statistical analyses for this end point

### Primary: Anti-HBs antibody concentrations in subjects receiving the additional vaccine dose.

|                 |                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------|
| End point title | Anti-HBs antibody concentrations in subjects receiving the additional vaccine dose. <sup>[6]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------|

End point description:

Subjects losing seroprotective anti-HBs antibody titres (i.e. titres < 10 mIU/ml) at any long term time point, received an Engerix™ challenge dose. The table presents the geometric mean concentrations for anti-HBs antibodies, expressed as Milli-International Units per milliliter (mIU/mL).

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

End point timeframe:

Before and One month after additional vaccination

Notes:

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

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

| End point values                         | Twinrix Adult<br>Y2-Y5  | Twinrix Junior<br>Y2-Y5 |  |  |
|------------------------------------------|-------------------------|-------------------------|--|--|
| Subject group type                       | Reporting group         | Reporting group         |  |  |
| Number of subjects analysed              | 11                      | 5                       |  |  |
| Units: mIU/mL                            |                         |                         |  |  |
| geometric mean (confidence interval 95%) |                         |                         |  |  |
| Before vaccination (n= 6; 1)             | 4.9 (2.1 to 11.1)       | 2.4 (0.9 to 6.5)        |  |  |
| Post vaccination (n= 11; 5)              | 521.3 (158.2 to 1718.1) | 509.7 (173.5 to 1497.9) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms in children aged 1 to 5 years.

|                 |                                                                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms in children aged 1 to 5 years. <sup>[7]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited local symptoms assessed include pain, redness and swelling at the vaccine injection site. Any= regardless of intensity grade; Grade 3 Pain= spontaneously painful

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

End point timeframe:

during the 4-day follow-up period after any vaccination

Notes:

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

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

| End point values            | Twinrix Adult   | Twinrix Junior  |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 112             | 122             |  |  |
| Units: subjects             |                 |                 |  |  |
| Pain, any                   | 53              | 56              |  |  |
| Pain, Grade 3               | 2               | 1               |  |  |
| Redness, any                | 31              | 45              |  |  |
| Redness, >25 mm             | 1               | 2               |  |  |
| Swelling, any               | 26              | 29              |  |  |
| Swelling, >25 mm            | 1               | 2               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms in children aged 6 to 11 years.

|                 |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms in children aged 6 to 11 years. <sup>[8]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited local symptoms assessed include pain, redness and swelling at the vaccine injection site. Any= regardless of intensity grade; Grade 3 Pain= spontaneously painful

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

End point timeframe:

during the 4-day follow-up period after any vaccination

Notes:

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

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

| End point values            | Twinrix Adult   | Twinrix Junior  |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 138             | 125             |  |  |
| Units: subjects             |                 |                 |  |  |
| Pain, any                   | 82              | 72              |  |  |
| Pain, Grade 3               | 3               | 2               |  |  |

|                 |    |    |  |  |
|-----------------|----|----|--|--|
| Redness, any    | 32 | 31 |  |  |
| Redness, >25mm  | 0  | 1  |  |  |
| Swelling, any   | 13 | 23 |  |  |
| Swelling, >25mm | 0  | 2  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms in children aged 1 to 5 years.

|                 |                                                                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms in children aged 1 to 5 years. <sup>[9]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited general symptoms assessed include drowsiness, irritability/fussiness, loss of appetite and fever. Any= regardless of intensity grade or relationship to vaccination; grade 3= prevented normal activity; Related= considered by the investigator to be causally related to the vaccination

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

End point timeframe:

during the 4-day follow-up period after any vaccination

Notes:

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

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

| End point values                            | Twinrix Adult   | Twinrix Junior  |  |  |
|---------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                          | Reporting group | Reporting group |  |  |
| Number of subjects analysed                 | 112             | 122             |  |  |
| Units: subjects                             |                 |                 |  |  |
| Drowsiness, Any                             | 24              | 39              |  |  |
| Drowsiness, Grade 3                         | 2               | 3               |  |  |
| Drowsiness, Related                         | 23              | 36              |  |  |
| Irritability/Fussiness, Any                 | 36              | 52              |  |  |
| Irritability/Fussiness, Grade 3             | 0               | 1               |  |  |
| Irritability/Fussiness, Related             | 29              | 48              |  |  |
| Loss of appetite, Any                       | 20              | 37              |  |  |
| Loss of appetite, Grade 3                   | 2               | 0               |  |  |
| Loss of appetite, Related                   | 16              | 33              |  |  |
| Fever (axillary), $\geq 37^{\circ}\text{C}$ | 13              | 19              |  |  |
| Fever (axillary), $> 39.5^{\circ}\text{C}$  | 0               | 1               |  |  |
| Fever (axillary), Related                   | 13              | 16              |  |  |

## Statistical analyses

No statistical analyses for this end point

**Primary: Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms in children aged 6 to 11 years.**

|                 |                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms in children aged 6 to 11 years. <sup>[10]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited general symptoms assessed include fatigue, fever, gastrointestinal symptoms and headache. Any= regardless of intensity grade or relationship to vaccination; grade 3= prevented normal activity; Related= considered by the investigator to be causally related to the vaccination

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

End point timeframe:

during the 4-day follow-up period after any vaccination

Notes:

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

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

| End point values                            | Twinrix Adult   | Twinrix Junior  |  |  |
|---------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                          | Reporting group | Reporting group |  |  |
| Number of subjects analysed                 | 138             | 125             |  |  |
| Units: subjects                             |                 |                 |  |  |
| Fatigue, Any                                | 30              | 36              |  |  |
| Fatigue, Grade 3                            | 1               | 3               |  |  |
| Fatigue, Related                            | 28              | 30              |  |  |
| Gastrointestinal, Any                       | 21              | 26              |  |  |
| Gastrointestinal, Grade 3                   | 1               | 4               |  |  |
| Gastrointestinal, Related                   | 14              | 17              |  |  |
| Headache, Any                               | 25              | 40              |  |  |
| Headache, Grade 3                           | 1               | 1               |  |  |
| Headache, Related                           | 20              | 30              |  |  |
| Fever (axillary), $\geq 37^{\circ}\text{C}$ | 8               | 16              |  |  |
| Fever (axillary), $> 39.5^{\circ}\text{C}$  | 0               | 1               |  |  |
| Fever (axillary), Related                   | 5               | 8               |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of subjects reporting Serious Adverse Events (SAEs) determined by the investigator to have a causal relationship to primary vaccination or due to lack of vaccine efficacy.**

|                 |                                                                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects reporting Serious Adverse Events (SAEs) determined by the investigator to have a causal relationship to primary vaccination or due to lack of vaccine efficacy. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

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

End point timeframe:

From last study visit of the primary study up to Year 5 long term follow-up

| End point values            | Twinrix Adult<br>Y2-Y5 | Twinrix Junior<br>Y2-Y5 |  |  |
|-----------------------------|------------------------|-------------------------|--|--|
| Subject group type          | Reporting group        | Reporting group         |  |  |
| Number of subjects analysed | 139                    | 137                     |  |  |
| Units: subjects             |                        |                         |  |  |
| SAE(s)                      | 0                      | 0                       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms

|                 |                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Number of subjects receiving an additional vaccine dose and reporting solicited local symptoms |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

Solicited local symptoms assessed include pain, redness and swelling at the vaccine injection site. Any= regardless of intensity grade; Grade 3 Pain= spontaneously painful

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

End point timeframe:

during the 4-day follow-up period after additional vaccination

| End point values            | Twinrix Adult<br>Y2-Y5 | Twinrix Junior<br>Y2-Y5 |  |  |
|-----------------------------|------------------------|-------------------------|--|--|
| Subject group type          | Reporting group        | Reporting group         |  |  |
| Number of subjects analysed | 11                     | 5                       |  |  |
| Units: subjects             |                        |                         |  |  |
| Pain, any                   | 6                      | 0                       |  |  |
| Pain, grade 3               | 0                      | 0                       |  |  |
| Redness, any                | 1                      | 0                       |  |  |
| Redness, >20mm              | 0                      | 0                       |  |  |
| Swelling, any               | 0                      | 0                       |  |  |
| Swelling, >20mm             | 0                      | 0                       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms.

|                                                                                                                                                                                                                                                                                                                              |                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                              | Number of subjects receiving an additional vaccine dose and reporting solicited general symptoms. |
| End point description:<br>Solicited general symptoms assessed include fatigue, fever, gastrointestinal symptoms and headache.<br>Any= regardless of intensity grade or relationship to vaccination; grade 3= prevented normal activity;<br>Related= considered by the investigator to be causally related to the vaccination |                                                                                                   |
| End point type                                                                                                                                                                                                                                                                                                               | Secondary                                                                                         |
| End point timeframe:<br>During the 4-day follow-up period after additional vaccination                                                                                                                                                                                                                                       |                                                                                                   |

| End point values                            | Twinrix Adult<br>Y2-Y5 | Twinrix Junior<br>Y2-Y5 |  |  |
|---------------------------------------------|------------------------|-------------------------|--|--|
| Subject group type                          | Reporting group        | Reporting group         |  |  |
| Number of subjects analysed                 | 11                     | 5                       |  |  |
| Units: subjects                             |                        |                         |  |  |
| Fatigue, any                                | 3                      | 0                       |  |  |
| Fatigue, grade 3                            | 0                      | 0                       |  |  |
| Fatigue, related                            | 3                      | 0                       |  |  |
| Fever (axillary), $\geq 37^{\circ}\text{C}$ | 0                      | 0                       |  |  |
| Fever (axillary), $> 39.5^{\circ}\text{C}$  | 0                      | 0                       |  |  |
| Fever (axillary), related                   | 0                      | 0                       |  |  |
| Gastrointestinal, any                       | 2                      | 0                       |  |  |
| Gastrointestinal, grade 3                   | 0                      | 0                       |  |  |
| Gastrointestinal, related                   | 2                      | 0                       |  |  |
| Headache, any                               | 4                      | 0                       |  |  |
| Headache, grade 3                           | 0                      | 0                       |  |  |
| Headache, related                           | 4                      | 0                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects receiving an additional vaccine dose and reporting unsolicited adverse events (AEs).

|                                                                                                                                                                                                                                           |                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                           | Number of subjects receiving an additional vaccine dose and reporting unsolicited adverse events (AEs). |
| End point description:<br>An Adverse Event is 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. |                                                                                                         |
| End point type                                                                                                                                                                                                                            | Secondary                                                                                               |
| End point timeframe:<br>During the 30-day follow-up period after additional vaccination.                                                                                                                                                  |                                                                                                         |

| End point values            | Twinrix Adult<br>Y2-Y5 | Twinrix Junior<br>Y2-Y5 |  |  |
|-----------------------------|------------------------|-------------------------|--|--|
| Subject group type          | Reporting group        | Reporting group         |  |  |
| Number of subjects analysed | 11                     | 5                       |  |  |
| Units: subjects             |                        |                         |  |  |
| AEs                         | 2                      | 0                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects receiving an additional vaccine dose and reporting any Serious Adverse Events

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Number of subjects receiving an additional vaccine dose and reporting any Serious Adverse Events |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

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

End point timeframe:

At least one month after vaccination

| End point values            | Twinrix Adult<br>Y2-Y5 | Twinrix Junior<br>Y2-Y5 |  |  |
|-----------------------------|------------------------|-------------------------|--|--|
| Subject group type          | Reporting group        | Reporting group         |  |  |
| Number of subjects analysed | 11                     | 5                       |  |  |
| Units: subjects             |                        |                         |  |  |
| SAEs                        | 0                      | 0                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects receiving an additional vaccine dose and reporting unsolicited adverse events (AEs).

|                 |                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects receiving an additional vaccine dose and reporting unsolicited adverse events (AEs). |
|-----------------|---------------------------------------------------------------------------------------------------------|

End point description:

An Adverse Event is 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.

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

End point timeframe:

During the 30-day follow-up period after additional vaccination.

| End point values            | Twinrix Adult   | Twinrix Junior      |  |  |
|-----------------------------|-----------------|---------------------|--|--|
| Subject group type          | Reporting group | Reporting group     |  |  |
| Number of subjects analysed | 254             | 254 <sup>[11]</sup> |  |  |
| Units: subjects             |                 |                     |  |  |
| AEs                         | 139             | 169                 |  |  |

Notes:

[11] - Safety data were not available for 2 subjects

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects receiving an additional vaccine dose and reporting any Serious Adverse Events

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Number of subjects receiving an additional vaccine dose and reporting any Serious Adverse Events |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or may evolve into one of the outcomes listed above.

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

End point timeframe:

At least one month after vaccination

| End point values            | Twinrix Adult   | Twinrix Junior      |  |  |
|-----------------------------|-----------------|---------------------|--|--|
| Subject group type          | Reporting group | Reporting group     |  |  |
| Number of subjects analysed | 254             | 254 <sup>[12]</sup> |  |  |
| Units: subjects             |                 |                     |  |  |
| SAEs                        | 5               | 5                   |  |  |

Notes:

[12] - Safety data were not available for 2 subjects

## Statistical analyses

No statistical analyses for this end point

### Secondary: Anti-hepatitis A (HAV) antibody concentrations

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Anti-hepatitis A (HAV) antibody concentrations |
|-----------------|------------------------------------------------|

End point description:

Geometric mean concentration for anti-HAV antibodies expressed as Milli-International Units per milliliter (mIU/mL)

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

End point timeframe:

Before (PRE) and 7 Months after vaccination (POST)

| End point values                         | Twinrix Adult           | Twinrix Junior           |  |  |
|------------------------------------------|-------------------------|--------------------------|--|--|
| Subject group type                       | Reporting group         | Reporting group          |  |  |
| Number of subjects analysed              | 201                     | 188                      |  |  |
| Units: mIU/mL                            |                         |                          |  |  |
| geometric mean (confidence interval 95%) |                         |                          |  |  |
| PRE (N=154;138)                          | 7.5 (7.5 to 7.5)        | 7.5 (7.5 to 7.5)         |  |  |
| POST (N=201;188)                         | 8412.1 (7483 to 9456.5) | 9256.8 (8160 to 10501.2) |  |  |

### Statistical analyses

No statistical analyses for this end point

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

|                                                                                                                                                |                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| End point title                                                                                                                                | Anti-hepatitis B (HBs) antibody concentrations |
| End point description:<br>Geometric mean concentration for anti-HBs antibodies expressed as Milli-International Units per milliliter (mIU/mL). |                                                |
| End point type                                                                                                                                 | Secondary                                      |
| End point timeframe:<br>Before (PRE) and 7 Months after vaccination (POST)                                                                     |                                                |

| End point values                         | Twinrix Adult           | Twinrix Junior               |  |  |
|------------------------------------------|-------------------------|------------------------------|--|--|
| Subject group type                       | Reporting group         | Reporting group              |  |  |
| Number of subjects analysed              | 201                     | 188                          |  |  |
| Units: mIU/mL                            |                         |                              |  |  |
| geometric mean (confidence interval 95%) |                         |                              |  |  |
| PRE (N=154;138)                          | 7894.4 (1.7 to 1.7)     | 1.7 (1.7 to 1.7)             |  |  |
| POST (N=201;188)                         | 1.7 (6130.9 to 10165.1) | 13683.1 (11314.5 to 16547.5) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: During the 4-day (Day 0-3) follow-up period after the additional vaccination.

Unsolicited AEs: During the 31-day (Day 0-30) period after the additional vaccination; SAEs: During the entire study period

Adverse event reporting additional description:

The number of occurrences reported for solicited symptoms, adverse events, and serious adverse events were not available for posting. The number of subjects affected by each specific event was indicated as the number of occurrences.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 7.1    |

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Twinrix Adult |
|-----------------------|---------------|

Reporting group description:

Subjects received 2 doses of combined hepatitis A / hepatitis B vaccine (adult formulation).

|                       |                |
|-----------------------|----------------|
| Reporting group title | Twinrix Junior |
|-----------------------|----------------|

Reporting group description:

Subjects received 3 doses of combined hepatitis A / hepatitis B vaccine (junior formulation).

| Serious adverse events                            | Twinrix Adult   | Twinrix Junior  |  |
|---------------------------------------------------|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 5 / 254 (1.97%) | 5 / 254 (1.97%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    |                 |                 |  |
| Injury, poisoning and procedural complications    |                 |                 |  |
| Injury                                            |                 |                 |  |
| alternative assessment type: Non-systematic       |                 |                 |  |
| subjects affected / exposed                       | 4 / 254 (1.57%) | 0 / 254 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders   |                 |                 |  |
| Asthma                                            |                 |                 |  |
| alternative assessment type: Non-systematic       |                 |                 |  |
| subjects affected / exposed                       | 0 / 254 (0.00%) | 1 / 254 (0.39%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Dyspnea                                         |                 |                 |  |
| alternative assessment type: Non-systematic     |                 |                 |  |
| subjects affected / exposed                     | 0 / 254 (0.00%) | 1 / 254 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Eczema                                          |                 |                 |  |
| alternative assessment type: Non-systematic     |                 |                 |  |
| subjects affected / exposed                     | 0 / 254 (0.00%) | 1 / 254 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Glomerulonephritis                              |                 |                 |  |
| alternative assessment type: Non-systematic     |                 |                 |  |
| subjects affected / exposed                     | 0 / 254 (0.00%) | 1 / 254 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abscess                                         |                 |                 |  |
| alternative assessment type: Non-systematic     |                 |                 |  |
| subjects affected / exposed                     | 0 / 254 (0.00%) | 1 / 254 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection viral                                 |                 |                 |  |
| alternative assessment type: Non-systematic     |                 |                 |  |
| subjects affected / exposed                     | 0 / 254 (0.00%) | 1 / 254 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis media                                    |                 |                 |  |
| alternative assessment type: Non-systematic     |                 |                 |  |
| subjects affected / exposed                     | 1 / 254 (0.39%) | 0 / 254 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngitis                                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| alternative assessment type: Non-systematic     |                 |                 |  |
| subjects affected / exposed                     | 1 / 254 (0.39%) | 1 / 254 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| alternative assessment type: Non-systematic     |                 |                 |  |
| subjects affected / exposed                     | 0 / 254 (0.00%) | 1 / 254 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| 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>                     | <b>Twinrix Adult</b> | <b>Twinrix Junior</b> |  |
|-------------------------------------------------------|----------------------|-----------------------|--|
| Total subjects affected by non-serious adverse events |                      |                       |  |
| subjects affected / exposed                           | 135 / 254 (53.15%)   | 128 / 254 (50.39%)    |  |
| Nervous system disorders                              |                      |                       |  |
| Syncope vasovagal (FU)                                |                      |                       |  |
| subjects affected / exposed <sup>[1]</sup>            | 1 / 11 (9.09%)       | 0 / 5 (0.00%)         |  |
| occurrences (all)                                     | 1                    | 0                     |  |
| Headache (AEs) (Primary)                              |                      |                       |  |
| alternative assessment type: Non-systematic           |                      |                       |  |
| subjects affected / exposed                           | 13 / 254 (5.12%)     | 18 / 254 (7.09%)      |  |
| occurrences (all)                                     | 13                   | 18                    |  |
| General disorders and administration site conditions  |                      |                       |  |
| Redness at the injection site (FU)                    |                      |                       |  |
| subjects affected / exposed <sup>[2]</sup>            | 1 / 11 (9.09%)       | 0 / 5 (0.00%)         |  |
| occurrences (all)                                     | 1                    | 0                     |  |
| Pain at the injection site (FU)                       |                      |                       |  |
| subjects affected / exposed <sup>[3]</sup>            | 6 / 11 (54.55%)      | 0 / 5 (0.00%)         |  |
| occurrences (all)                                     | 6                    | 0                     |  |
| Fatigue (FU)                                          |                      |                       |  |
| subjects affected / exposed <sup>[4]</sup>            | 3 / 11 (27.27%)      | 0 / 5 (0.00%)         |  |
| occurrences (all)                                     | 3                    | 0                     |  |
| Gastrointestinal disorder (FU)                        |                      |                       |  |

|                                             |                    |                    |
|---------------------------------------------|--------------------|--------------------|
| subjects affected / exposed <sup>[5]</sup>  | 2 / 11 (18.18%)    | 0 / 5 (0.00%)      |
| occurrences (all)                           | 2                  | 0                  |
| Headache (FU)                               |                    |                    |
| subjects affected / exposed <sup>[6]</sup>  | 4 / 11 (36.36%)    | 0 / 5 (0.00%)      |
| occurrences (all)                           | 4                  | 0                  |
| Pain (Primary)                              |                    |                    |
| subjects affected / exposed <sup>[7]</sup>  | 135 / 250 (54.00%) | 128 / 247 (51.82%) |
| occurrences (all)                           | 135                | 128                |
| Redness (Primary)                           |                    |                    |
| subjects affected / exposed <sup>[8]</sup>  | 63 / 250 (25.20%)  | 76 / 247 (30.77%)  |
| occurrences (all)                           | 63                 | 76                 |
| Swelling (Primary)                          |                    |                    |
| subjects affected / exposed <sup>[9]</sup>  | 39 / 250 (15.60%)  | 52 / 247 (21.05%)  |
| occurrences (all)                           | 39                 | 52                 |
| Drowsiness (Primary)                        |                    |                    |
| subjects affected / exposed <sup>[10]</sup> | 24 / 112 (21.43%)  | 39 / 122 (31.97%)  |
| occurrences (all)                           | 24                 | 39                 |
| Irritability/Fussiness (Primary)            |                    |                    |
| subjects affected / exposed <sup>[11]</sup> | 36 / 112 (32.14%)  | 52 / 122 (42.62%)  |
| occurrences (all)                           | 36                 | 52                 |
| Loss of appetite (Primary)                  |                    |                    |
| subjects affected / exposed <sup>[12]</sup> | 20 / 112 (17.86%)  | 37 / 122 (30.33%)  |
| occurrences (all)                           | 20                 | 37                 |
| Fever (Primary)                             |                    |                    |
| subjects affected / exposed                 | 21 / 254 (8.27%)   | 35 / 254 (13.78%)  |
| occurrences (all)                           | 21                 | 35                 |
| Fatigue (Primary)                           |                    |                    |
| subjects affected / exposed <sup>[13]</sup> | 30 / 138 (21.74%)  | 36 / 125 (28.80%)  |
| occurrences (all)                           | 30                 | 36                 |
| Gastrointestinal (Primary)                  |                    |                    |
| subjects affected / exposed <sup>[14]</sup> | 21 / 138 (15.22%)  | 26 / 125 (20.80%)  |
| occurrences (all)                           | 21                 | 26                 |
| Headache (Primary)                          |                    |                    |
| subjects affected / exposed <sup>[15]</sup> | 25 / 138 (18.12%)  | 40 / 125 (32.00%)  |
| occurrences (all)                           | 25                 | 40                 |
| Fever (AEs) (Primary)                       |                    |                    |

|                                                                                                                                                                          |                        |                         |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|-------------------------|--|
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                                          | 14 / 254 (5.51%)<br>14 | 26 / 254 (10.24%)<br>26 |  |
| Injection site reaction (Primary)<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                     | 17 / 254 (6.69%)<br>17 | 21 / 254 (8.27%)<br>21  |  |
| Blood and lymphatic system disorders<br>Pharyngitis (Primary)<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)         | 21 / 254 (8.27%)<br>21 | 31 / 254 (12.20%)<br>31 |  |
| Reproductive system and breast disorders<br>Balanitis (FU)<br>subjects affected / exposed <sup>[16]</sup><br>occurrences (all)                                           | 1 / 11 (9.09%)<br>1    | 0 / 5 (0.00%)<br>0      |  |
| Gastrointestinal disorders<br>Vomiting (Primary)<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                      | 15 / 254 (5.91%)<br>15 | 16 / 254 (6.30%)<br>16  |  |
| Diarrhea (Primary)<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                    | 10 / 254 (3.94%)<br>10 | 13 / 254 (5.12%)<br>13  |  |
| Respiratory, thoracic and mediastinal disorders<br>Coughing (Primary)<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 11 / 254 (4.33%)<br>11 | 34 / 254 (13.39%)<br>34 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia (FU)<br>subjects affected / exposed <sup>[17]</sup><br>occurrences (all)                                   | 1 / 11 (9.09%)<br>1    | 0 / 5 (0.00%)<br>0      |  |
| Infections and infestations                                                                                                                                              |                        |                         |  |

|                                             |                   |                   |  |
|---------------------------------------------|-------------------|-------------------|--|
| Upper respiratory tract infection (Primary) |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 35 / 254 (13.78%) | 54 / 254 (21.26%) |  |
| occurrences (all)                           | 35                | 54                |  |
| Rhinitis (Primary)                          |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 13 / 254 (5.12%)  | 27 / 254 (10.63%) |  |
| occurrences (all)                           | 13                | 27                |  |
| Otitis media (Primary)                      |                   |                   |  |
| alternative assessment type: Non-systematic |                   |                   |  |
| subjects affected / exposed                 | 11 / 254 (4.33%)  | 15 / 254 (5.91%)  |  |
| occurrences (all)                           | 11                | 15                |  |

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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[12] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[13] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[14] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[15] - 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: Solicited local and general symptoms were only tabulated for subjects with a symptom sheet filled-in.

[16] - 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: There were less subjects enrolled in the follow-up phase of the study than in the primary phase.

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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 July 2001 | <ul style="list-style-type: none"><li>• To account for the competitive enrolment that is to be used for this study, extra randomization numbers and vaccine supplies will be needed at the study centres.</li><li>• The study site in The Netherlands under Professor R.A. Coutinho and the study site in Croatia under Professor Berislav Borčić will now not be used and, in consequence, can be deleted from the study protocol. To replace these two sites, a new study site in Belgium has been incorporated (UCL, Brussels under Dr Etienne Sokal).</li><li>• Anne Howard has been appointed as the Australian Study Monitor for this project, replacing Serge De Bartolo, therefore, her contact details are now included.</li><li>• Inmaculada Nuñez Arias has been appointed as one of the Spanish Study Monitors for this project, replacing Sandra Sistiaga, therefore, her contact details are now included.</li><li>• The section of the title pages requiring the signatures of the Principal Investigators has been deleted due to its redundancy in the modified protocol.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported