



## Clinical trial results:

**An Open-label, randomised, controlled, multi-centre study of the immunogenicity and safety of a booster dose of two different Hepatitis B vaccines to explore the anamnestic immune response in healthy 4 to 7 year-old children previously vaccinated at about 3, 5 and 11 to 13 months of age with either HEXAVAC or INFANRIX-HEXA**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2007-005168-29  |
| Trial protocol           | IT              |
| Global end of trial date | 04 January 2010 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 27 April 2016 |
| First version publication date | 17 July 2015  |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | HXV01C |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00693186 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sanofi Pasteur MSD S.N.C.  |
| Sponsor organisation address | 162 avenue Jean Jaurès - CS 50712, Lyon Cedex 07, France, 69367                              |
| Public contact               | Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C.,<br>ClinicalTrialsDisclosure@spmsd.com |
| Scientific contact           | Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C.,<br>ClinicalTrialsDisclosure@spmsd.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                       | 04 January 2010 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 04 January 2010 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 04 January 2010 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

Immunogenicity: To describe in subjects vaccinated with 3 doses of HEXAVAC® or 3 doses of INFANRIX-HEXA® during the first 2 years of life the percentage of subjects with an anti-HBs antibody titre  $\geq 10$  mIU/mL (i.e. seroprotection rate) 1 month after a booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO® 5 µg (modified process) or ENGERIX-B® 10 µg.

Note: "HBVaxPRO® 5 µg (modified process)" was referred to "HBVaxPRO" and "ENERGIX-B® 10 µg" was referred to "ENERGIX-B" to facilitate reading.

Protection of trial subjects:

Healthy subjects with known sensitivity and/or allergy to any component of the study vaccine were not vaccinated.

Vaccines were administered by qualified study personnel.

After each vaccination, subjects were kept under observation for at least 20 minutes to ensure their safety.

Background therapy:

Subjects were previously vaccinated with 3 doses of HEXAVAC or 3 doses of INFANRIX-HEXA during their first 2 years of life (at about 3, 5, and 11 to 13 months of age).

Evidence for comparator:

This study was designed to explore the immune memory against Hepatitis B in healthy 4 to 7 year-old children previously vaccinated with HEXAVAC or INFANRIX-HEXA as part as the routine immunisation program. Two different Hepatitis B vaccines were used for this purpose: HBVaxPRO (namely study product) and ENGERIX-B (namely study comparator). ENGERIX-B was used as it was the one licensed for children and adolescents from birth to 15 years of age at the time the study started.

Note: The lot of HBVaxPRO used in the study expired on 14 March 2009. Consequently, the study was continued with ENGERIX-B only for all subjects from 11 March 2009.

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 27 October 2008 |
| 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 | Italy: 410 |
| Worldwide total number of subjects   | 410        |
| EEA total number of subjects         | 410        |

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)  | 0   |
| 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:

Study subjects were enrolled in 5 active centres in Italy.

### Pre-assignment

Screening details:

410 subjects were included and vaccinated during Part I of the study (period 1: booster dose).

405 subjects completed period 1.

15 subjects were vaccinated during Part II of the study: all received 1 extra-dose of Hepatitis B vaccine and 3 of them also received a 2nd extra-dose (period 2: extra-doses).

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Booster dose            |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

Blinding implementation details:

Not applicable as this study was open-label.

For immunogenicity data, serology tests were performed by laboratory staffs which were blinded to the previous hexavalent vaccine history and to which study vaccine each subject received.

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | HEXAVAC / HBVaxPRO (period 1) |

Arm description:

# Subjects previously vaccinated with 3 doses of HEXAVAC (at 3, 5, and 11 to 13 months of age) received 1 booster dose of HBVaxPRO (Hepatitis B virus surface antigen, recombinant 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular route at 4 to 7 years of age.

# Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | HBVaxPRO® 5 µg (modified process) |
| Investigational medicinal product code |                                   |
| Other name                             | HBVaxPRO                          |
| Pharmaceutical forms                   | Suspension for injection          |
| Routes of administration               | Intramuscular use                 |

Dosage and administration details:

0.5 mL, intramuscular route (deltoid muscle), 1 dose at 4 to 7 years of age.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | HEXAVAC / ENGERIX-B (period 1) |
|------------------|--------------------------------|

Arm description:

# Subjects previously vaccinated with 3 doses of HEXAVAC (at 3, 5, and 11 to 13 months of age) received 1 booster dose of ENGERIX-B (Hepatitis B virus surface antigen (rDNA) 10 µg, adsorbed on amorphous aluminium oxide hydrated 0.25 mg) by intramuscular route at 4 to 7 years of age.

# Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.

|  |  |
|--|--|
| Arm type                               | Active comparator                              |
| Investigational medicinal product name | ENGRIX-B® 10 µg                                |
| Investigational medicinal product code |  |
| Other name                             | ENGRIX-B                                       |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe |
| Routes of administration               | Intramuscular use                              |

Dosage and administration details:

0.5 mL, intramuscular route (deltoid muscle), 1 dose at 4 to 7 years of age.

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | INFANRIX-HEXA / HBVaxPRO (period 1) |
|------------------|-------------------------------------|

Arm description:

# Subjects previously vaccinated with 3 doses of INFANRIX-HEXA (at 3, 5, and 11 to 13 months of age) received 1 booster dose of HBVaxPRO (Hepatitis B virus surface antigen, recombinant 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular route at 4 to 7 years of age.

# Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | HBVaxPRO® 5 µg (modified process) |
| Investigational medicinal product code |                                   |
| Other name                             | HBVaxPRO                          |
| Pharmaceutical forms                   | Suspension for injection          |
| Routes of administration               | Intramuscular use                 |

Dosage and administration details:

0.5 mL, intramuscular route (deltoid muscle), 1 dose at 4 to 7 years of age.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | INFANRIX-HEXA / ENGERIX-B (period 1) |
|------------------|--------------------------------------|

Arm description:

# Subjects previously vaccinated with 3 doses of INFANRIX-HEXA (at 3, 5, and 11 to 13 months of age) received 1 booster dose of ENGERIX-B (Hepatitis B virus surface antigen (rDNA) 10 µg, adsorbed on amorphous aluminium oxide hydrated 0.25 mg) by intramuscular route at 4 to 7 years of age.

# Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.

|  |  |
|--|--|
| Arm type                               | Active comparator                              |
| Investigational medicinal product name | ENGRIX-B® 10 µg                                |
| Investigational medicinal product code |  |
| Other name                             | ENGRIX-B                                       |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe |
| Routes of administration               | Intramuscular use                              |

Dosage and administration details:

0.5 mL, intramuscular route (deltoid muscle), 1 dose at 4 to 7 years of age.

| Number of subjects in period 1 | HEXAVAC / HBVaxPRO (period 1) | HEXAVAC / ENGERIX-B (period 1) | INFANRIX-HEXA / HBVaxPRO (period 1) |
|--------------------------------|-------------------------------|--------------------------------|-------------------------------------|
| Started                        | 34                            | 167                            | 28                                  |
| Completed                      | 33                            | 164                            | 28                                  |
| Not completed                  | 1                             | 3                              | 0                                   |
| Consent withdrawn by subject   | 1                             | -                              | -                                   |
| Lost to follow-up              | -                             | 3                              | -                                   |

| Number of subjects in period 1 | INFANRIX-HEXA / ENGERIX-B (period 1) |
|--------------------------------|--------------------------------------|
| Started                        | 181                                  |

|                              |     |
|------------------------------|-----|
| Completed                    | 180 |
| Not completed                | 1   |
| Consent withdrawn by subject | 1   |
| Lost to follow-up            | -   |

## Period 2

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

Blinding implementation details:

Not applicable as this study was open-label.

For immunogenicity data, serology tests were performed by laboratory staffs which were blinded to the previous hexavalent vaccine history and to which study vaccine each subject received.

## Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | HEXAVAC / HBVaxPRO (period 2) |

Arm description:

# Subject previously vaccinated as planned during period 1 with post-booster anti-HBs Ab titre <10 mIU/mL (N=1, Local Italian Laboratory) received 1 extra-dose of HBVaxPRO by intramuscular route 2 months after the booster dose.

# Blood sample was collected 1 month (D28 to D42) after the extra-dose.

Note: Local Italian laboratory (Laboratorio Epatite, Università degli Studi di Milano) was used to obtain results on an ongoing basis in order to invite children to continue in part II of the study to receive 1 or 2 additional doses.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | HBVaxPRO® 5 µg (modified process) |
| Investigational medicinal product code |                                   |
| Other name                             | HBVaxPRO                          |
| Pharmaceutical forms                   | Suspension for injection          |
| Routes of administration               | Intramuscular use                 |

Dosage and administration details:

0.5 mL, intramuscular route (deltoid muscle), 1 extra-dose 2 months after the booster dose.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | HEXAVAC / ENGERIX-B (period 2) |
|------------------|--------------------------------|

Arm description:

# Subjects previously vaccinated as planned during period 1 with post-booster anti-HBs Ab titre <10 mIU/mL (N=13, Local Italian laboratory) received 1 extra-dose of ENGERIX-B by intramuscular route 2 months after the booster dose.

Out of these 13 subjects, 3 with post-extra-dose 1 anti-HBs Ab titre <10 mIU/mL (local Italian laboratory) received a 2nd extra-dose of ENGERIX-B 6 months after the booster dose.

# Blood samples were collected 1 month (D28 to D42) after each extra-dose.

Note: Local Italian laboratory (Laboratorio Epatite, Università degli Studi di Milano) was used to obtain results on an ongoing basis in order to invite children to continue in part II of the study to receive 1 or 2 additional doses.

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

|  |  |
|--|--|
| Investigational medicinal product name | ENGERIX-B® 10 µg                               |
| Investigational medicinal product code |  |
| Other name                             | ENGERIX-B                                      |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe |
| Routes of administration               | Intramuscular use                              |

Dosage and administration details:

0.5 mL, intramuscular route (deltoid muscle), 1st extra-dose 2 months after the booster dose, 2nd extra-dose 6 months after the booster dose.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | INFANRIX-HEXA / ENGERIX-B (period 2) |
|------------------|--------------------------------------|

Arm description:

# Subject previously vaccinated as planned during period 1 with post-booster anti-HBs Ab titre <10 mIU/mL (N=1, Local Italian Laboratory) received 1 extra-dose of ENGERIX-B by intramuscular route 2 months after the booster dose.

# Blood sample was collected 1 month (D28 to D42) after the extra-dose.

Note: Local Italian laboratory (Laboratorio Epatite, Università degli Studi di Milano) was used to obtain results on an ongoing basis in order to invite children to continue in part II of the study to receive 1 or 2 additional doses.

|  |  |
|--|--|
| Arm type                               | Active comparator                              |
| Investigational medicinal product name | ENGERIX-B® 10 µg                               |
| Investigational medicinal product code |  |
| Other name                             | ENGERIX-B                                      |
| Pharmaceutical forms                   | Suspension for injection in pre-filled syringe |
| Routes of administration               | Intramuscular use                              |

Dosage and administration details:

0.5 mL, intramuscular route (deltoid muscle), 1 extra-dose 2 months after the booster dose.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | HEXAVAC / HBVaxPRO (period 2) | HEXAVAC / ENGERIX-B (period 2) | INFANRIX-HEXA / ENGERIX-B (period 2) |
|---|-------------------------------|--------------------------------|--------------------------------------|
| Started   | 1                             | 13                             | 1                                    |
| Completed   | 1                             | 13                             | 1                                    |

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: For subjects' follow-up, only subjects of period 1 with post-booster anti-HBs antibody titre <10 mIU/mL and anti-HBc antibody titre test negative as measured at the local Italian laboratory were proposed 1 or 2 extra-doses of a Hepatitis B vaccine respectively 2 and 6 months after the booster dose of either HBVaxPRO or ENGERIX-B.

Thus, only 15 subjects continued in period 2 of the study.

## Baseline characteristics

### Reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | HEXAVAC / HBVaxPRO (period 1)        |
| Reporting group description:   |                                      |
| # Subjects previously vaccinated with 3 doses of HEXAVAC (at 3, 5, and 11 to 13 months of age) received 1 booster dose of HBVaxPRO (Hepatitis B virus surface antigen, recombinant 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular route at 4 to 7 years of age.       |                                      |
| # Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.  |                                      |
| Reporting group title  | HEXAVAC / ENGERIX-B (period 1)       |
| Reporting group description:   |                                      |
| # Subjects previously vaccinated with 3 doses of HEXAVAC (at 3, 5, and 11 to 13 months of age) received 1 booster dose of ENGERIX-B (Hepatitis B virus surface antigen (rDNA) 10 µg, adsorbed on amorphous aluminium oxide hydrated 0.25 mg) by intramuscular route at 4 to 7 years of age.                      |                                      |
| # Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.  |                                      |
| Reporting group title  | INFANRIX-HEXA / HBVaxPRO (period 1)  |
| Reporting group description:   |                                      |
| # Subjects previously vaccinated with 3 doses of INFANRIX-HEXA (at 3, 5, and 11 to 13 months of age) received 1 booster dose of HBVaxPRO (Hepatitis B virus surface antigen, recombinant 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular route at 4 to 7 years of age. |                                      |
| # Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.  |                                      |
| Reporting group title  | INFANRIX-HEXA / ENGERIX-B (period 1) |
| Reporting group description:   |                                      |
| # Subjects previously vaccinated with 3 doses of INFANRIX-HEXA (at 3, 5, and 11 to 13 months of age) received 1 booster dose of ENGERIX-B (Hepatitis B virus surface antigen (rDNA) 10 µg, adsorbed on amorphous aluminium oxide hydrated 0.25 mg) by intramuscular route at 4 to 7 years of age.                |                                      |
| # Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.  |                                      |

| Reporting group values   | HEXAVAC / HBVaxPRO (period 1)        | HEXAVAC / ENGERIX-B (period 1) | INFANRIX-HEXA / HBVaxPRO (period 1) |
|--|--------------------------------------|--------------------------------|-------------------------------------|
| Number of subjects   | 34                                   | 167                            | 28                                  |
| Age categorical  |                                      |                                |                                     |
| Age (years) at booster dose.   |                                      |                                |                                     |
| Units: Subjects  |                                      |                                |                                     |
| Children (2-11 years)  | 34                                   | 167                            | 28                                  |
| Age continuous   |                                      |                                |                                     |
| Age at booster dose, Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation. |                                      |                                |                                     |
| Units: years   |                                      |                                |                                     |
| arithmetic mean  | 6.6                                  | 5.7                            | 5.9                                 |
| standard deviation   | ± 0.9                                | ± 0.9                          | ± 0.7                               |
| Gender categorical   |                                      |                                |                                     |
| Units: Subjects  |                                      |                                |                                     |
| Female   | 12                                   | 88                             | 15                                  |
| Male   | 22                                   | 79                             | 13                                  |
| Reporting group values   | INFANRIX-HEXA / ENGERIX-B (period 1) | Total                          |                                     |



|  |       |     |  |
|--|-------|-----|--|
| Number of subjects   | 181   | 410 |  |
| Age categorical  |       |     |  |
| Age (years) at booster dose.   |       |     |  |
| Units: Subjects  |       |     |  |
| Children (2-11 years)  | 181   | 410 |  |
| Age continuous   |       |     |  |
| Age at booster dose, Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation. |       |     |  |
| Units: years   |       |     |  |
| arithmetic mean  | 5.7   |     |  |
| standard deviation   | ± 0.7 | -   |  |
| Gender categorical   |       |     |  |
| Units: Subjects  |       |     |  |
| Female   | 89    | 204 |  |
| Male   | 92    | 206 |  |

## End points

### End points reporting groups

|   |                                      |
|---|--------------------------------------|
| Reporting group title   | HEXAVAC / HBVaxPRO (period 1)        |
| Reporting group description:<br># Subjects previously vaccinated with 3 doses of HEXAVAC (at 3, 5, and 11 to 13 months of age) received 1 booster dose of HBVaxPRO (Hepatitis B virus surface antigen, recombinant 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular route at 4 to 7 years of age.<br># Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.   |                                      |
| Reporting group title   | HEXAVAC / ENGERIX-B (period 1)       |
| Reporting group description:<br># Subjects previously vaccinated with 3 doses of HEXAVAC (at 3, 5, and 11 to 13 months of age) received 1 booster dose of ENGERIX-B (Hepatitis B virus surface antigen (rDNA) 10 µg, adsorbed on amorphous aluminium oxide hydrated 0.25 mg) by intramuscular route at 4 to 7 years of age.<br># Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.  |                                      |
| Reporting group title   | INFANRIX-HEXA / HBVaxPRO (period 1)  |
| Reporting group description:<br># Subjects previously vaccinated with 3 doses of INFANRIX-HEXA (at 3, 5, and 11 to 13 months of age) received 1 booster dose of HBVaxPRO (Hepatitis B virus surface antigen, recombinant 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular route at 4 to 7 years of age.<br># Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.   |                                      |
| Reporting group title   | INFANRIX-HEXA / ENGERIX-B (period 1) |
| Reporting group description:<br># Subjects previously vaccinated with 3 doses of INFANRIX-HEXA (at 3, 5, and 11 to 13 months of age) received 1 booster dose of ENGERIX-B (Hepatitis B virus surface antigen (rDNA) 10 µg, adsorbed on amorphous aluminium oxide hydrated 0.25 mg) by intramuscular route at 4 to 7 years of age.<br># Blood samples were collected on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.  |                                      |
| Reporting group title   | HEXAVAC / HBVaxPRO (period 2)        |
| Reporting group description:<br># Subject previously vaccinated as planned during period 1 with post-booster anti-HBs Ab titre <10 mIU/mL (N=1, Local Italian Laboratory) received 1 extra-dose of HBVaxPRO by intramuscular route 2 months after the booster dose.<br># Blood sample was collected 1 month (D28 to D42) after the extra-dose.<br>Note: Local Italian laboratory (Laboratorio Epatite, Università degli Studi di Milano) was used to obtain results on an ongoing basis in order to invite children to continue in part II of the study to receive 1 or 2 additional doses.   |                                      |
| Reporting group title   | HEXAVAC / ENGERIX-B (period 2)       |
| Reporting group description:<br># Subjects previously vaccinated as planned during period 1 with post-booster anti-HBs Ab titre <10 mIU/mL (N=13, Local Italian laboratory) received 1 extra-dose of ENGERIX-B by intramuscular route 2 months after the booster dose.<br>Out of these 13 subjects, 3 with post-extra-dose 1 anti-HBs Ab titre <10 mIU/mL (local Italian laboratory) received a 2nd extra-dose of ENGERIX-B 6 months after the booster dose.<br># Blood samples were collected 1 month (D28 to D42) after each extra-dose.<br>Note: Local Italian laboratory (Laboratorio Epatite, Università degli Studi di Milano) was used to obtain results on an ongoing basis in order to invite children to continue in part II of the study to receive 1 or 2 additional doses. |                                      |
| Reporting group title   | INFANRIX-HEXA / ENGERIX-B (period 2) |
| Reporting group description:<br># Subject previously vaccinated as planned during period 1 with post-booster anti-HBs Ab titre <10 mIU/mL (N=1, Local Italian Laboratory) received 1 extra-dose of ENGERIX-B by intramuscular route 2 months after the booster dose.<br># Blood sample was collected 1 month (D28 to D42) after the extra-dose.<br>Note: Local Italian laboratory (Laboratorio Epatite, Università degli Studi di Milano) was used to obtain results on an ongoing basis in order to invite children to continue in part II of the study to receive 1 or 2 additional doses.  |                                      |

**Primary: Seroprotection rate: percentage of subjects with an anti-Hepatitis B surface (anti-HBs) antibody titre  $\geq 10$  mIU/mL 1 month after the booster dose of either HBVaxPRO or ENGERIX-B**

|                 |   |
|-----------------|---|
| End point title | Seroprotection rate: percentage of subjects with an anti-Hepatitis B surface (anti-HBs) antibody titre $\geq 10$ mIU/mL 1 month after the booster dose of either HBVaxPRO or ENGERIX-B <sup>[1]</sup> |
|-----------------|---|

End point description:

Percentage of subjects with an anti-HBs titre  $\geq 10$  mIU/mL measured by the Ortho enhanced chemiluminescence (ECi) assay at PPD Vaccines and Biologics LLC, USA, 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B.

Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation.

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

End point timeframe:

1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B.

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: Objectives were only descriptive. Thus no formal statistical hypothesis was tested in this study.

| End point values                 | HEXAVAC / HBVaxPRO (period 1) | HEXAVAC / ENGERIX-B (period 1) | INFANRIX-HEXA / HBVaxPRO (period 1) | INFANRIX-HEXA / ENGERIX-B (period 1) |
|----------------------------------|-------------------------------|--------------------------------|-------------------------------------|--------------------------------------|
| Subject group type               | Reporting group               | Reporting group                | Reporting group                     | Reporting group                      |
| Number of subjects analysed      | 33                            | 160                            | 27                                  | 171                                  |
| Units: Percentage of subjects    |                               |                                |                                     |                                      |
| number (confidence interval 95%) |                               |                                |                                     |                                      |
| Anti-HBs $\geq 10$ mIU/mL        | 90.9 (75.7 to 98.1)           | 91.3 (85.8 to 95.1)            | 100 (87.2 to 100)                   | 97.7 (94.1 to 99.4)                  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of subjects with an anti-Hepatitis B surface (anti-HBs) antibody titre #  $\geq 5$  mIU/mL, #  $\geq 10$  mIU/mL, and #  $\geq 100$  mIU/mL pre-booster and 1 month after the booster dose of either HBVaxPRO or ENGERIX-B**

|                 |   |
|-----------------|---|
| End point title | Percentage of subjects with an anti-Hepatitis B surface (anti-HBs) antibody titre # $\geq 5$ mIU/mL, # $\geq 10$ mIU/mL, and # $\geq 100$ mIU/mL pre-booster and 1 month after the booster dose of either HBVaxPRO or ENGERIX-B |
|-----------------|---|

End point description:

Percentage of subjects with an anti-HBs titre #  $\geq 5$  mIU/mL, #  $\geq 10$  mIU/mL, and #  $\geq 100$  mIU/mL measured by the Ortho enhanced chemiluminescence (ECi) assay at PPD Vaccines and Biologics LLC, USA, on Day 0 (D0) before booster dose (pre-booster) and 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B (post-booster).

Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| # Pre-booster: Day 0 (D0) before booster dose.  |           |
| # Post-booster: 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B. |           |

| End point values                        | HEXAVAC /<br>HBVaxPRO<br>(period 1) | HEXAVAC /<br>ENERGIX-B<br>(period 1) | INFANRIX-<br>HEXA /<br>HBVaxPRO<br>(period 1) | INFANRIX-<br>HEXA /<br>ENERGIX-B<br>(period 1) |
|---|-------------------------------------|--------------------------------------|---|--|
| Subject group type                      | Reporting group                     | Reporting group                      | Reporting group                               | Reporting group                                |
| Number of subjects analysed             | 33                                  | 160                                  | 27  | 171  |
| Units: Percentage of subjects           |                                     |                                      |   |  |
| number (confidence interval 95%)        |                                     |                                      |   |  |
| Pre-booster anti-HBs $\geq 5$ mIU/mL    | 63.6 (45.1 to 79.6)                 | 44.7 (36.8 to 52.7)                  | 77.8 (57.7 to 91.4)                           | 84.8 (78.5 to 89.8)                            |
| Post-booster anti-HBs $\geq 5$ mIU/mL   | 97 (84.2 to 99.9)                   | 91.3 (85.8 to 95.1)                  | 100 (87.2 to 100)                             | 98.2 (95 to 99.6)                              |
| Pre-booster anti-HBs $\geq 10$ mIU/mL   | 57.6 (39.2 to 74.5)                 | 35.8 (28.4 to 43.8)                  | 77.8 (57.7 to 91.4)                           | 81.9 (75.3 to 87.3)                            |
| Post-booster anti-HBs $\geq 10$ mIU/mL  | 90.9 (75.7 to 98.1)                 | 91.3 (85.8 to 95.1)                  | 100 (87.2 to 100)                             | 97.7 (94.1 to 99.4)                            |
| Pre-booster anti-HBs $\geq 100$ mIU/mL  | 9.1 (1.9 to 24.3)                   | 5.7 (2.6 to 10.5)                    | 40.7 (22.4 to 61.2)                           | 43.3 (35.7 to 51.1)                            |
| Post-booster anti-HBs $\geq 100$ mIU/mL | 90.9 (75.7 to 98.1)                 | 81.3 (74.3 to 87)                    | 96.3 (81 to 99.9)                             | 95.3 (91 to 98)                                |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric Mean Titres (GMT) of anti-HBs antibodies pre-booster and 1 month after the booster dose of either HBVaxPRO or ENGERIX-B

|  |   |
|--|---|
| End point title  | Geometric Mean Titres (GMT) of anti-HBs antibodies pre-booster and 1 month after the booster dose of either HBVaxPRO or ENGERIX-B |
| End point description:   |   |
| Study participants were blood sampled on Day 0 (D0) before booster dose (pre-booster) and 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B (post-booster). |   |
| Anti-HBs antibody titres expressed in mIU/mL were measured by the Ortho enhanced chemiluminescence (ECi) assay at PPD Vaccines and Biologics LLC, USA.   |   |
| Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation.   |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| # Pre-booster: Day 0 (D0) before booster dose.   |   |
| # Post-booster: 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B.  |   |

| End point values                         | HEXAVAC /<br>HBVaxPRO<br>(period 1) | HEXAVAC /<br>ENGERIX-B<br>(period 1) | INFANRIX-<br>HEXA /<br>HBVaxPRO<br>(period 1) | INFANRIX-<br>HEXA /<br>ENGERIX-B<br>(period 1) |
|--|-------------------------------------|--------------------------------------|---|--|
| Subject group type                       | Reporting group                     | Reporting group                      | Reporting group                               | Reporting group                                |
| Number of subjects analysed              | 33                                  | 160                                  | 27  | 171  |
| Units: Titres                            |                                     |                                      |   |  |
| geometric mean (confidence interval 95%) |                                     |                                      |   |  |
| Pre-booster anti-HBs GMT                 | 13 (7 to 22)                        | 8 (6 to 10)                          | 50 (23 to 109)                                | 61 (45 to 82)                                  |
| Post-booster anti-HBs GMT                | 1255 (554 to 2846)                  | 878 (581 to 1327)                    | 6564 (2917 to 14772)                          | 7420 (5227 to 10531)                           |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric Mean Titres Ratios (GMTR) of individual post-/pre-booster anti-HBs antibody titres 1 month after the booster dose of either HBVaxPRO or ENGERIX-B

|                 |   |
|-----------------|---|
| End point title | Geometric Mean Titres Ratios (GMTR) of individual post-/pre-booster anti-HBs antibody titres 1 month after the booster dose of either HBVaxPRO or ENGERIX-B |
|-----------------|---|

End point description:

Study participants were blood sampled on Day 0 (D0) before booster dose (pre-booster) and 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B (post-booster).

Anti-HBs antibody titres were measured by the Ortho enhanced chemiluminescence (ECi) assay at PPD Vaccines and Biologics LLC, USA.

Individual post- (1 month) / pre-booster (D0) anti-HBs titres ratios were measured.

Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation.

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

End point timeframe:

1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B.

| End point values                         | HEXAVAC /<br>HBVaxPRO<br>(period 1) | HEXAVAC /<br>ENGERIX-B<br>(period 1) | INFANRIX-<br>HEXA /<br>HBVaxPRO<br>(period 1) | INFANRIX-<br>HEXA /<br>ENGERIX-B<br>(period 1) |
|--|-------------------------------------|--------------------------------------|---|--|
| Subject group type                       | Reporting group                     | Reporting group                      | Reporting group                               | Reporting group                                |
| Number of subjects analysed              | 33                                  | 160                                  | 27  | 171  |
| Units: Not applicable                    |                                     |                                      |   |  |
| geometric mean (confidence interval 95%) |                                     |                                      |   |  |
| Anti-HBs GMTR                            | 100 (57 to 175)                     | 111 (80 to 154)                      | 131 (83 to 205)                               | 122 (96 to 155)                                |

## Statistical analyses

**Secondary: Global summary of safety from D0 to D14 after the booster dose of either HBVaxPRO or ENGERIX-B**

|   |  |
|---|--|
| End point title   | Global summary of safety from D0 to D14 after the booster dose of either HBVaxPRO or ENGERIX-B |
| End point description:  |  |
| Adverse events (AEs) occurring after injection of the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B were recorded as follows.<br>1/ From D0 to D4: # solicited injection-site adverse reactions (ISRs) (erythema, pain, and swelling), and # solicited systemic AE (pyrexia),<br>2/ From D0 to D14: # unsolicited ISRs, and # unsolicited systemic AEs.<br>AEs at injection sites were always considered as related to vaccine (ISRs). The investigator had to assess whether systemic AEs were vaccine-related systemic AEs or not.<br>Analysis was done on the Safety Analysis Set (N=407), i.e. all subjects who received at least 1 of the booster study vaccines and who had safety follow-up data. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Day 0 (D0) to D14 after injection of the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B.  |  |

| End point values                                  | HEXAVAC / HBVaxPRO (period 1) | HEXAVAC / ENGERIX-B (period 1) | INFANRIX-HEXA / HBVaxPRO (period 1) | INFANRIX-HEXA / ENGERIX-B (period 1) |
|---|-------------------------------|--------------------------------|-------------------------------------|--------------------------------------|
| Subject group type                                | Reporting group               | Reporting group                | Reporting group                     | Reporting group                      |
| Number of subjects analysed                       | 34                            | 164                            | 28                                  | 181                                  |
| Units: Percentage of subjects                     |                               |                                |                                     |                                      |
| number (confidence interval 95%)                  |                               |                                |                                     |                                      |
| At least 1 ISR or systemic AE (D0-D14)            | 47.1 (29.8 to 64.9)           | 38.4 (30.9 to 46.3)            | 35.7 (18.6 to 55.9)                 | 45.9 (38.4 to 53.4)                  |
| At least 1 ISR (D0-D14)                           | 20.6 (8.7 to 37.9)            | 24.4 (18 to 31.7)              | 28.6 (13.2 to 48.7)                 | 38.1 (31 to 45.6)                    |
| At least 1 solicited ISR (D0-D4)                  | 20.6 (8.7 to 37.9)            | 24.4 (18 to 31.7)              | 28.6 (13.2 to 48.7)                 | 37.6 (30.5 to 45.1)                  |
| Injection-site erythema (D0-D4)                   | 0 (0 to 10.3)                 | 1.2 (0.1 to 4.3)               | 3.6 (0.1 to 18.3)                   | 8.8 (5.1 to 14)                      |
| Injection-site pain (D0-D4)                       | 20.6 (8.7 to 37.9)            | 23.2 (16.9 to 30.4)            | 25 (10.7 to 44.9)                   | 32.6 (25.8 to 39.9)                  |
| Injection-site swelling (D0-D4)                   | 0 (0 to 10.3)                 | 1.8 (0.4 to 5.3)               | 7.1 (0.9 to 23.5)                   | 7.2 (3.9 to 12)                      |
| At least 1 systemic AE (D0-D14)                   | 29.4 (15.1 to 47.5)           | 18.3 (12.7 to 25.1)            | 17.9 (6.1 to 36.9)                  | 20.4 (14.8 to 27.1)                  |
| At least 1 solicited systemic AE: pyrexia (D0-D4) | 8.8 (1.9 to 23.7)             | 3.7 (1.4 to 7.8)               | 3.6 (0.1 to 18.3)                   | 2.8 (0.9 to 6.3)                     |
| At least 1 vaccine-related pyrexia (D0-D4)        | 0 (0 to 10.3)                 | 1.8 (0.4 to 5.3)               | 3.6 (0.1 to 18.3)                   | 1.7 (0.3 to 4.8)                     |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Individual anti-HBs antibody titres 1 month after each extra-dose as**

**measured at PPD Vaccines and Biologics LLC, USA**

|                 |  |
|-----------------|--|
| End point title | Individual anti-HBs antibody titres 1 month after each extra-dose as measured at PPD Vaccines and Biologics LLC, USA |
|-----------------|--|

End point description:

# Study participants were blood sampled 1 month after each extra-dose of either HBVaxPRO or ENGERIX-B.

# Individual post extra-doses anti-HBs Ab titres expressed in mIU/mL were measured by the Ortho enhanced chemiluminescence (ECi) assay at the USA laboratory in 15 subjects 1 month after extra-dose 1, and in 3 subjects 1 month after extra-dose 2 of either HBVaxPRO or ENGERIX-B.

Note: "0" means not applicable, "2.5" means anti-HBs titre &lt;5 mIU/mL.

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

End point timeframe:

1 month after each extra-dose of either HBVaxPRO or ENGERIX-B.

| End point values            | HEXAVAC /<br>HBVaxPRO<br>(period 2) | HEXAVAC /<br>ENERGIX-B<br>(period 2) | INFANRIX-<br>HEXA /<br>ENERGIX-B<br>(period 2) |  |
|-----------------------------|-------------------------------------|--------------------------------------|--|--|
| Subject group type          | Reporting group                     | Reporting group                      | Reporting group                                |  |
| Number of subjects analysed | 1                                   | 13                                   | 1  |  |
| Units: Titres (mIU/mL)      |                                     |                                      |  |  |
| number (not applicable)     |                                     |                                      |  |  |
| Subject 04005 extra-dose 1  | 19.8                                | 0                                    | 0  |  |
| Subject 04012 extra-dose 1  | 0                                   | 401                                  | 0  |  |
| Subject 04029 extra-dose 1  | 0                                   | 2.5                                  | 0  |  |
| Subject 04029 extra-dose 2  | 0                                   | 52.8                                 | 0  |  |
| Subject 04037 extra-dose 1  | 0                                   | 15.8                                 | 0  |  |
| Subject 04051 extra-dose 1  | 0                                   | 2.5                                  | 0  |  |
| Subject 04051 extra-dose 2  | 0                                   | 269                                  | 0  |  |
| Subject 04056 extra-dose 1  | 0                                   | 190                                  | 0  |  |
| Subject 04059 extra-dose 1  | 0                                   | 237                                  | 0  |  |
| Subject 04063 extra-dose 1  | 0                                   | 680                                  | 0  |  |
| Subject 04080 extra-dose 1  | 0                                   | 154                                  | 0  |  |
| Subject 04086 extra-dose 1  | 0                                   | 11.5                                 | 0  |  |
| Subject 04114 extra-dose 1  | 0                                   | 36.9                                 | 0  |  |
| Subject 04136 extra-dose 1  | 0                                   | 2.5                                  | 0  |  |
| Subject 04136 extra-dose 2  | 0                                   | 2.5                                  | 0  |  |
| Subject 05049 extra-dose 1  | 0                                   | 93.3                                 | 0  |  |
| Subject 07026 extra-dose 1  | 0                                   | 6.5                                  | 0  |  |
| Subject 01031 extra-dose 1  | 0                                   | 0                                    | 383  |  |

**Statistical analyses**

No statistical analyses for this end point

**Post-hoc: Percentage of subjects with an anti-HBs antibody titre  $\geq 10$  mIU/mL and  $\geq 100$  mIU/mL 1 month after the booster dose of either HBVaxPRO or ENGERIX-B according to the pre-booster anti-HBs antibody titres ( $< 10$  mIU/mL or  $\geq 10$  mIU/mL)**

|   |   |
|---|---|
| End point title   | Percentage of subjects with an anti-HBs antibody titre $\geq 10$ mIU/mL and $\geq 100$ mIU/mL 1 month after the booster dose of either HBVaxPRO or ENGERIX-B according to the pre-booster anti-HBs antibody titres ( $< 10$ mIU/mL or $\geq 10$ mIU/mL) |
| End point description:<br>Percentage of subjects with an anti-HBs titre $\geq 10$ mIU/mL and $\geq 100$ mIU/mL measured by the Ortho enhanced chemiluminescence (ECi) assay at PPD Vaccines and Biologics LLC, USA, 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B, according to the pre-booster anti-HBs antibody titres ( $< 10$ mIU/mL or $\geq 10$ mIU/mL).<br>Post-hoc analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation.<br>Note: (N=***, ***, ***, ***) represents the number of assessed subjects in the HEXAVAC / HBVaxPRO, HEXAVAC / ENGERIX-B, INFANRIX-HEXA / HBVaxPRO, and INFANRIX-HEXA / ENGERIX-B groups, respectively. |   |
| End point type  | Post-hoc  |
| End point timeframe:<br>1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B.   |   |

| End point values   | HEXAVAC / HBVaxPRO (period 1) | HEXAVAC / ENGERIX-B (period 1) | INFANRIX-HEXA / HBVaxPRO (period 1) | INFANRIX-HEXA / ENGERIX-B (period 1) |
|--|-------------------------------|--------------------------------|-------------------------------------|--------------------------------------|
| Subject group type   | Reporting group               | Reporting group                | Reporting group                     | Reporting group                      |
| Number of subjects analysed                                  | 33                            | 159 <sup>[2]</sup>             | 27                                  | 171                                  |
| Units: Percentage of subjects                                |                               |                                |                                     |                                      |
| number (confidence interval 95%)                             |                               |                                |                                     |                                      |
| Pre- $< 10$ , post-booster $\geq 10$ (N=14, 102, 6, 31)      | 78.6 (49.2 to 95.3)           | 86.3 (78 to 92.3)              | 100 (54.1 to 100)                   | 90.3 (74.2 to 98)                    |
| Pre- $< 10$ , post-booster $\geq 100$ (N=14, 102, 6, 31)     | 78.6 (49.2 to 95.3)           | 70.6 (60.7 to 79.2)            | 83.3 (35.9 to 99.6)                 | 77.4 (58.9 to 90.4)                  |
| Pre- $\geq 10$ , post-booster $\geq 10$ (N=19, 57, 21, 140)  | 100 (82.4 to 100)             | 100 (93.7 to 100)              | 100 (83.9 to 100)                   | 99.3 (96.1 to 100)                   |
| Pre- $\geq 10$ , post-booster $\geq 100$ (N=19, 57, 21, 140) | 100 (82.4 to 100)             | 100 (93.7 to 100)              | 100 (83.9 to 100)                   | 99.3 (96.1 to 100)                   |

Notes:

[2] - 1 pre-booster missing data

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: Geometric Mean Titres (GMT) of anti-HBs antibodies 1 month after the booster dose of either HBVaxPRO or ENGERIX-B according to the pre-booster anti-HBs antibody titres

|                 |   |
|-----------------|---|
| End point title | Geometric Mean Titres (GMT) of anti-HBs antibodies 1 month after the booster dose of either HBVaxPRO or ENGERIX-B according to the pre-booster anti-HBs antibody titres |
|-----------------|---|

End point description:

Study participants were blood sampled on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.

Anti-HBs antibody titres expressed in mIU/mL were measured by the Ortho enhanced chemiluminescence (ECi) assay at PPD Vaccines and Biologics LLC, USA.

Post-hoc analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation.

Note: (N=\*\*\*, \*\*\*, \*\*\*, \*\*\*) represents the number of assessed subjects in the HEXAVAC / HBVaxPRO, HEXAVAC / ENGERIX-B, INFANRIX-HEXA / HBVaxPRO, and INFANRIX-HEXA / ENGERIX-B groups, respectively.



|   |          |
|---|----------|
| End point type  | Post-hoc |
| End point timeframe:  |          |
| # Pre-booster: Day 0 (D0) before booster dose.  |          |
| # Post-booster: 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B. |          |

| End point values                               | HEXAVAC /<br>HBVaxPRO<br>(period 1) | HEXAVAC /<br>ENERGIX-B<br>(period 1) | INFANRIX-<br>HEXA /<br>HBVaxPRO<br>(period 1) | INFANRIX-<br>HEXA /<br>ENERGIX-B<br>(period 1) |
|--|-------------------------------------|--------------------------------------|---|--|
| Subject group type                             | Reporting group                     | Reporting group                      | Reporting group                               | Reporting group                                |
| Number of subjects analysed                    | 33                                  | 159 <sup>[3]</sup>                   | 27  | 171  |
| Units: Titres                                  |                                     |                                      |   |  |
| geometric mean (confidence interval 95%)       |                                     |                                      |   |  |
| Pre- <10, pre-booster GMT (N=14, 102, 6, 31)   | 3 (2 to 4)                          | 3 (3 to 3)                           | 3 (3 to 3)                                    | 3 (3 to 3)                                     |
| Pre- <10, post-booster GMT (N=14, 102, 6, 31)  | 239 (60 to 944)                     | 291 (178 to 476)                     | 564 (104 to 3054)                             | 307 (141 to 665)                               |
| Pre- ≥10, pre-booster GMT (N=19, 57, 21, 140)  | 36 (21 to 62)                       | 48 (34 to 68)                        | 118 (67 to 207)                               | 119 (92 to 153)                                |
| Pre- ≥10, post-booster GMT (N=19, 57, 21, 140) | 4266 (2297 to 7921)                 | 6372 (4257 to 9538)                  | 13233 (6447 to 27162)                         | 15023 (11327 to 19925)                         |

Notes:

[3] - 1 pre-booster missing data

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: Geometric Mean Titres Ratios (GMTR) of individual post-/pre-booster anti-HBs antibody titres 1 month after the booster dose of either HBVaxPRO or ENGERIX-B according to the pre-booster anti-HBs antibody titres

|                 |   |
|-----------------|---|
| End point title | Geometric Mean Titres Ratios (GMTR) of individual post-/pre-booster anti-HBs antibody titres 1 month after the booster dose of either HBVaxPRO or ENGERIX-B according to the pre-booster anti-HBs antibody titres |
|-----------------|---|

End point description:

Study participants were blood sampled on Day 0 (D0) before booster dose (pre-booster) and 1 month (D28 to D42) after the booster dose.

Anti-HBs antibody titres were measured by the Ortho enhanced chemiluminescence (ECi) assay at PPD Vaccines and Biologics LLC, USA.

Individual post- (D28-D42) / pre-booster (D0) anti-HBs titres ratios were calculated.

Post-hoc analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects without protocol violation which may interfere with the immunogenicity evaluation.

Note: (N=\*\*\*, \*\*\*, \*\*\*, \*\*\*) represents the number of assessed subjects in the HEXAVAC / HBVaxPRO, HEXAVAC / ENGERIX-B, INFANRIX-HEXA / HBVaxPRO, and INFANRIX-HEXA / ENGERIX-B groups, respectively.

|   |          |
|---|----------|
| End point type  | Post-hoc |
| End point timeframe:  |          |
| 1 month after the booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO or ENGERIX-B. |          |

| <b>End point values</b>                             | HEXAVAC /<br>HBVaxPRO<br>(period 1) | HEXAVAC /<br>ENGERIX-B<br>(period 1) | INFANRIX-<br>HEXA /<br>HBVaxPRO<br>(period 1) | INFANRIX-<br>HEXA /<br>ENGERIX-B<br>(period 1) |
|---|-------------------------------------|--------------------------------------|---|--|
| Subject group type                                  | Reporting group                     | Reporting group                      | Reporting group                               | Reporting group                                |
| Number of subjects analysed                         | 33                                  | 159 <sup>[4]</sup>                   | 27  | 171  |
| Units: Not applicable                               |                                     |                                      |   |  |
| geometric mean (confidence interval<br>95%)         |                                     |                                      |   |  |
| Pre-booster <10 mIU/mL, GMTR (N=14,<br>102, 6, 31)  | 80 (23 to 279)                      | 100 (62 to<br>161)                   | 226 (42 to<br>1222)                           | 104 (49 to<br>221)                             |
| Pre-booster ≥10 mIU/mL, GMTR (N=19,<br>57, 21, 140) | 117 (72 to<br>191)                  | 133 (92 to<br>193)                   | 112 (72 to<br>173)                            | 127 (99 to<br>162)                             |

Notes:

[4] - 1 pre-booster missing data

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Unsolicited non-serious adverse events (AEs) were collected from D0 to D14 after booster dose.

Serious AEs were collected through period 1.

Deaths and vaccine-related serious AEs were collected throughout the study.

Adverse event reporting additional description:

Analysis of AEs was performed on the Safety Analysis Set, i.e. all randomised subjects who received at least 1 vaccination and who had safety follow-up (N=407).

Unsolicited non-serious systemic AEs (vaccine-related or not) with incidence  $\geq 1\%$  in at least 1 reporting group are presented hereafter.

None of the serious AEs were vaccine-related.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | HBVaxPRO (HEXAVAC) |
|-----------------------|--------------------|

Reporting group description:

# Subjects previously vaccinated with 3 doses of HEXAVAC (at 3, 5, and 11 to 13 months of age) received 1 booster dose of HBVaxPRO (Hepatitis B virus surface antigen, recombinant 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular route at 4 to 7 years of age.

# Respectively, 8 (23.5%) subjects reported at least 1 non-serious systemic AE and 1 (2.9%) subject reported 1 vaccine-related non-serious systemic AE within 14 days after booster dose.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | HBVaxPRO (INFANRIX-HEXA) |
|-----------------------|--------------------------|

Reporting group description:

# Subjects previously vaccinated with 3 doses of INFANRIX-HEXA (at 3, 5, and 11 to 13 months of age) received 1 booster dose of HBVaxPRO (Hepatitis B virus surface antigen, recombinant 5 µg, adsorbed on amorphous aluminium hydroxyphosphate sulphate 0.25 mg) by intramuscular route at 4 to 7 years of age.

# 5 (17.9%) subjects reported at least 1 non-serious systemic AE within 14 days after booster dose. No vaccine-related non-serious systemic AE was reported in this reporting group.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | ENGRIX-B (HEXAVAC) |
|-----------------------|--------------------|

Reporting group description:

# Subjects previously vaccinated with 3 doses of HEXAVAC (at 3, 5, and 11 to 13 months of age) received 1 booster dose of ENGRIX-B (Hepatitis B virus surface antigen (rDNA) 10 µg, adsorbed on amorphous aluminium oxide hydrated 0.25 mg) by intramuscular route at 4 to 7 years of age.

# Respectively, 26 (15.9%) subjects reported at least 1 non-serious systemic AE and 2 (1.2%) subjects reported at least 1 vaccine-related non-serious systemic AE within 14 days after booster dose.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | ENGRIX-B (INFANRIX-HEXA) |
|-----------------------|--------------------------|

Reporting group description:

# Subjects previously vaccinated with 3 doses of INFANRIX-HEXA (at 3, 5, and 11 to 13 months of age) received 1 booster dose of ENGRIX-B (Hepatitis B virus surface antigen (rDNA) 10 µg, adsorbed on amorphous aluminium oxide hydrated 0.25 mg) by intramuscular route at 4 to 7 years of age.

# Respectively, 34 (18.8%) subjects reported at least 1 non-serious systemic AE and 6 (3.3%) subjects reported at least 1 vaccine-related non-serious systemic AE within 14 days after booster dose.

| Serious adverse events                            | HBVaxPRO<br>(HEXAVAC) | HBVaxPRO<br>(INFANRIX-HEXA) | ENGRIX-B<br>(HEXAVAC) |
|---|-----------------------|-----------------------------|-----------------------|
| Total subjects affected by serious adverse events |                       |                             |                       |
| subjects affected / exposed                       | 0 / 34 (0.00%)        | 0 / 28 (0.00%)              | 3 / 164 (1.83%)       |
| number of deaths (all causes)                     | 0                     | 0                           | 0                     |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| number of deaths resulting from adverse events       | 0              | 0              | 0               |
| General disorders and administration site conditions |                |                |                 |
| Chest pain   |                |                |                 |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 28 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Infections and infestations                          |                |                |                 |
| Infectious mononucleosis                             |                |                |                 |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 28 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Parotitis  |                |                |                 |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 28 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Tracheobronchitis mycoplasmal                        |                |                |                 |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 28 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders                   |                |                |                 |
| Diabetes mellitus inadequate control                 |                |                |                 |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 28 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |

| <b>Serious adverse events</b>                        | ENERGIX-B<br>(INFANRIX-HEXA) |  |  |
|--|------------------------------|--|--|
| Total subjects affected by serious adverse events    |                              |  |  |
| subjects affected / exposed                          | 1 / 181 (0.55%)              |  |  |
| number of deaths (all causes)                        | 0                            |  |  |
| number of deaths resulting from adverse events       | 0                            |  |  |
| General disorders and administration site conditions |                              |  |  |
| Chest pain   |                              |  |  |
| subjects affected / exposed                          | 0 / 181 (0.00%)              |  |  |
| occurrences causally related to treatment / all      | 0 / 0                        |  |  |
| deaths causally related to treatment / all           | 0 / 0                        |  |  |

|  |                                   |  |  |
|--|-----------------------------------|--|--|
| Infections and infestations<br>Infectious mononucleosis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                    | 0 / 181 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Parotitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 0 / 181 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Tracheobronchitis mycoplasmal<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 0 / 181 (0.00%)<br>0 / 0<br>0 / 0 |  |  |
| Metabolism and nutrition disorders<br>Diabetes mellitus inadequate control<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 181 (0.55%)<br>0 / 1<br>0 / 0 |  |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | HBVaxPRO<br>(HEXAVAC) | HBVaxPRO<br>(INFANRIX-HEXA) | ENGRIX-B<br>(HEXAVAC) |
|---|-----------------------|-----------------------------|-----------------------|
| Total subjects affected by non-serious adverse events |                       |                             |                       |
| subjects affected / exposed                           | 8 / 34 (23.53%)       | 5 / 28 (17.86%)             | 26 / 164 (15.85%)     |
| Nervous system disorders                              |                       |                             |                       |
| Headache  |                       |                             |                       |
| subjects affected / exposed                           | 1 / 34 (2.94%)        | 0 / 28 (0.00%)              | 0 / 164 (0.00%)       |
| occurrences (all)                                     | 1                     | 0                           | 0                     |
| General disorders and administration site conditions  |                       |                             |                       |
| Pyrexia   |                       |                             |                       |
| subjects affected / exposed                           | 1 / 34 (2.94%)        | 1 / 28 (3.57%)              | 9 / 164 (5.49%)       |
| occurrences (all)                                     | 1                     | 1                           | 9                     |
| Ear and labyrinth disorders                           |                       |                             |                       |
| Ear pain  |                       |                             |                       |

|  |                     |                     |                      |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 34 (2.94%)<br>1 | 0 / 28 (0.00%)<br>0 | 2 / 164 (1.22%)<br>2 |
| Gastrointestinal disorders                       |                     |                     |                      |
| Diarrhoea  |                     |                     |                      |
| subjects affected / exposed                      | 1 / 34 (2.94%)      | 1 / 28 (3.57%)      | 1 / 164 (0.61%)      |
| occurrences (all)                                | 1                   | 1                   | 1                    |
| Vomiting   |                     |                     |                      |
| subjects affected / exposed                      | 0 / 34 (0.00%)      | 0 / 28 (0.00%)      | 2 / 164 (1.22%)      |
| occurrences (all)                                | 0                   | 0                   | 2                    |
| Respiratory, thoracic and mediastinal disorders  |                     |                     |                      |
| Cough  |                     |                     |                      |
| subjects affected / exposed                      | 1 / 34 (2.94%)      | 1 / 28 (3.57%)      | 2 / 164 (1.22%)      |
| occurrences (all)                                | 1                   | 1                   | 2                    |
| Oropharyngeal pain                               |                     |                     |                      |
| subjects affected / exposed                      | 2 / 34 (5.88%)      | 0 / 28 (0.00%)      | 0 / 164 (0.00%)      |
| occurrences (all)                                | 2                   | 0                   | 0                    |
| Productive cough                                 |                     |                     |                      |
| subjects affected / exposed                      | 0 / 34 (0.00%)      | 0 / 28 (0.00%)      | 0 / 164 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                    |
| Infections and infestations                      |                     |                     |                      |
| Ear infection                                    |                     |                     |                      |
| subjects affected / exposed                      | 0 / 34 (0.00%)      | 2 / 28 (7.14%)      | 1 / 164 (0.61%)      |
| occurrences (all)                                | 0                   | 3                   | 1                    |
| Influenza  |                     |                     |                      |
| subjects affected / exposed                      | 1 / 34 (2.94%)      | 0 / 28 (0.00%)      | 0 / 164 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                    |
| Nasopharyngitis                                  |                     |                     |                      |
| subjects affected / exposed                      | 1 / 34 (2.94%)      | 1 / 28 (3.57%)      | 0 / 164 (0.00%)      |
| occurrences (all)                                | 1                   | 1                   | 0                    |
| Pharyngitis                                      |                     |                     |                      |
| subjects affected / exposed                      | 0 / 34 (0.00%)      | 1 / 28 (3.57%)      | 2 / 164 (1.22%)      |
| occurrences (all)                                | 0                   | 1                   | 2                    |
| Rhinitis   |                     |                     |                      |
| subjects affected / exposed                      | 0 / 34 (0.00%)      | 1 / 28 (3.57%)      | 0 / 164 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                    |
| Tonsillitis                                      |                     |                     |                      |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 28 (0.00%) | 1 / 164 (0.61%) |
| occurrences (all)           | 0              | 0              | 1               |

|   |                              |  |  |
|---|------------------------------|--|--|
| <b>Non-serious adverse events</b>                     | ENERGIX-B<br>(INFANRIX-HEXA) |  |  |
| Total subjects affected by non-serious adverse events |                              |  |  |
| subjects affected / exposed                           | 34 / 181 (18.78%)            |  |  |
| Nervous system disorders                              |                              |  |  |
| Headache  |                              |  |  |
| subjects affected / exposed                           | 2 / 181 (1.10%)              |  |  |
| occurrences (all)                                     | 2                            |  |  |
| General disorders and administration site conditions  |                              |  |  |
| Pyrexia   |                              |  |  |
| subjects affected / exposed                           | 12 / 181 (6.63%)             |  |  |
| occurrences (all)                                     | 12                           |  |  |
| Ear and labyrinth disorders                           |                              |  |  |
| Ear pain  |                              |  |  |
| subjects affected / exposed                           | 1 / 181 (0.55%)              |  |  |
| occurrences (all)                                     | 1                            |  |  |
| Gastrointestinal disorders                            |                              |  |  |
| Diarrhoea   |                              |  |  |
| subjects affected / exposed                           | 1 / 181 (0.55%)              |  |  |
| occurrences (all)                                     | 1                            |  |  |
| Vomiting  |                              |  |  |
| subjects affected / exposed                           | 2 / 181 (1.10%)              |  |  |
| occurrences (all)                                     | 3                            |  |  |
| Respiratory, thoracic and mediastinal disorders       |                              |  |  |
| Cough   |                              |  |  |
| subjects affected / exposed                           | 6 / 181 (3.31%)              |  |  |
| occurrences (all)                                     | 6                            |  |  |
| Oropharyngeal pain                                    |                              |  |  |
| subjects affected / exposed                           | 1 / 181 (0.55%)              |  |  |
| occurrences (all)                                     | 1                            |  |  |
| Productive cough                                      |                              |  |  |
| subjects affected / exposed                           | 2 / 181 (1.10%)              |  |  |
| occurrences (all)                                     | 2                            |  |  |
| Infections and infestations                           |                              |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Ear infection               |                 |  |  |
| subjects affected / exposed | 6 / 181 (3.31%) |  |  |
| occurrences (all)           | 7               |  |  |
| Influenza                   |                 |  |  |
| subjects affected / exposed | 0 / 181 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Nasopharyngitis             |                 |  |  |
| subjects affected / exposed | 2 / 181 (1.10%) |  |  |
| occurrences (all)           | 2               |  |  |
| Pharyngitis                 |                 |  |  |
| subjects affected / exposed | 4 / 181 (2.21%) |  |  |
| occurrences (all)           | 4               |  |  |
| Rhinitis                    |                 |  |  |
| subjects affected / exposed | 1 / 181 (0.55%) |  |  |
| occurrences (all)           | 1               |  |  |
| Tonsillitis                 |                 |  |  |
| subjects affected / exposed | 2 / 181 (1.10%) |  |  |
| occurrences (all)           | 2               |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 10 December 2008 | Continuation of the study with ENGERIX-B for all subjects from 11 March 2009 due to expiration of the lot of HBVaxPRO used in the study on 14 March 2009. |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported