



## Clinical trial results:

**An open, single centre study to evaluate the long-term antibody persistence and immune memory between 16 and 20 years after the primary study HAB-028 (208127/021) in which healthy adults were vaccinated with Twinrix Adult following a three-dose schedule.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2009-014275-53 |
| Trial protocol           | BE             |
| Global end of trial date | 25 July 2014   |

### Results information

|                                |                                                                       |
|--------------------------------|-----------------------------------------------------------------------|
| Result version number          | v3 (current)                                                          |
| This version publication date  | 15 September 2018                                                     |
| First version publication date | 07 August 2015                                                        |
| Version creation reason        | • Correction of full data set<br>Results update after CTRS vs CSR QC. |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 112267 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01000324 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                         |
|------------------------------|---------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | GlaxoSmithKline Biologicals                                                                             |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, B-1330                                                        |
| Public contact               | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact           | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                |
|------------------------------------------------------|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 18 August 2015 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 25 July 2014   |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 25 July 2014   |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate anti-HAV and anti-HBs antibody persistence at Years 16, 17, 18, 19 and 20 after a three-dose primary vaccination course with Twinrix Adult.

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of the vaccine.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 06 November 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 40 |
| Worldwide total number of subjects   | 40          |
| EEA total number of subjects         | 40          |

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)                 | 0  |
| Adults (18-64 years)                      | 40 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects who entered the study at Year 16, Year 17, 18 and Year 19 time points were subjects who completed the primary study and who returned for blood sampling at the considered time point.

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

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

Arm description:

Pooled group of subjects from groups who were vaccinated with either Lot 1, Lot 2 or Lot 3 of Twinrix in the primary study according to a 0, 1, 6-Month schedule

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | Engerix-B                |
| Investigational medicinal product code |                          |
| Other name                             | HBV                      |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intramuscular use        |

Dosage and administration details:

Engerix-B was administered to subjects who are not seroprotected against hepatitis B.

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Havrix                   |
| Investigational medicinal product code |                          |
| Other name                             | HAV                      |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intramuscular use        |

Dosage and administration details:

Havrix was administered to subjects who are seronegative for anti-HAV antibodies.

|                                       |               |
|---------------------------------------|---------------|
| <b>Number of subjects in period 1</b> | Twinrix Group |
| Started                               | 40            |
| Completed                             | 40            |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Twinrix Group |
|-----------------------|---------------|

Reporting group description:

Pooled group of subjects from groups who were vaccinated with either Lot 1, Lot 2 or Lot 3 of Twinrix in the primary study according to a 0, 1, 6-Month schedule

| Reporting group values                             | Twinrix Group | Total |  |
|----------------------------------------------------|---------------|-------|--|
| Number of subjects                                 | 40            | 40    |  |
| Age categorical                                    |               |       |  |
| 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                                       |               |       |  |
| arithmetic mean                                    | 35.5          |       |  |
| standard deviation                                 | ± 2.87        | -     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female                                             | 29            | 29    |  |
| Male                                               | 11            | 11    |  |

## End points

### End points reporting groups

|                                                                                                                                                                  |               |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Reporting group title                                                                                                                                            | Twinrix Group |
| Reporting group description:                                                                                                                                     |               |
| Pooled group of subjects from groups who were vaccinated with either Lot 1, Lot 2 or Lot 3 of Twinrix in the primary study according to a 0, 1, 6-Month schedule |               |

### Primary: Number of subjects with anti-hepatitis A (anti-HAV) antibody concentration equal to or above 15 milli-international units per milliliter (mIU/mL)

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with anti-hepatitis A (anti-HAV) antibody concentration equal to or above 15 milli-international units per milliliter (mIU/mL) <sup>[1]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The analysis was performed on LT Total cohort that included all subjects who returned at each annual time point and who belonged to the Total Vaccinated cohort in the primary study

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

End point timeframe:

At Year 16

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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                                        |                 |  |  |  |
|----------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                | Twinrix Group   |  |  |  |
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 23              |  |  |  |
| Units: Subjects                        |                 |  |  |  |
| Anti-HAV $\geq$ 15 mIU/mL [at Year 16] | 23              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with anti-hepatitis A (anti-HAV) antibody concentration equal to or above 15 milli-international units per milliliter (mIU/mL)

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with anti-hepatitis A (anti-HAV) antibody concentration equal to or above 15 milli-international units per milliliter (mIU/mL) <sup>[2]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The analysis was performed on LT Total cohort that included all subjects who returned at each annual time point and who belonged to the Total Vaccinated cohort in the primary study

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

End point timeframe:

At Year 17

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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                                        |                 |  |  |  |
|----------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                | Twinrix Group   |  |  |  |
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 19              |  |  |  |
| Units: Subjects                        |                 |  |  |  |
| Anti-HAV $\geq$ 15 mIU/mL [at Year 17] | 19              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with anti-hepatitis A (anti-HAV) antibody concentration equal to or above 15 milli-international units per milliliter (mIU/mL)

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with anti-hepatitis A (anti-HAV) antibody concentration equal to or above 15 milli-international units per milliliter (mIU/mL) <sup>[3]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The analysis was performed on LT Total cohort that included all subjects who returned at each annual time point and who belonged to the Total Vaccinated cohort in the primary study

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

End point timeframe:

At Year 18

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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                                        |                 |  |  |  |
|----------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                | Twinrix Group   |  |  |  |
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 10              |  |  |  |
| Units: Subjects                        |                 |  |  |  |
| Anti-HAV $\geq$ 15 mIU/mL [at Year 18] | 10              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with anti-hepatitis A (anti-HAV) antibody concentration equal to or above 15 milli-international units per milliliter (mIU/mL)

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with anti-hepatitis A (anti-HAV) antibody concentration equal to or above 15 milli-international units per milliliter (mIU/mL) <sup>[4]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The analysis was performed on LT Total cohort that included all subjects who returned at each annual time point and who belonged to the Total Vaccinated cohort in the primary study

|                                                                                                                                                                     |         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| End point type                                                                                                                                                      | Primary |
| End point timeframe:                                                                                                                                                |         |
| At Year 19                                                                                                                                                          |         |
| Notes:                                                                                                                                                              |         |
| [4] - 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 scope of this endpoint was descriptive, no statistical analyses were conducted.                                                                  |         |

|                                        |                 |  |  |  |
|----------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                | Twinrix Group   |  |  |  |
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 17              |  |  |  |
| Units: Subjects                        |                 |  |  |  |
| Anti-HAV $\geq 15$ mIU/mL [at Year 19] | 17              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Concentration of anti-hepatitis A (anti-HAV) antibodies

|                                                                                                                                                                     |                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title                                                                                                                                                     | Concentration of anti-hepatitis A (anti-HAV) antibodies <sup>[5]</sup> |
| End point description:                                                                                                                                              |                                                                        |
| Concentrations are given as Geometric Mean Concentrations (GMCs).                                                                                                   |                                                                        |
| End point type                                                                                                                                                      | Primary                                                                |
| End point timeframe:                                                                                                                                                |                                                                        |
| At Year 17                                                                                                                                                          |                                                                        |
| 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 scope of this endpoint was descriptive, no statistical analyses were conducted.                                                                  |                                                                        |

|                                          |                        |  |  |  |
|------------------------------------------|------------------------|--|--|--|
| <b>End point values</b>                  | Twinrix Group          |  |  |  |
| Subject group type                       | Reporting group        |  |  |  |
| Number of subjects analysed              | 19                     |  |  |  |
| Units: mIU/mL                            |                        |  |  |  |
| geometric mean (confidence interval 95%) | 479.2 (298.2 to 769.9) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Concentration of anti-hepatitis A (anti-HAV) antibodies

|                                                                   |                                                                        |
|-------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title                                                   | Concentration of anti-hepatitis A (anti-HAV) antibodies <sup>[6]</sup> |
| End point description:                                            |                                                                        |
| Concentrations are given as Geometric Mean Concentrations (GMCs). |                                                                        |
| End point type                                                    | Primary                                                                |

End point timeframe:

At Year 18

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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                                          |                         |  |  |  |
|------------------------------------------|-------------------------|--|--|--|
| <b>End point values</b>                  | Twinrix Group           |  |  |  |
| Subject group type                       | Reporting group         |  |  |  |
| Number of subjects analysed              | 10                      |  |  |  |
| Units: mIU/mL                            |                         |  |  |  |
| geometric mean (confidence interval 95%) | 653.2 (333.2 to 1280.6) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Concentration of anti-hepatitis A (anti-HAV) antibodies

End point title Concentration of anti-hepatitis A (anti-HAV) antibodies<sup>[7]</sup>

End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs).

End point type Primary

End point timeframe:

At Year 19

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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                                          |                         |  |  |  |
|------------------------------------------|-------------------------|--|--|--|
| <b>End point values</b>                  | Twinrix Group           |  |  |  |
| Subject group type                       | Reporting group         |  |  |  |
| Number of subjects analysed              | 17                      |  |  |  |
| Units: mIU/mL                            |                         |  |  |  |
| geometric mean (confidence interval 95%) | 728.7 (469.6 to 1130.5) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut-off values

End point title Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut-off values<sup>[8]</sup>

End point description:

Anti-HBs antibody cut-off values assessed include 6.2 and 10 milli-international units per milliliter



(mIU/mL).

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| At Year 16           |         |

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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Twinrix Group   |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 23              |  |  |  |
| Units: Subjects             |                 |  |  |  |
| ≥ 6.2 mIU/mL                | 20              |  |  |  |
| ≥ 10 mIU/mL                 | 20              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut-off values

|                 |                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut-off values <sup>[9]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Anti-HBs antibody cut-off values assessed include 6.2 and 10 milli-international units per milliliter (mIU/mL).

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| At Year 17           |         |

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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Twinrix Group   |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 19              |  |  |  |
| Units: Subjects             |                 |  |  |  |
| ≥ 6.2 mIU/mL                | 17              |  |  |  |
| >=10 mIU/mL                 | 17              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with anti-hepatitis B surface antigen (anti-HBs)

**antibody concentrations equal to or above the cut-off values**

|                 |                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut-off values <sup>[10]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Anti-HBs antibody cut-off values assessed include 6.2 and 10 milli-international units per milliliter (mIU/mL).

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

End point timeframe:

At Year 18

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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Twinrix Group   |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 10              |  |  |  |
| Units: Subjects             |                 |  |  |  |
| ≥ 6.2 mIU/mL                | 9               |  |  |  |
| ≥ 10 mIU/mL                 | 9               |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut-off values**

|                 |                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects with anti-hepatitis B surface antigen (anti-HBs) antibody concentrations equal to or above the cut-off values <sup>[11]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Anti-HBs antibody cut-off values assessed include 6.2 and 10 milli-international units per milliliter (mIU/mL).

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

End point timeframe:

At Year 19

Notes:

[11] - 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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Twinrix Group   |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 18              |  |  |  |
| Units: Subjects             |                 |  |  |  |
| ≥ 6.2 mIU/mL                | 17              |  |  |  |
| ≥ 10 mIU/mL                 | 17              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Concentration of anti-hepatitis B surface antigen (anti-HBs) antibodies

|                 |                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Concentration of anti-hepatitis B surface antigen (anti-HBs) antibodies <sup>[12]</sup> |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs).

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

End point timeframe:

At Year 16

Notes:

[12] - 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 scope of this endpoint was descriptive, no statistical analyses were conducted.

| End point values                         | Twinrix Group         |  |  |  |
|------------------------------------------|-----------------------|--|--|--|
| Subject group type                       | Reporting group       |  |  |  |
| Number of subjects analysed              | 23                    |  |  |  |
| Units: mIU/mL                            |                       |  |  |  |
| geometric mean (confidence interval 95%) | 138.7 (61.3 to 313.7) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Concentration of anti-hepatitis B surface antigen (anti-HBs) antibodies

|                 |                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Concentration of anti-hepatitis B surface antigen (anti-HBs) antibodies <sup>[13]</sup> |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs).

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

End point timeframe:

At Year 17

Notes:

[13] - 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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                                          |                       |  |  |  |
|------------------------------------------|-----------------------|--|--|--|
| <b>End point values</b>                  | Twinrix Group         |  |  |  |
| Subject group type                       | Reporting group       |  |  |  |
| Number of subjects analysed              | 19                    |  |  |  |
| Units: mIU/mL                            |                       |  |  |  |
| geometric mean (confidence interval 95%) | 165.1 (64.8 to 420.7) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Concentration of anti-hepatitis B surface antigen (anti-HBs) antibodies

|                 |                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Concentration of anti-hepatitis B surface antigen (anti-HBs) antibodies <sup>[14]</sup> |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs).

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

End point timeframe:

At Year 18

Notes:

[14] - 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 scope of this endpoint was descriptive, no statistical analyses were conducted.

|                                          |                        |  |  |  |
|------------------------------------------|------------------------|--|--|--|
| <b>End point values</b>                  | Twinrix Group          |  |  |  |
| Subject group type                       | Reporting group        |  |  |  |
| Number of subjects analysed              | 10                     |  |  |  |
| Units: mIU/mL                            |                        |  |  |  |
| geometric mean (confidence interval 95%) | 278.3 (70.3 to 1101.3) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Concentration of anti-hepatitis B surface antigen (anti-HBs) antibodies

|                 |                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Concentration of anti-hepatitis B surface antigen (anti-HBs) antibodies <sup>[15]</sup> |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs).

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

End point timeframe:

At Year 19

Notes:

[15] - 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 scope of this endpoint was descriptive, no statistical analyses were conducted.

| End point values                         | Twinrix Group         |  |  |  |
|------------------------------------------|-----------------------|--|--|--|
| Subject group type                       | Reporting group       |  |  |  |
| Number of subjects analysed              | 18                    |  |  |  |
| Units: mIU/mL                            |                       |  |  |  |
| geometric mean (confidence interval 95%) | 198.4 (80.1 to 491.3) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects seropositive for anti-hepatitis A virus antibodies (anti-HAV) and anti-hepatitis B surface antigen (anti-HBs) antibodies and with anti-HBs antibody concentrations $\geq 10$ milli-international units per milliliter (mIU/mL).

|                 |                                                                                                                                                                                                                                                                    |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of subjects seropositive for anti-hepatitis A virus antibodies (anti-HAV) and anti-hepatitis B surface antigen (anti-HBs) antibodies and with anti-HBs antibody concentrations $\geq 10$ milli-international units per milliliter (mIU/mL). <sup>[16]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Seropositivity for anti-HAV antibodies is defined as antibody concentrations  $\geq 15$  milliinternational units per milliliter (mIU/mL). Seropositivity for anti-HBs antibodies is defined as antibody concentrations  $\geq 6.2$  mIU/mL..

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

End point timeframe:

At Year 20

Notes:

[16] - 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 scope of this endpoint was descriptive, no statistical analyses were conducted.

| End point values                               | Twinrix Group   |  |  |  |
|------------------------------------------------|-----------------|--|--|--|
| Subject group type                             | Reporting group |  |  |  |
| Number of subjects analysed                    | 18              |  |  |  |
| Units: Subjects                                |                 |  |  |  |
| anti-HAV $\geq 15$ mIU/mL [at Year 20] (N=18)  | 18              |  |  |  |
| anti-HBs $\geq 6.2$ mIU/mL [at Year 20] (N=18) | 17              |  |  |  |
| anti-HBs $\geq 10$ mIU/mL [at Year 20] (N=18)  | 17              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Anti-HAV and anti-HBs Geometric Mean Concentrations (GMCs)

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | Anti-HAV and anti-HBs Geometric Mean Concentrations |
|-----------------|-----------------------------------------------------|

End point description:

Concentrations were expressed as GMCs in mIU/mL.

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

End point timeframe:

At Year 20

Notes:

[17] - 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 scope of this endpoint was descriptive, no statistical analyses were conducted.

| End point values                         | Twinrix Group         |  |  |  |
|------------------------------------------|-----------------------|--|--|--|
| Subject group type                       | Reporting group       |  |  |  |
| Number of subjects analysed              | 18                    |  |  |  |
| Units: mIU/mL                            |                       |  |  |  |
| geometric mean (confidence interval 95%) |                       |  |  |  |
| anti-HAV [at Year 20] (N=18)             | 511.9 (343.8 to 762)  |  |  |  |
| anti-HBs [at Year 20] (N=18)             | 195.8 (79.9 to 480.0) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Concentration of anti-hepatitis A (anti-HAV) antibodies

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Concentration of anti-hepatitis A (anti-HAV) antibodies |
|-----------------|---------------------------------------------------------|

End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs).

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

End point timeframe:

At Year 16

| End point values                         | Twinrix Group          |  |  |  |
|------------------------------------------|------------------------|--|--|--|
| Subject group type                       | Reporting group        |  |  |  |
| Number of subjects analysed              | 23                     |  |  |  |
| Units: mIU/mL                            |                        |  |  |  |
| geometric mean (confidence interval 95%) | 614.2 (404.1 to 933.6) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with immune response to the challenge vaccine

## antigen

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | Number of subjects with immune response to the challenge vaccine antigen |
|-----------------|--------------------------------------------------------------------------|

End point description:

None of the subjects received a challenge dose at Years 16, 17 and 18 while, one subject received the challenge dose at Year 19.

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

End point timeframe:

Before, 14 days and one month after the challenge dose at Year 19.

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                         | Twinrix Group   |  |  |  |
| Subject group type                              | Reporting group |  |  |  |
| Number of subjects analysed                     | 1               |  |  |  |
| Units: Subjects                                 |                 |  |  |  |
| Subjects with immune response to challenge dose | 1               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Anti-hepatitis B Virus (Anti-HBs) Antibody Concentration

|                 |                                                          |
|-----------------|----------------------------------------------------------|
| End point title | Anti-hepatitis B Virus (Anti-HBs) Antibody Concentration |
|-----------------|----------------------------------------------------------|

End point description:

Concentrations are given as Geometric Mean Concentrations (GMCs) expressed as mIU/mL.

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

End point timeframe:

At Year 18, 14 days and 30 days post challenge dose (Year 19)

|                                          |                        |  |  |  |
|------------------------------------------|------------------------|--|--|--|
| <b>End point values</b>                  | Twinrix Group          |  |  |  |
| Subject group type                       | Reporting group        |  |  |  |
| Number of subjects analysed              | 1 <sup>[18]</sup>      |  |  |  |
| Units: mIU/mL                            |                        |  |  |  |
| geometric mean (confidence interval 95%) |                        |  |  |  |
| [Subject 1; at year 18]                  | 13.26 (13.26 to 13.26) |  |  |  |
| [Subject 1; 14 days post challenge dose] | 21926 (21926 to 21926) |  |  |  |
| [Subject 1; 30 days post challenge dose] | 12736 (12736 to 12736) |  |  |  |

Notes:

[18] - One subject received the challenge dose at Year 19.

## 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:

A SAE is any untoward medical occurrence that: resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

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

End point timeframe:

Up to Year 20.

| End point values            | Twinrix Group   |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 40              |  |  |  |
| Units: Subjects             |                 |  |  |  |
| Any SAE(s)                  | 0               |  |  |  |

## 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:

A serious adverse event was any untoward medical occurrence that: resulted in death, was life threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

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

End point timeframe:

During the 31-day (Day 0 to 30) period after administration of the challenge dose at Year 19.

| End point values            | Twinrix Group   |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 1               |  |  |  |
| Units: Subjects             |                 |  |  |  |
| Any SAE(s)                  | 0               |  |  |  |



## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting unsolicited adverse events (AE).

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

End point description:

An unsolicited AE was defined as any AE (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as occurrence of any unsolicited symptom regardless of intensity grade or relation to vaccination.

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

End point timeframe:

During the 31-day (Day 0 to 30) period after administration of the challenge dose at Year 19.

| End point values            | Twinrix Group   |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 1               |  |  |  |
| Units: Subjects             |                 |  |  |  |
| Any AE(s)                   | 1               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs: During the 31-day (Days 0 to 30) follow-up period after the challenge dose and from the beginning of the long term follow-up to Year 20; Unsolicited symptoms: During the 31-day (Days 0 to 30) follow-up period after the challenge dose.

Adverse event reporting additional description:

As no challenge dose was administered during Years 16, 17, 18 and 20 time points, SAEs and other adverse events were not assessed. 1 subject received the challenge dose at Year 19 for whom the SAEs and other adverse events were assessed during the 31 day period post challenge dose. SAEs were also collected for the entire safety follow-up.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Twinrix Group |
|-----------------------|---------------|

Reporting group description:

Pooled group of subjects from groups who were vaccinated with either Lot 1, Lot 2 or Lot 3 of Twinrix in the primary study according to a 0, 1, 6-Month schedule

| Serious adverse events                            | Twinrix Group  |  |  |
|---------------------------------------------------|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 40 (0.00%) |  |  |
| number of deaths (all causes)                     | 0              |  |  |
| number of deaths resulting from adverse events    |                |  |  |

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

| Non-serious adverse events                            | Twinrix Group   |  |  |
|-------------------------------------------------------|-----------------|--|--|
| Total subjects affected by non-serious adverse events |                 |  |  |
| subjects affected / exposed                           | 1 / 40 (2.50%)  |  |  |
| General disorders and administration site conditions  |                 |  |  |
| Oropharyngeal pain                                    |                 |  |  |
| alternative assessment type: Non-systematic           |                 |  |  |
| subjects affected / exposed <sup>[1]</sup>            | 1 / 1 (100.00%) |  |  |
| occurrences (all)                                     | 1               |  |  |
| Musculoskeletal and connective tissue disorders       |                 |  |  |

|                                                                                              |                      |  |  |
|----------------------------------------------------------------------------------------------|----------------------|--|--|
| Musculoskeletal stiffness<br>subjects affected / exposed <sup>[2]</sup><br>occurrences (all) | 1 / 1 (100.00%)<br>1 |  |  |
|----------------------------------------------------------------------------------------------|----------------------|--|--|

---

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: Only 1 subject received the challenge dose at Year 19 for whom the other adverse events were assessed during the 31 day period post challenge dose.

[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: Only 1 subject received the challenge dose at Year 19 for whom the other adverse events were assessed during the 31 day period post challenge dose.

## **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