



## Clinical trial results:

### A Phase III Safety and Efficacy Study to Compare Immune Responses following Injection with Either Two Doses of HEPLISAV™ or Three Doses of Engerix-B®

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2006-006743-31  |
| Trial protocol           | DE              |
| Global end of trial date | 03 October 2008 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 25 June 2022 |
| First version publication date | 25 June 2022 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | DV2-HBV-10 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00435812 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Dynavax Technologies Corporation   |
| Sponsor organisation address | 2100 Powell Street, Suite 720, Emeryville, United States, California 94608                     |
| Public contact               | Robert Janssen, Dynavax Technologies Corporation, 01 510-665-0414 x:1414, rjanssen@dynavax.com |
| Scientific contact           | Robert Janssen, Dynavax Technologies Corporation, 01 510-665-0414 x:1414, rjanssen@dynavax.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                       | 23 November 2009 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 14 March 2008    |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 03 October 2008  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary efficacy objective of this trial is to compare the proportion of subjects who exhibit seroprotective immune response (SPR - anti-HBsAg antibodies [anti-HBsAg]  $\geq 10$  mIU/ml by AUSAB® assay) when measured at Week 12 following vaccination with HEPLISAV at 0 and 1 month to the proportion of subjects who exhibit SPRs when measured at Week 28 following vaccination with Engerix-B at 0, 1 and 6 months.

Protection of trial subjects:

This study was conducted in accordance with the protocol, good clinical practice (GCP) as defined in the International Conference on Harmonisation (ICH) guidelines, country-specific laws and regulations governing clinical studies of investigational products, and the Declaration of Helsinki (1989).

Subjects could withdraw their consent to participate at any time without prejudice. Also, the investigator could withdraw a subject from further treatment if, in the investigator's clinical judgment, it was in the best interest of the subject or if the subject was unable to comply with protocol requirements.

For subjects who were discontinued from the study due to adverse events (AEs), the AE was monitored until resolution or, if the event was determined to be chronic it was monitored until it was stable. If the event remained unresolved at the conclusion of the study, a clinical assessment was made by the investigator and medical monitor to determine whether continued follow-up of the event was warranted. Subjects who were not seroprotected at Week 28 were offered an optional additional injection of Engerix-B and were provided with the anti-HBsAg test results following the additional injection. The optional additional vaccination and test results were outside of protocol procedures and were not captured in the database.

In the event the Sponsor stopped the study prior to completion, subjects were to be offered Engerix-B.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 12 December 2006 |
| 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 | Canada: 1489 |
| Country: Number of subjects enrolled | Germany: 939 |
| Worldwide total number of subjects   | 2428         |
| EEA total number of subjects         | 939          |

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)                     | 0    |
| Adolescents (12-17 years)                 | 13   |
| Adults (18-64 years)                      | 2415 |
| From 65 to 84 years                       | 0    |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

11-55 yrs recruited in Canada, 18-55 yrs recruited in Germany (age adjustment in 1st Amendment).  
Canada recruitment period: 12-Dec-2006 to 11-July-2007. Germany recruitment period 08-Feb-2007 to 11-July-2007.

2400 subjects planned (1018 ISS-HBsAg: 1800; Engerix-B: 600); 2428 subjects enrolled and analyzed (1018 ISS-HBsAg: 1820; Engerix-B: 608)

### Pre-assignment

Screening details:

Medical history, medical evaluation, vital signs, serum pregnancy, urine pregnancy prior to injection, Anti-HBsAg, Hepatitis screen, ANA and anti-ds DNA screens were all performed in the period of -28 to -3 days prior to the first study injection (at Day 0)

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator, Monitor |

Blinding implementation details:

The subjects and the study personnel who evaluated them were blinded to treatment assignment. Independent pharmacists or nurses who had no other study responsibilities were not blinded so they could prepare and/or administer the study injections. In addition, an unblinded study monitor with no other study responsibilities performed drug accountability.

SAEs were evaluated by the medical monitor, who remained blinded to treatment assignment.

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | 1018 ISS-HBsAg group |

Arm description:

Subjects in the 1018 ISS-HBsAg group received active vaccine (Hepilisav-B) at Weeks 0 and 4 and saline placebo at Week 24

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | 1018 ISS-HBsAg         |
| Investigational medicinal product code |                        |
| Other name                             | HEPLISAV, Hepilisav-B  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intramuscular use      |

Dosage and administration details:

The test product (1018 ISS-HBsAg) was 20 mcg HBsAg with 3000 mcg 1018 immunostimulatory sequence (ISS) adjuvant. Subjects received a single intramuscular injection (total injection volume 0.5 mL) into the right or left deltoid muscle at Weeks 0 and 4 (placebo at Week 24). The arm used for injection was alternated with each injection.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Engerix-B group |
|------------------|-----------------|

Arm description:

3-dose regimen of Engerix-B (Weeks 0, 4 and 24)

|  |                        |
|--|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Engerix-B              |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intramuscular use      |

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**Dosage and administration details:**

Engerix-B (20 mcg HBsAg combined with 500 mcg alum adjuvant/mL; GlaxoSmithKline Biologicals) administered as a single intramuscular injection (1.0 mL) into the deltoid muscle at Weeks 0, 4, and 24. The arm used for injection was alternated with each injection.

| <b>Number of subjects in period 1</b> | 1018 ISS-HBsAg group | Engerix-B group |
|---------------------------------------|----------------------|-----------------|
| Started                               | 1820                 | 608             |
| Completed                             | 1757                 | 590             |
| Not completed                         | 63                   | 18              |
| Subject Non-Compliance                | 3                    | 2               |
| Consent withdrawn by subject          | 18                   | 2               |
| Adverse event, non-fatal              | 2                    | 2               |
| Other                                 | 8                    | 2               |
| Lost to follow-up                     | 30                   | 10              |
| Protocol deviation                    | 2                    | -               |

## Baseline characteristics

### Reporting groups

|  |                      |
|--|----------------------|
| Reporting group title  | 1018 ISS-HBsAg group |
| Reporting group description:<br>Subjects in the 1018 ISS-HBsAg group received active vaccine (Heplisav-B) at Weeks 0 and 4 and saline placebo at Week 24 |                      |
| Reporting group title  | Engerix-B group      |
| Reporting group description:<br>3-dose regimen of Engerix-B (Weeks 0, 4 and 24)  |                      |

| Reporting group values   | 1018 ISS-HBsAg group | Engerix-B group | Total |
|--|----------------------|-----------------|-------|
| Number of subjects   | 1820                 | 608             | 2428  |
| Age categorical  |                      |                 |       |
| The effect of age on immunogenicity was evaluated in 4 age strata:<br>Subjects 18 to 55 years of age<br>Subjects 18-39 years of age<br>Subjects 40-55 years of age<br>Subjects 11 to 17 years of age<br>Safety analysis populations:<br>Subjects 11-39 years of age, and subjects 40-55 years of age |                      |                 |       |
| Units: Subjects  |                      |                 |       |
| In utero   | 0                    | 0               | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks)  | 0                    | 0               | 0     |
| Newborns (0-27 days)   | 0                    | 0               | 0     |
| Infants and toddlers (28 days-23 months)   | 0                    | 0               | 0     |
| Children (2-11 years)  | 0                    | 0               | 0     |
| Adolescents (12-17 years)  | 0                    | 0               | 0     |
| Adults (18-64 years)   | 0                    | 0               | 0     |
| From 65-84 years   | 0                    | 0               | 0     |
| 85 years and over  | 0                    | 0               | 0     |
| 11-17 years  | 11                   | 2               | 13    |
| 18-39 years  | 818                  | 275             | 1093  |
| 40-55 years  | 991                  | 331             | 1322  |
| 11-39  | 0                    | 0               | 0     |
| Age continuous   |                      |                 |       |
| Age mean (SD) by treatment group   |                      |                 |       |
| Units: years   |                      |                 |       |
| arithmetic mean  | 39.7                 | 39.8            |       |
| standard deviation   | ± 9.56               | ± 9.11          | -     |
| Gender categorical   |                      |                 |       |
| Male or female   |                      |                 |       |
| Units: Subjects  |                      |                 |       |
| Female   | 959                  | 346             | 1305  |
| Male   | 861                  | 262             | 1123  |

## Subject analysis sets

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | 1018 ISS-HBsAg PP |
| Subject analysis set type  | Per protocol      |

Subject analysis set description:

The primary immunogenicity analysis was based on the PP population. The PP analysis population comprised all subjects who met eligibility criteria, did not violate the protocol in a substantial manner, received all protocol-specified study injections, had their primary serology and all injections within the specified day ranges as defined in Section 8.5 of the SAP, and had serology at their primary endpoint (Week 12 for 1018 ISS-HBsAg group).

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | Engerix-B PP |
| Subject analysis set type  | Per protocol |

Subject analysis set description:

The primary immunogenicity analysis was based on the PP population. The PP analysis population comprised all subjects who met eligibility criteria, did not violate the protocol in a substantial manner, received all protocol-specified study injections, had their primary serology and all injections within the specified day ranges as defined in Section 8.5 of the SAP, and had serology at their primary endpoint (Week 28 for Engerix-B group).

|                            |                       |
|----------------------------|-----------------------|
| Subject analysis set title | 1018 ISS-HBsAg Safety |
| Subject analysis set type  | Safety analysis       |

Subject analysis set description:

Enrolled subjects who received at least 1 study injection and had any post-baseline safety data.

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Engerix-B Safety |
| Subject analysis set type  | Safety analysis  |

Subject analysis set description:

Enrolled subjects who received at least 1 study injection and had any post-baseline safety data

| Reporting group values   | 1018 ISS-HBsAg PP | Engerix-B PP | 1018 ISS-HBsAg Safety |
|--|-------------------|--------------|-----------------------|
| Number of subjects   | 1520              | 523          | 1820                  |
| Age categorical  |                   |              |                       |
| The effect of age on immunogenicity was evaluated in 4 age strata:<br>Subjects 18 to 55 years of age<br>Subjects 18-39 years of age<br>Subjects 40-55 years of age<br>Subjects 11 to 17 years of age<br>Safety analysis populations:<br>Subjects 11-39 years of age, and subjects 40-55 years of age |                   |              |                       |
| Units: Subjects  |                   |              |                       |
| In utero   | 0                 | 0            | 0                     |
| Preterm newborn infants (gestational age < 37 wks)   | 0                 | 0            | 0                     |
| Newborns (0-27 days)   | 0                 | 0            | 0                     |
| Infants and toddlers (28 days-23 months)   | 0                 | 0            | 0                     |
| Children (2-11 years)  | 0                 | 0            | 0                     |
| Adolescents (12-17 years)  | 0                 | 0            | 0                     |
| Adults (18-64 years)   | 0                 | 0            | 0                     |
| From 65-84 years   | 0                 | 0            | 0                     |
| 85 years and over  | 0                 | 0            | 0                     |
| 11-17 years  | 10                | 2            | 0                     |
| 18-39 years  | 654               | 222          | 0                     |
| 40-55 years  | 856               | 299          | 991                   |
| 11-39  | 0                 | 0            | 829                   |

|                                  |        |        |        |
|----------------------------------|--------|--------|--------|
| Age continuous                   |        |        |        |
| Age mean (SD) by treatment group |        |        |        |
| Units: years                     |        |        |        |
| arithmetic mean                  | 40.1   | 40.4   | 39.9   |
| standard deviation               | ± 9.46 | ± 8.94 | ± 9.36 |
| Gender categorical               |        |        |        |
| Male or female                   |        |        |        |
| Units: Subjects                  |        |        |        |
| Female                           | 815    | 304    | 959    |
| Male                             | 705    | 219    | 861    |

|  |                  |  |  |
|--|------------------|--|--|
| <b>Reporting group values</b>  | Engerix-B Safety |  |  |
| Number of subjects   | 608              |  |  |
| Age categorical  |                  |  |  |
| The effect of age on immunogenicity was evaluated in 4 age strata:<br>Subjects 18 to 55 years of age<br>Subjects 18-39 years of age<br>Subjects 40-55 years of age<br>Subjects 11 to 17 years of age<br>Safety analysis populations:<br>Subjects 11-39 years of age, and subjects 40-55 years of age |                  |  |  |
| Units: Subjects  |                  |  |  |
| In utero   | 0                |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks)  | 0                |  |  |
| Newborns (0-27 days)   | 0                |  |  |
| Infants and toddlers (28 days-23<br>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                |  |  |
| 11-17 years  | 0                |  |  |
| 18-39 years  | 0                |  |  |
| 40-55 years  | 331              |  |  |
| 11-39  | 277              |  |  |
| Age continuous   |                  |  |  |
| Age mean (SD) by treatment group   |                  |  |  |
| Units: years   |                  |  |  |
| arithmetic mean  | 39.8             |  |  |
| standard deviation   | ± 9.01           |  |  |
| Gender categorical   |                  |  |  |
| Male or female   |                  |  |  |
| Units: Subjects  |                  |  |  |
| Female   | 346              |  |  |
| Male   | 262              |  |  |



## End points

### End points reporting groups

|   |                       |
|---|-----------------------|
| Reporting group title   | 1018 ISS-HBsAg group  |
| Reporting group description:<br>Subjects in the 1018 ISS-HBsAg group received active vaccine (Heplisav-B) at Weeks 0 and 4 and saline placebo at Week 24  |                       |
| Reporting group title   | Engerix-B group       |
| Reporting group description:<br>3-dose regimen of Engerix-B (Weeks 0, 4 and 24)   |                       |
| Subject analysis set title  | 1018 ISS-HBsAg PP     |
| Subject analysis set type   | Per protocol          |
| Subject analysis set description:<br>The primary immunogenicity analysis was based on the PP population. The PP analysis population comprised all subjects who met eligibility criteria, did not violate the protocol in a substantial manner, received all protocol-specified study injections, had their primary serology and all injections within the specified day ranges as defined in Section 8.5 of the SAP, and had serology at their primary endpoint (Week 12 for 1018 ISS-HBsAg group). |                       |
| Subject analysis set title  | Engerix-B PP          |
| Subject analysis set type   | Per protocol          |
| Subject analysis set description:<br>The primary immunogenicity analysis was based on the PP population. The PP analysis population comprised all subjects who met eligibility criteria, did not violate the protocol in a substantial manner, received all protocol-specified study injections, had their primary serology and all injections within the specified day ranges as defined in Section 8.5 of the SAP, and had serology at their primary endpoint (Week 28 for Engerix-B group).      |                       |
| Subject analysis set title  | 1018 ISS-HBsAg Safety |
| Subject analysis set type   | Safety analysis       |
| Subject analysis set description:<br>Enrolled subjects who received at least 1 study injection and had any post-baseline safety data.   |                       |
| Subject analysis set title  | Engerix-B Safety      |
| Subject analysis set type   | Safety analysis       |
| Subject analysis set description:<br>Enrolled subjects who received at least 1 study injection and had any post-baseline safety data  |                       |

### Primary: Primary Immunogenicity Analysis: SPR after the final active injection

|  |   |
|--|---|
| End point title  | Primary Immunogenicity Analysis: SPR after the final active injection |
| End point description:<br>SPR at 12 weeks post last active injection                       |   |
| End point type   | Primary   |
| End point timeframe:<br>Week 12 for 1018 ISS-HBsAg group, and Week 28 for Engerix-B group. |   |

| End point values            | 1018 ISS-HBsAg PP    | Engerix-B PP         |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 1520                 | 523                  |  |  |
| Units: percent              |                      |                      |  |  |
| number (not applicable)     | 95.02                | 81.36                |  |  |

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>   | Primary immunogenicity analysis  |
| Statistical analysis description:<br>The primary immunogenicity analysis determined the difference in the SPR between Engerix-B at Week 28 and 1018 ISS-HBsAg at Week 12 with a 2 sided 95% CI on the difference (Engerix-B minus 1018 ISS-HBsAg) in SPR. If the upper limit of this CI is below the pre-specified non-inferiority criterion (+10%), 1018 ISS-HBsAg was non-inferior to Engerix-B in SPR. |                                  |
| Comparison groups   | 1018 ISS-HBsAg PP v Engerix-B PP |
| Number of subjects included in analysis   | 2043                             |
| Analysis specification  | Pre-specified                    |
| Analysis type   | non-inferiority                  |
| P-value   | = 0.05                           |
| Method  | t-test, 2-sided                  |

## Secondary: Secondary Immunogenicity Analysis: SPR measured 4 weeks after the first injection (onset of response)

|   |   |
|---|---|
| End point title   | Secondary Immunogenicity Analysis: SPR measured 4 weeks after the first injection (onset of response) |
| End point description:  |   |
| End point type  | Secondary   |
| End point timeframe:<br>4 weeks after the first injection for both treatment groups |   |

| End point values            | 1018 ISS-HBsAg PP    | Engerix-B PP         |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 1510                 | 521                  |  |  |
| Units: percent              |                      |                      |  |  |
| number (not applicable)     | 23.54                | 4.06                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Safety: Solicited post-injection reactions

|                 |  |
|-----------------|--|
| End point title | Safety: Solicited post-injection reactions |
|-----------------|--|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Days 0-6 following each injection (Wks 0, 4 and 24)

| End point values            | 1018 ISS-<br>HBsAg Safety | Engerix-B<br>Safety  |  |  |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type          | Subject analysis set      | Subject analysis set |  |  |
| Number of subjects analysed | 1820                      | 608                  |  |  |
| Units: percent              |                           |                      |  |  |
| number (not applicable)     | 52.0                      | 48.4                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Safety: Change in ANA levels from baseline

|                 |  |
|-----------------|--|
| End point title | Safety: Change in ANA levels from baseline |
|-----------------|--|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 28

| End point values             | 1018 ISS-<br>HBsAg Safety | Engerix-B<br>Safety  |  |  |
|------------------------------|---------------------------|----------------------|--|--|
| Subject group type           | Subject analysis set      | Subject analysis set |  |  |
| Number of subjects analysed  | 1820                      | 608                  |  |  |
| Units: percent               |                           |                      |  |  |
| number (not applicable)      |                           |                      |  |  |
| 1 dilution increase          | 1.7                       | 1.3                  |  |  |
| 2 dilution increase          | 0.5                       | 1.0                  |  |  |
| 3 dilution increase          | 0.1                       | 0                    |  |  |
| 4 dilution increase          | 0                         | 0                    |  |  |
| >4 dilution increase         | 0                         | 0                    |  |  |
| At least 2 dilution increase | 0.6                       | 1.0                  |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Other pre-specified: Safety: Change in Anti-ds DNA levels from baseline**

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|                 |  |
|-----------------|--|
| End point title | Safety: Change in Anti-ds DNA levels from baseline |
|-----------------|--|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 28

---

| End point values            | 1018 ISS-<br>HBsAg Safety | Engerix-B<br>Safety  |  |  |
|-----------------------------|---------------------------|----------------------|--|--|
| Subject group type          | Subject analysis set      | Subject analysis set |  |  |
| Number of subjects analysed | 1820                      | 608                  |  |  |
| Units: percent              |                           |                      |  |  |
| number (not applicable)     |                           |                      |  |  |
| Negative to negative        | 94.8                      | 94.6                 |  |  |
| Negative to positive        | 0.5                       | 0.5                  |  |  |
| Positive to negative        | 0.3                       | 0.5                  |  |  |
| Positive to positive        | 0                         | 0                    |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Any AE that began on or after the day of the first study injection, or any AE that began before the day of the first study injection and worsened on or after the day of the first study injection, and are referred to simply as AEs

Adverse event reporting additional description:

All AEs described in this section were treatment emergent, defined according to the timeframe above. Note that AEs are referred to as unsolicited adverse experiences in the CSR.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | 1018 ISS-HBsAg |
|-----------------------|----------------|

Reporting group description:

Subjects receiving the experimental vaccine

|                       |           |
|-----------------------|-----------|
| Reporting group title | Engerix-B |
|-----------------------|-----------|

Reporting group description:

Subjects received active comparator vaccine

| Serious adverse events  | 1018 ISS-HBsAg    | Engerix-B        |  |
|---|-------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                   |                  |  |
| subjects affected / exposed   | 28 / 1820 (1.54%) | 13 / 608 (2.14%) |  |
| number of deaths (all causes)                                       | 0                 | 0                |  |
| number of deaths resulting from adverse events                      | 0                 | 0                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                  |  |
| Breast cancer   |                   |                  |  |
| subjects affected / exposed   | 2 / 1820 (0.11%)  | 0 / 608 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0            |  |
| Breast cancer recurrent   |                   |                  |  |
| subjects affected / exposed   | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0            |  |
| Meningioma  |                   |                  |  |
| subjects affected / exposed   | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0            |  |

|  |                  |                 |  |
|--|------------------|-----------------|--|
| Papillary thyroid cancer                                 |                  |                 |  |
| subjects affected / exposed                              | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all          | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0           |  |
| Surgical and medical procedures                          |                  |                 |  |
| Meningioma surgery                                       |                  |                 |  |
| subjects affected / exposed                              | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all          | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0           |  |
| Immune system disorders                                  |                  |                 |  |
| Anti-neutrophil cytoplasmic antibody positive vasculitis |                  |                 |  |
| subjects affected / exposed                              | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0           |  |
| Reproductive system and breast disorders                 |                  |                 |  |
| Prostatitis  |                  |                 |  |
| subjects affected / exposed                              | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all          | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0           |  |
| menorrhagia  |                  |                 |  |
| subjects affected / exposed                              | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0           |  |
| Ovarian cyst   |                  |                 |  |
| subjects affected / exposed                              | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders          |                  |                 |  |
| Pulmonary embolism                                       |                  |                 |  |
| subjects affected / exposed                              | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all          | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0           |  |
| Pneumothorax   |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Wegener's Granulomatosis                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Asthma  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Psychiatric disorders                           |                  |                 |  |
| Depression                                      |                  |                 |  |
| subjects affected / exposed                     | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Delirium tremens                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                  |                 |  |
| Jaw fracture                                    |                  |                 |  |
| subjects affected / exposed                     | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ankle fracture                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dislocation of joint prosthesis                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Meniscus lesion                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Patella fracture                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sternal fracture                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Tendon rupture                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ulna fracture                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Femur fracture                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Joint injury                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cardiac disorders                               |                  |                 |  |
| Supraventricular tachycardia                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Angina pectoris                                 |                  |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Arrhythmia                                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nervous system disorders                        |                  |                 |  |
| Cerebral ischaemia                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Guillain-Barre syndrome                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders                      |                  |                 |  |
| Gastritis                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatitis                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatobiliary disorders                         |                  |                 |  |
| Cholecystitis acute                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal and urinary disorders                     |                  |                 |  |
| Renal failure                                   |                  |                 |  |

|  |                  |                 |  |
|--|------------------|-----------------|--|
| subjects affected / exposed                            | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0           |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                  |                 |  |
| Bursitis   |                  |                 |  |
| subjects affected / exposed                            | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0           |  |
| Gouty arthritis  |                  |                 |  |
| subjects affected / exposed                            | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0           |  |
| Intervertebral disc protrusion                         |                  |                 |  |
| subjects affected / exposed                            | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all        | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0           |  |
| <b>Infections and infestations</b>                     |                  |                 |  |
| Tonsillitis  |                  |                 |  |
| subjects affected / exposed                            | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0           |  |
| Adnexitis  |                  |                 |  |
| subjects affected / exposed                            | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all        | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0           |  |
| Liver abscess  |                  |                 |  |
| subjects affected / exposed                            | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all        | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0           |  |
| Septic shock   |                  |                 |  |
| subjects affected / exposed                            | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences causally related to treatment / all        | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | 1018 ISS-HBsAg       | Engerix-B          |  |
|---|----------------------|--------------------|--|
| Total subjects affected by non-serious adverse events               |                      |                    |  |
| subjects affected / exposed   | 1098 / 1820 (60.33%) | 376 / 608 (61.84%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                      |                    |  |
| Skin papilloma  |                      |                    |  |
| subjects affected / exposed   | 10 / 1820 (0.55%)    | 3 / 608 (0.49%)    |  |
| occurrences (all)   | 10                   | 3                  |  |
| Breast cancer   |                      |                    |  |
| subjects affected / exposed   | 2 / 1820 (0.11%)     | 0 / 608 (0.00%)    |  |
| occurrences (all)   | 2                    | 0                  |  |
| Benign breast neoplasm  |                      |                    |  |
| subjects affected / exposed   | 1 / 1820 (0.05%)     | 0 / 608 (0.00%)    |  |
| occurrences (all)   | 1                    | 0                  |  |
| Benign neoplasm of adrenal gland                                    |                      |                    |  |
| subjects affected / exposed   | 1 / 1820 (0.05%)     | 0 / 608 (0.00%)    |  |
| occurrences (all)   | 1                    | 0                  |  |
| Nasal neoplasm  |                      |                    |  |
| subjects affected / exposed   | 1 / 1820 (0.05%)     | 0 / 608 (0.00%)    |  |
| occurrences (all)   | 1                    | 0                  |  |
| Melanocytic naevus  |                      |                    |  |
| subjects affected / exposed   | 2 / 1820 (0.11%)     | 3 / 608 (0.49%)    |  |
| occurrences (all)   | 2                    | 3                  |  |
| Basal cell carcinoma  |                      |                    |  |
| subjects affected / exposed   | 1 / 1820 (0.05%)     | 0 / 608 (0.00%)    |  |
| occurrences (all)   | 1                    | 0                  |  |
| Haemangioma of skin   |                      |                    |  |
| subjects affected / exposed   | 0 / 1820 (0.00%)     | 1 / 608 (0.16%)    |  |
| occurrences (all)   | 0                    | 1                  |  |
| Vascular disorders  |                      |                    |  |

|                              |                   |                  |
|------------------------------|-------------------|------------------|
| Hypertension                 |                   |                  |
| subjects affected / exposed  | 38 / 1820 (2.09%) | 17 / 608 (2.80%) |
| occurrences (all)            | 38                | 17               |
| Circulatory collapse         |                   |                  |
| subjects affected / exposed  | 2 / 1820 (0.11%)  | 1 / 608 (0.16%)  |
| occurrences (all)            | 2                 | 1                |
| Phlebitis                    |                   |                  |
| subjects affected / exposed  | 1 / 1820 (0.05%)  | 1 / 608 (0.16%)  |
| occurrences (all)            | 1                 | 1                |
| Hypotension                  |                   |                  |
| subjects affected / exposed  | 1 / 1820 (0.05%)  | 2 / 608 (0.33%)  |
| occurrences (all)            | 1                 | 2                |
| Thrombosis                   |                   |                  |
| subjects affected / exposed  | 0 / 1820 (0.00%)  | 1 / 608 (0.16%)  |
| occurrences (all)            | 0                 | 1                |
| Venous insufficiency         |                   |                  |
| subjects affected / exposed  | 0 / 1820 (0.00%)  | 1 / 608 (0.16%)  |
| occurrences (all)            | 0                 | 1                |
| Deep vein thrombosis         |                   |                  |
| subjects affected / exposed  | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |
| occurrences (all)            | 1                 | 0                |
| Haematoma                    |                   |                  |
| subjects affected / exposed  | 1 / 1820 (0.05%)  | 1 / 608 (0.16%)  |
| occurrences (all)            | 1                 | 1                |
| Peripheral vascular disorder |                   |                  |
| subjects affected / exposed  | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |
| occurrences (all)            | 1                 | 0                |
| Varicose vein                |                   |                  |
| subjects affected / exposed  | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |
| occurrences (all)            | 1                 | 0                |
| Flushing                     |                   |                  |
| subjects affected / exposed  | 0 / 1820 (0.00%)  | 1 / 608 (0.16%)  |
| occurrences (all)            | 0                 | 1                |
| Raynaud's phenomenon         |                   |                  |
| subjects affected / exposed  | 0 / 1820 (0.00%)  | 1 / 608 (0.16%)  |
| occurrences (all)            | 0                 | 1                |

|  |                   |                  |  |
|--|-------------------|------------------|--|
| Surgical and medical procedures                      |                   |                  |  |
| Meningioma surgery                                   |                   |                  |  |
| subjects affected / exposed                          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                                    | 1                 | 0                |  |
| Wart excision  |                   |                  |  |
| subjects affected / exposed                          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                                    | 1                 | 0                |  |
| Inguinal hernia repair                               |                   |                  |  |
| subjects affected / exposed                          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                                    | 1                 | 0                |  |
| Wisdom teeth removal                                 |                   |                  |  |
| subjects affected / exposed                          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                                    | 1                 | 0                |  |
| General disorders and administration site conditions |                   |                  |  |
| Pyrexia  |                   |                  |  |
| subjects affected / exposed                          | 21 / 1820 (1.15%) | 11 / 608 (1.81%) |  |
| occurrences (all)                                    | 21                | 11               |  |
| Fatigue  |                   |                  |  |
| subjects affected / exposed                          | 24 / 1820 (1.32%) | 4 / 608 (0.66%)  |  |
| occurrences (all)                                    | 24                | 4                |  |
| Influenza like illness                               |                   |                  |  |
| subjects affected / exposed                          | 11 / 1820 (0.60%) | 3 / 608 (0.49%)  |  |
| occurrences (all)                                    | 11                | 3                |  |
| Oedema peripheral                                    |                   |                  |  |
| subjects affected / exposed                          | 9 / 1820 (0.49%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                                    | 9                 | 1                |  |
| Chills   |                   |                  |  |
| subjects affected / exposed                          | 3 / 1820 (0.16%)  | 2 / 608 (0.33%)  |  |
| occurrences (all)                                    | 3                 | 2                |  |
| Malaise  |                   |                  |  |
| subjects affected / exposed                          | 5 / 1820 (0.27%)  | 6 / 608 (0.99%)  |  |
| occurrences (all)                                    | 5                 | 6                |  |
| Pain   |                   |                  |  |
| subjects affected / exposed                          | 3 / 1820 (0.16%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                                    | 3                 | 1                |  |
| Chest discomfort                                     |                   |                  |  |

|                                |                  |                 |
|--------------------------------|------------------|-----------------|
| subjects affected / exposed    | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)              | 2                | 0               |
| Polyp                          |                  |                 |
| subjects affected / exposed    | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)              | 2                | 0               |
| Asthenia                       |                  |                 |
| subjects affected / exposed    | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)              | 2                | 0               |
| Axillary pain                  |                  |                 |
| subjects affected / exposed    | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)              | 1                | 0               |
| Chest pain                     |                  |                 |
| subjects affected / exposed    | 4 / 1820 (0.22%) | 1 / 608 (0.16%) |
| occurrences (all)              | 4                | 1               |
| Cyst                           |                  |                 |
| subjects affected / exposed    | 2 / 1820 (0.11%) | 2 / 608 (0.33%) |
| occurrences (all)              | 2                | 2               |
| Feeling cold                   |                  |                 |
| subjects affected / exposed    | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)              | 1                | 0               |
| Hangover                       |                  |                 |
| subjects affected / exposed    | 2 / 1820 (0.11%) | 1 / 608 (0.16%) |
| occurrences (all)              | 2                | 1               |
| local swelling                 |                  |                 |
| subjects affected / exposed    | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)              | 1                | 0               |
| Thirst                         |                  |                 |
| subjects affected / exposed    | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)              | 1                | 0               |
| Feeling abnormal               |                  |                 |
| subjects affected / exposed    | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)              | 0                | 1               |
| lower extremity mass           |                  |                 |
| subjects affected / exposed    | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)              | 0                | 1               |
| Vessel puncture site haematoma |                  |                 |

|                                      |                   |                 |
|--------------------------------------|-------------------|-----------------|
| subjects affected / exposed          | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |
| occurrences (all)                    | 0                 | 1               |
| Vessel puncture site reaction        |                   |                 |
| subjects affected / exposed          | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |
| occurrences (all)                    | 0                 | 1               |
| Injection site bruising              |                   |                 |
| subjects affected / exposed          | 11 / 1820 (0.60%) | 2 / 608 (0.33%) |
| occurrences (all)                    | 11                | 2               |
| Injection site discomfort            |                   |                 |
| subjects affected / exposed          | 3 / 1820 (0.16%)  | 0 / 608 (0.00%) |
| occurrences (all)                    | 3                 | 0               |
| Injection site pruritus              |                   |                 |
| subjects affected / exposed          | 3 / 1820 (0.16%)  | 1 / 608 (0.16%) |
| occurrences (all)                    | 3                 | 1               |
| Facial pain                          |                   |                 |
| subjects affected / exposed          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)                    | 1                 | 0               |
| Injection site haematoma             |                   |                 |
| subjects affected / exposed          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)                    | 1                 | 0               |
| Injection site pain                  |                   |                 |
| subjects affected / exposed          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)                    | 1                 | 0               |
| Injection site warmth                |                   |                 |
| subjects affected / exposed          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)                    | 1                 | 0               |
| Non-cardiac chest pain               |                   |                 |
| subjects affected / exposed          | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)                    | 1                 | 0               |
| Injection site reaction              |                   |                 |
| subjects affected / exposed          | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |
| occurrences (all)                    | 0                 | 1               |
| Peripheral coldness                  |                   |                 |
| subjects affected / exposed          | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |
| occurrences (all)                    | 0                 | 1               |
| Anti-neutrophil cytoplasmic antibody |                   |                 |

|  |                   |                 |  |
|--|-------------------|-----------------|--|
| positive vasculitis                      |                   |                 |  |
| subjects affected / exposed              | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                        | 0                 | 1               |  |
| Contrast media allergy                   |                   |                 |  |
| subjects affected / exposed              | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                        | 0                 | 1               |  |
| Immune system disorders                  |                   |                 |  |
| Seasonal allergy                         |                   |                 |  |
| subjects affected / exposed              | 6 / 1820 (0.33%)  | 3 / 608 (0.49%) |  |
| occurrences (all)                        | 6                 | 3               |  |
| Allergy to arthropod bite                |                   |                 |  |
| subjects affected / exposed              | 2 / 1820 (0.11%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                        | 2                 | 0               |  |
| Hypersensitivity                         |                   |                 |  |
| subjects affected / exposed              | 3 / 1820 (0.16%)  | 2 / 608 (0.33%) |  |
| occurrences (all)                        | 3                 | 2               |  |
| Food allergy                             |                   |                 |  |
| subjects affected / exposed              | 3 / 1820 (0.16%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                        | 3                 | 1               |  |
| house dust allergy                       |                   |                 |  |
| subjects affected / exposed              | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                        | 1                 | 0               |  |
| Allergy to plants                        |                   |                 |  |
| subjects affected / exposed              | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                        | 1                 | 0               |  |
| Reproductive system and breast disorders |                   |                 |  |
| Dysmenorrhoea                            |                   |                 |  |
| subjects affected / exposed              | 21 / 1820 (1.15%) | 8 / 608 (1.32%) |  |
| occurrences (all)                        | 21                | 8               |  |
| Menstrual disorder                       |                   |                 |  |
| subjects affected / exposed              | 5 / 1820 (0.27%)  | 2 / 608 (0.33%) |  |
| occurrences (all)                        | 5                 | 2               |  |
| Amenorrhoea                              |                   |                 |  |
| subjects affected / exposed              | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                        | 1                 | 0               |  |
| Breast cyst                              |                   |                 |  |



|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Breast pain                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Breast swelling             |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Dyspareunia                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Menopausal disorder         |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Menorrhagia                 |                  |                 |
| subjects affected / exposed | 6 / 1820 (0.33%) | 2 / 608 (0.33%) |
| occurrences (all)           | 6                | 2               |
| Ovarian cyst                |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 1 / 608 (0.16%) |
| occurrences (all)           | 3                | 1               |
| Pelvic pain                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Postmenopausal haemorrhage  |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Prostatitis                 |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)           | 3                | 0               |
| Vulvovaginal pruritus       |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Metrorrhagia                |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Vaginal haemorrhage         |                  |                 |

|                                       |                  |                 |  |
|---------------------------------------|------------------|-----------------|--|
| subjects affected / exposed           | 1 / 1820 (0.05%) | 2 / 608 (0.33%) |  |
| occurrences (all)                     | 1                | 2               |  |
| Vulva cyst                            |                  |                 |  |
| subjects affected / exposed           | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                     | 0                | 1               |  |
| Vulvovaginal dryness                  |                  |                 |  |
| subjects affected / exposed           | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                     | 0                | 1               |  |
| Erectile dysfunction                  |                  |                 |  |
| subjects affected / exposed           | 3 / 1820 (0.16%) | 1 / 608 (0.16%) |  |
| occurrences (all)                     | 3                | 1               |  |
| Breast discomfort                     |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Hot flush                             |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |  |
| occurrences (all)                     | 1                | 1               |  |
| Menopausal symptoms                   |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Premenstrual syndrome                 |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Sexual dysfunction                    |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Vaginal discharge                     |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Vulvovaginal discomfort               |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Balanitis                             |                  |                 |  |
| subjects affected / exposed           | 0 / 1820 (0.00%) | 2 / 608 (0.33%) |  |
| occurrences (all)                     | 0                | 2               |  |
| Respiratory, thoracic and mediastinal |                  |                 |  |

|                              |                   |                  |  |
|------------------------------|-------------------|------------------|--|
| disorders                    |                   |                  |  |
| Pharyngolaryngeal pain       |                   |                  |  |
| subjects affected / exposed  | 80 / 1820 (4.40%) | 25 / 608 (4.11%) |  |
| occurrences (all)            | 80                | 25               |  |
| Cough                        |                   |                  |  |
| subjects affected / exposed  | 57 / 1820 (3.13%) | 17 / 608 (2.80%) |  |
| occurrences (all)            | 57                | 17               |  |
| Nasal congestion             |                   |                  |  |
| subjects affected / exposed  | 31 / 1820 (1.70%) | 4 / 608 (0.66%)  |  |
| occurrences (all)            | 31                | 4                |  |
| Sinus headache               |                   |                  |  |
| subjects affected / exposed  | 14 / 1820 (0.77%) | 3 / 608 (0.49%)  |  |
| occurrences (all)            | 14                | 3                |  |
| Rhinorrhoea                  |                   |                  |  |
| subjects affected / exposed  | 8 / 1820 (0.44%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)            | 8                 | 0                |  |
| Asthma                       |                   |                  |  |
| subjects affected / exposed  | 9 / 1820 (0.49%)  | 2 / 608 (0.33%)  |  |
| occurrences (all)            | 9                 | 2                |  |
| Rhinitis allergic            |                   |                  |  |
| subjects affected / exposed  | 5 / 1820 (0.27%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)            | 5                 | 0                |  |
| Respiratory tract congestion |                   |                  |  |
| subjects affected / exposed  | 5 / 1820 (0.27%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)            | 5                 | 0                |  |
| Dyspnoea                     |                   |                  |  |
| subjects affected / exposed  | 4 / 1820 (0.22%)  | 2 / 608 (0.33%)  |  |
| occurrences (all)            | 4                 | 2                |  |
| Epistaxis                    |                   |                  |  |
| subjects affected / exposed  | 2 / 1820 (0.11%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)            | 2                 | 1                |  |
| Pharyngitis                  |                   |                  |  |
| subjects affected / exposed  | 2 / 1820 (0.11%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)            | 2                 | 0                |  |
| Dry throat                   |                   |                  |  |

|                                    |                  |                 |
|------------------------------------|------------------|-----------------|
| subjects affected / exposed        | 1 / 1820 (0.05%) | 2 / 608 (0.33%) |
| occurrences (all)                  | 1                | 2               |
| Hypoxia                            |                  |                 |
| subjects affected / exposed        | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                  | 1                | 0               |
| Nasal dryness                      |                  |                 |
| subjects affected / exposed        | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                  | 1                | 0               |
| Nasal polyps                       |                  |                 |
| subjects affected / exposed        | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)                  | 2                | 0               |
| Pneumothorax                       |                  |                 |
| subjects affected / exposed        | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)                  | 2                | 0               |
| Postnasal drip                     |                  |                 |
| subjects affected / exposed        | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)                  | 2                | 0               |
| Sleep apnoea syndrome              |                  |                 |
| subjects affected / exposed        | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                  | 1                | 0               |
| Sneezing                           |                  |                 |
| subjects affected / exposed        | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)                  | 1                | 1               |
| Upper respiratory tract congestion |                  |                 |
| subjects affected / exposed        | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                  | 1                | 0               |
| Vocal cord disorder                |                  |                 |
| subjects affected / exposed        | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                  | 1                | 0               |
| Wheezing                           |                  |                 |
| subjects affected / exposed        | 3 / 1820 (0.16%) | 1 / 608 (0.16%) |
| occurrences (all)                  | 3                | 1               |
| Nasal discomfort                   |                  |                 |
| subjects affected / exposed        | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)                  | 0                | 1               |
| Pleuritic pain                     |                  |                 |

|                                       |                  |                 |  |
|---------------------------------------|------------------|-----------------|--|
| subjects affected / exposed           | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                     | 0                | 1               |  |
| Sinus congestion                      |                  |                 |  |
| subjects affected / exposed           | 9 / 1820 (0.49%) | 4 / 608 (0.66%) |  |
| occurrences (all)                     | 9                | 4               |  |
| Pulmonary embolism                    |                  |                 |  |
| subjects affected / exposed           | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 3                | 0               |  |
| Adenoidal hypertrophy                 |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Bronchial hyperreactivity             |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Bronchitis chronic                    |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Chronic obstructive pulmonary disease |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Dysphonia                             |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Pleurisy                              |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Wegener's Granulomatosis              |                  |                 |  |
| subjects affected / exposed           | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                     | 1                | 0               |  |
| Pleural effusion                      |                  |                 |  |
| subjects affected / exposed           | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                     | 0                | 1               |  |
| Psychiatric disorders                 |                  |                 |  |
| Sleep disorder                        |                  |                 |  |

|  |                   |                  |  |
|--|-------------------|------------------|--|
| subjects affected / exposed              | 21 / 1820 (1.15%) | 10 / 608 (1.64%) |  |
| occurrences (all)                        | 21                | 10               |  |
| Stress                                   |                   |                  |  |
| subjects affected / exposed              | 4 / 1820 (0.22%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                        | 4                 | 1                |  |
| Mood swings                              |                   |                  |  |
| subjects affected / exposed              | 2 / 1820 (0.11%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                        | 2                 | 1                |  |
| Nightmare                                |                   |                  |  |
| subjects affected / exposed              | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                        | 1                 | 0                |  |
| Restlessness                             |                   |                  |  |
| subjects affected / exposed              | 1 / 1820 (0.05%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                        | 1                 | 1                |  |
| Delirium tremens                         |                   |                  |  |
| subjects affected / exposed              | 0 / 1820 (0.00%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                        | 0                 | 1                |  |
| Nervousness                              |                   |                  |  |
| subjects affected / exposed              | 0 / 1820 (0.00%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                        | 0                 | 1                |  |
| Panic disorder                           |                   |                  |  |
| subjects affected / exposed              | 3 / 1820 (0.16%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                        | 3                 | 0                |  |
| Anxiety disorder                         |                   |                  |  |
| subjects affected / exposed              | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                        | 1                 | 0                |  |
| Generalised anxiety disorder             |                   |                  |  |
| subjects affected / exposed              | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                        | 1                 | 0                |  |
| Attention deficit hyperactivity disorder |                   |                  |  |
| subjects affected / exposed              | 0 / 1820 (0.00%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                        | 0                 | 1                |  |
| Investigations                           |                   |                  |  |
| Antinuclear antibody increased           |                   |                  |  |

|  |                   |                 |  |
|--|-------------------|-----------------|--|
| subjects affected / exposed                    | 2 / 1820 (0.11%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                              | 2                 | 1               |  |
| Alanine aminotransferase increased             |                   |                 |  |
| subjects affected / exposed                    | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                              | 0                 | 1               |  |
| Aspartate aminotransferase increased           |                   |                 |  |
| subjects affected / exposed                    | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                              | 0                 | 1               |  |
| Blood creatine phosphokinase increased         |                   |                 |  |
| subjects affected / exposed                    | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                              | 0                 | 1               |  |
| Bleeding time prolonged                        |                   |                 |  |
| subjects affected / exposed                    | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                              | 1                 | 0               |  |
| Blood pressure increased                       |                   |                 |  |
| subjects affected / exposed                    | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                              | 1                 | 0               |  |
| Hepatitis C positive                           |                   |                 |  |
| subjects affected / exposed                    | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                              | 1                 | 0               |  |
| Injury, poisoning and procedural complications |                   |                 |  |
| Joint injury                                   |                   |                 |  |
| subjects affected / exposed                    | 14 / 1820 (0.77%) | 7 / 608 (1.15%) |  |
| occurrences (all)                              | 14                | 7               |  |
| Contusion                                      |                   |                 |  |
| subjects affected / exposed                    | 10 / 1820 (0.55%) | 3 / 608 (0.49%) |  |
| occurrences (all)                              | 10                | 3               |  |
| Muscle strain                                  |                   |                 |  |
| subjects affected / exposed                    | 13 / 1820 (0.71%) | 5 / 608 (0.82%) |  |
| occurrences (all)                              | 13                | 5               |  |
| Post procedural complication                   |                   |                 |  |
| subjects affected / exposed                    | 14 / 1820 (0.77%) | 7 / 608 (1.15%) |  |
| occurrences (all)                              | 14                | 7               |  |
| Skin laceration                                |                   |                 |  |

|                                 |                  |                 |
|---------------------------------|------------------|-----------------|
| subjects affected / exposed     | 8 / 1820 (0.44%) | 6 / 608 (0.99%) |
| occurrences (all)               | 8                | 6               |
| Soft tissue injury              |                  |                 |
| subjects affected / exposed     | 5 / 1820 (0.27%) | 2 / 608 (0.33%) |
| occurrences (all)               | 5                | 2               |
| Epicondylitis                   |                  |                 |
| subjects affected / exposed     | 6 / 1820 (0.33%) | 6 / 608 (0.99%) |
| occurrences (all)               | 6                | 6               |
| Foot fracture                   |                  |                 |
| subjects affected / exposed     | 2 / 1820 (0.11%) | 2 / 608 (0.33%) |
| occurrences (all)               | 2                | 2               |
| meniscus lesion                 |                  |                 |
| subjects affected / exposed     | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)               | 3                | 0               |
| Thermal burn                    |                  |                 |
| subjects affected / exposed     | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)               | 2                | 0               |
| Wound                           |                  |                 |
| subjects affected / exposed     | 5 / 1820 (0.27%) | 0 / 608 (0.00%) |
| occurrences (all)               | 5                | 0               |
| Arthropod bite                  |                  |                 |
| subjects affected / exposed     | 5 / 1820 (0.27%) | 3 / 608 (0.49%) |
| occurrences (all)               | 5                | 3               |
| Arthropod sting                 |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 3 / 608 (0.49%) |
| occurrences (all)               | 1                | 3               |
| Back injury                     |                  |                 |
| subjects affected / exposed     | 5 / 1820 (0.27%) | 3 / 608 (0.49%) |
| occurrences (all)               | 5                | 3               |
| Clavicle fracture               |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Dislocation of joint prosthesis |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Incision site pain              |                  |                 |



|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Limb injury                 |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Multiple injuries           |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Muscle rupture              |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Patella fracture            |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Procedural pain             |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Rib fracture                |                  |                 |
| subjects affected / exposed | 5 / 1820 (0.27%) | 0 / 608 (0.00%) |
| occurrences (all)           | 5                | 0               |
| Road traffic accident       |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Sternal fracture            |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Tendon rupture              |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Ulna fracture               |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Brachial plexus injury      |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Burns first degree          |                  |                 |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Femur fracture              |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Heat stroke                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Neck injury                 |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 1 / 608 (0.16%) |
| occurrences (all)           | 2                | 1               |
| Sunburn                     |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Tibia fracture              |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Upper limb fracture         |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Whiplash injury             |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Ligament rupture            |                  |                 |
| subjects affected / exposed | 4 / 1820 (0.22%) | 0 / 608 (0.00%) |
| occurrences (all)           | 4                | 0               |
| Eye injury                  |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 2 / 608 (0.33%) |
| occurrences (all)           | 2                | 2               |
| Jaw fracture                |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Animal scratch              |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Ankle fracture              |                  |                 |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Facial bones fracture       |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Fall                        |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Fractured coccyx            |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Head injury                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Heart injury                |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Overdose                    |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Pelvic fracture             |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Periorbital haematoma       |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Post-traumatic pain         |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Radius fracture             |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Skeletal injury             |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Tooth fracture              |                  |                 |

|  |                            |                         |  |
|--|----------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 1820 (0.05%)<br>1      | 0 / 608 (0.00%)<br>0    |  |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)   | 1 / 1820 (0.05%)<br>1      | 1 / 608 (0.16%)<br>1    |  |
| Concussion<br>subjects affected / exposed<br>occurrences (all)   | 0 / 1820 (0.00%)<br>0      | 1 / 608 (0.16%)<br>1    |  |
| Thoracic vertebral fracture<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 1820 (0.00%)<br>0      | 1 / 608 (0.16%)<br>1    |  |
| Congenital, familial and genetic disorders<br>Gilbert's syndrome<br>subjects affected / exposed<br>occurrences (all) | 1 / 1820 (0.05%)<br>1      | 0 / 608 (0.00%)<br>0    |  |
| Cardiac disorders<br>Arrhythmia<br>subjects affected / exposed<br>occurrences (all)                                  | 8 / 1820 (0.44%)<br>8      | 4 / 608 (0.66%)<br>4    |  |
| Angina pectoris<br>subjects affected / exposed<br>occurrences (all)  | 3 / 1820 (0.16%)<br>3      | 0 / 608 (0.00%)<br>0    |  |
| Cardiac disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 1820 (0.00%)<br>0      | 1 / 608 (0.16%)<br>1    |  |
| Supraventricular tachycardia<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 1820 (0.00%)<br>0      | 1 / 608 (0.16%)<br>1    |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                             | 206 / 1820 (11.32%)<br>206 | 62 / 608 (10.20%)<br>62 |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 20 / 1820 (1.10%)<br>20    | 7 / 608 (1.15%)<br>7    |  |
| Migraine   |                            |                         |  |

|                             |                   |                 |
|-----------------------------|-------------------|-----------------|
| subjects affected / exposed | 18 / 1820 (0.99%) | 8 / 608 (1.32%) |
| occurrences (all)           | 18                | 8               |
| Paraesthesia                |                   |                 |
| subjects affected / exposed | 3 / 1820 (0.16%)  | 2 / 608 (0.33%) |
| occurrences (all)           | 3                 | 2               |
| Hypoaesthesia               |                   |                 |
| subjects affected / exposed | 2 / 1820 (0.11%)  | 3 / 608 (0.49%) |
| occurrences (all)           | 2                 | 3               |
| Sciatica                    |                   |                 |
| subjects affected / exposed | 2 / 1820 (0.11%)  | 3 / 608 (0.49%) |
| occurrences (all)           | 2                 | 3               |
| Syncope                     |                   |                 |
| subjects affected / exposed | 3 / 1820 (0.16%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 3                 | 1               |
| Cervical root pain          |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Loss of consciousness       |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Nerve compression           |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 2 / 608 (0.33%) |
| occurrences (all)           | 1                 | 2               |
| nerve root compression      |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Trigeminal neuralgia        |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Balance disorder            |                   |                 |
| subjects affected / exposed | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 0                 | 1               |
| Carpal tunnel syndrome      |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 2 / 608 (0.33%) |
| occurrences (all)           | 1                 | 2               |
| Lethargy                    |                   |                 |

|                             |                   |                 |
|-----------------------------|-------------------|-----------------|
| subjects affected / exposed | 1 / 1820 (0.05%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 1                 | 1               |
| Depression                  |                   |                 |
| subjects affected / exposed | 21 / 1820 (1.15%) | 4 / 608 (0.66%) |
| occurrences (all)           | 21                | 4               |
| Anxiety                     |                   |                 |
| subjects affected / exposed | 9 / 1820 (0.49%)  | 4 / 608 (0.66%) |
| occurrences (all)           | 9                 | 4               |
| Amnesia                     |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Dysphasia                   |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Facial spasm                |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Guillain-Barre syndrome     |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Post-traumatic headache     |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Restless legs syndrome      |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 2 / 608 (0.33%) |
| occurrences (all)           | 1                 | 2               |
| Tension headache            |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Tremor                      |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Tunnel vision               |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| facial palsy                |                   |                 |

|   |                         |                      |  |
|---|-------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                    | 0 / 1820 (0.00%)<br>0   | 1 / 608 (0.16%)<br>1 |  |
| Hyperreflexia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 1820 (0.00%)<br>0   | 1 / 608 (0.16%)<br>1 |  |
| Blood and lymphatic system disorders                                |                         |                      |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)         | 4 / 1820 (0.22%)<br>4   | 1 / 608 (0.16%)<br>1 |  |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all) | 3 / 1820 (0.16%)<br>3   | 1 / 608 (0.16%)<br>1 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)      | 0 / 1820 (0.00%)<br>0   | 1 / 608 (0.16%)<br>1 |  |
| Splenomegaly<br>subjects affected / exposed<br>occurrences (all)    | 0 / 1820 (0.00%)<br>0   | 1 / 608 (0.16%)<br>1 |  |
| Ear and labyrinth disorders   |                         |                      |  |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)        | 14 / 1820 (0.77%)<br>14 | 3 / 608 (0.49%)<br>3 |  |
| Otitis media<br>subjects affected / exposed<br>occurrences (all)    | 14 / 1820 (0.77%)<br>14 | 6 / 608 (0.99%)<br>6 |  |
| Otitis externa<br>subjects affected / exposed<br>occurrences (all)  | 5 / 1820 (0.27%)<br>5   | 0 / 608 (0.00%)<br>0 |  |
| Ear discomfort<br>subjects affected / exposed<br>occurrences (all)  | 3 / 1820 (0.16%)<br>3   | 1 / 608 (0.16%)<br>1 |  |
| Deafness<br>subjects affected / exposed<br>occurrences (all)        | 2 / 1820 (0.11%)<br>2   | 0 / 608 (0.00%)<br>0 |  |
| Labyrinthitis   |                         |                      |  |

|  |                         |                      |  |
|--|-------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 1820 (0.05%)<br>1   | 0 / 608 (0.00%)<br>0 |  |
| Tinnitus   |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 1820 (0.05%)<br>1   | 1 / 608 (0.16%)<br>1 |  |
| Vertigo  |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 1820 (0.11%)<br>2   | 0 / 608 (0.00%)<br>0 |  |
| Ear congestion                                   |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 1820 (0.05%)<br>1   | 0 / 608 (0.00%)<br>0 |  |
| Motion sickness                                  |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 1820 (0.00%)<br>0   | 2 / 608 (0.33%)<br>2 |  |
| Vertigo positional                               |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 1820 (0.00%)<br>0   | 1 / 608 (0.16%)<br>1 |  |
| Eye disorders                                    |                         |                      |  |
| Conjunctivitis                                   |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 13 / 1820 (0.71%)<br>13 | 4 / 608 (0.66%)<br>4 |  |
| Dry eye  |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 1820 (0.05%)<br>1   | 0 / 608 (0.00%)<br>0 |  |
| Eyelid oedema                                    |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 1820 (0.05%)<br>1   | 0 / 608 (0.00%)<br>0 |  |
| Hordeolum  |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 1820 (0.11%)<br>2   | 0 / 608 (0.00%)<br>0 |  |
| Lacrimation increased                            |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 1820 (0.05%)<br>1   | 1 / 608 (0.16%)<br>1 |  |
| Presbyopia                                       |                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 1820 (0.05%)<br>1   | 0 / 608 (0.00%)<br>0 |  |



|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| Vision blurred              |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 2 / 608 (0.33%) |
| occurrences (all)           | 2                | 2               |
| Blepharitis                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Blepharospasm               |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Blindness                   |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Conjunctivitis allergic     |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Corneal lesion              |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Eye inflammation            |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Eye irritation              |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Glaucoma                    |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Macular degeneration        |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Eye swelling                |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Asthenopia                  |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |

|  |                         |                        |  |
|--|-------------------------|------------------------|--|
| Conjunctivitis infective<br>subjects affected / exposed<br>occurrences (all)         | 1 / 1820 (0.05%)<br>1   | 1 / 608 (0.16%)<br>1   |  |
| Eye discharge<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 1820 (0.05%)<br>1   | 0 / 608 (0.00%)<br>0   |  |
| Iritis<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 1820 (0.05%)<br>1   | 0 / 608 (0.00%)<br>0   |  |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)                | 1 / 1820 (0.05%)<br>1   | 1 / 608 (0.16%)<br>1   |  |
| Gastrointestinal disorders   |                         |                        |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                        | 43 / 1820 (2.36%)<br>43 | 14 / 608 (2.30%)<br>14 |  |
| Tooth disorder<br>subjects affected / exposed<br>occurrences (all)                   | 39 / 1820 (2.14%)<br>39 | 17 / 608 (2.80%)<br>17 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                   | 33 / 1820 (1.81%)<br>33 | 12 / 608 (1.97%)<br>12 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                           | 32 / 1820 (1.76%)<br>32 | 20 / 608 (3.29%)<br>20 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                         | 14 / 1820 (0.77%)<br>14 | 10 / 608 (1.64%)<br>10 |  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | 15 / 1820 (0.82%)<br>15 | 7 / 608 (1.15%)<br>7   |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                        | 14 / 1820 (0.77%)<br>14 | 6 / 608 (0.99%)<br>6   |  |
| Abdominal discomfort   |                         |                        |  |

|                             |                   |                 |
|-----------------------------|-------------------|-----------------|
| subjects affected / exposed | 6 / 1820 (0.33%)  | 6 / 608 (0.99%) |
| occurrences (all)           | 6                 | 6               |
| Gingival disorder           |                   |                 |
| subjects affected / exposed | 10 / 1820 (0.55%) | 4 / 608 (0.66%) |
| occurrences (all)           | 10                | 4               |
| Constipation                |                   |                 |
| subjects affected / exposed | 4 / 1820 (0.22%)  | 4 / 608 (0.66%) |
| occurrences (all)           | 4                 | 4               |
| Flatulence                  |                   |                 |
| subjects affected / exposed | 3 / 1820 (0.16%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 3                 | 0               |
| Dysphagia                   |                   |                 |
| subjects affected / exposed | 4 / 1820 (0.22%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 4                 | 1               |
| Food poisoning              |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 1                 | 1               |
| Gastrointestinal disorder   |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Gingival pain               |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Haemorrhoids                |                   |                 |
| subjects affected / exposed | 3 / 1820 (0.16%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 3                 | 1               |
| sensitivity of teeth        |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Stomatitis                  |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Tongue coated               |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Anal fissure                |                   |                 |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| aphthous stomatitis         |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 2 / 608 (0.33%) |
| occurrences (all)           | 2                | 2               |
| Gastritis                   |                  |                 |
| subjects affected / exposed | 6 / 1820 (0.33%) | 1 / 608 (0.16%) |
| occurrences (all)           | 6                | 1               |
| Oral pain                   |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Abdominal distension        |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 1 / 608 (0.16%) |
| occurrences (all)           | 3                | 1               |
| Cheilosis                   |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Inguinal hernia             |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Lip swelling                |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Proctalgia                  |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Tooth deposit               |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Pancreatitis                |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Rectal haemorrhage          |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Hepatobiliary disorders     |                  |                 |

|  |                   |                 |  |
|--|-------------------|-----------------|--|
| Cholecystitis                          |                   |                 |  |
| subjects affected / exposed            | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                      | 1                 | 0               |  |
| Cholelithiasis                         |                   |                 |  |
| subjects affected / exposed            | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                      | 1                 | 0               |  |
| Hepatitis                              |                   |                 |  |
| subjects affected / exposed            | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                      | 1                 | 0               |  |
| Biliary colic                          |                   |                 |  |
| subjects affected / exposed            | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                      | 0                 | 1               |  |
| Cholecystitis acute                    |                   |                 |  |
| subjects affected / exposed            | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                      | 1                 | 0               |  |
| Hepatic steatosis                      |                   |                 |  |
| subjects affected / exposed            | 0 / 1820 (0.00%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                      | 0                 | 1               |  |
| Skin and subcutaneous tissue disorders |                   |                 |  |
| Acne                                   |                   |                 |  |
| subjects affected / exposed            | 12 / 1820 (0.66%) | 2 / 608 (0.33%) |  |
| occurrences (all)                      | 12                | 2               |  |
| Rash                                   |                   |                 |  |
| subjects affected / exposed            | 12 / 1820 (0.66%) | 3 / 608 (0.49%) |  |
| occurrences (all)                      | 12                | 3               |  |
| Urticaria                              |                   |                 |  |
| subjects affected / exposed            | 8 / 1820 (0.44%)  | 0 / 608 (0.00%) |  |
| occurrences (all)                      | 8                 | 0               |  |
| Dermatitis                             |                   |                 |  |
| subjects affected / exposed            | 12 / 1820 (0.66%) | 0 / 608 (0.00%) |  |
| occurrences (all)                      | 12                | 0               |  |
| Hyperhidrosis                          |                   |                 |  |
| subjects affected / exposed            | 4 / 1820 (0.22%)  | 1 / 608 (0.16%) |  |
| occurrences (all)                      | 4                 | 1               |  |
| Dermatitis allergic                    |                   |                 |  |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 5 / 1820 (0.27%) | 1 / 608 (0.16%) |
| occurrences (all)           | 5                | 1               |
| Photosensitivity reaction   |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 1 / 608 (0.16%) |
| occurrences (all)           | 2                | 1               |
| Rash maculo-papular         |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Rosacea                     |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)           | 3                | 0               |
| Acrodermatitis              |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Actinic keratosis           |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Anhidrosis                  |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Eczema                      |                  |                 |
| subjects affected / exposed | 6 / 1820 (0.33%) | 3 / 608 (0.49%) |
| occurrences (all)           | 6                | 3               |
| Erythema                    |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Hyperkeratosis              |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Lichen planus               |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Nail bed bleeding           |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Rash macular                |                  |                 |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Rash papular                |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Rash pruritic               |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Seborrhoeic dermatitis      |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Swelling face               |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Urticaria thermal           |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Dermal cyst                 |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 2 / 608 (0.33%) |
| occurrences (all)           | 0                | 2               |
| Dermatitis contact          |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 1 / 608 (0.16%) |
| occurrences (all)           | 3                | 1               |
| Skin lesion                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Pruritus                    |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)           | 3                | 0               |
| Acne cystic                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Alopecia                    |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Dry skin                    |                  |                 |

|                             |                  |                 |  |
|-----------------------------|------------------|-----------------|--|
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Ecchymosis                  |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Heat rash                   |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Ingrowing nail              |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Skin fissures               |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Skin ulcer                  |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Drug eruption               |                  |                 |  |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 0                | 1               |  |
| Hypoaesthesia facial        |                  |                 |  |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 0                | 1               |  |
| Neurodermatitis             |                  |                 |  |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 0                | 1               |  |
| Renal and urinary disorders |                  |                 |  |
| Cystitis                    |                  |                 |  |
| subjects affected / exposed | 3 / 1820 (0.16%) | 4 / 608 (0.66%) |  |
| occurrences (all)           | 3                | 4               |  |
| Dysuria                     |                  |                 |  |
| subjects affected / exposed | 3 / 1820 (0.16%) | 2 / 608 (0.33%) |  |
| occurrences (all)           | 3                | 2               |  |
| Nephrolithiasis             |                  |                 |  |
| subjects affected / exposed | 2 / 1820 (0.11%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 2                | 1               |  |



|                             |                  |                 |  |
|-----------------------------|------------------|-----------------|--|
| Pollakiuria                 |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 2 / 608 (0.33%) |  |
| occurrences (all)           | 1                | 2               |  |
| Renal colic                 |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 1                | 1               |  |
| Cystitis noninfective       |                  |                 |  |
| subjects affected / exposed | 0 / 1820 (0.00%) | 2 / 608 (0.33%) |  |
| occurrences (all)           | 0                | 2               |  |
| Polyuria                    |                  |                 |  |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 0                | 1               |  |
| Urogenital disorder         |                  |                 |  |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 0                | 1               |  |
| Calculus urinary            |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Urinary incontinence        |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 1                | 1               |  |
| Haematuria                  |                  |                 |  |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 0                | 1               |  |
| Ureteric stenosis           |                  |                 |  |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 0                | 1               |  |
| Endocrine disorders         |                  |                 |  |
| Goitre                      |                  |                 |  |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 1                | 0               |  |
| Hyperthyroidism             |                  |                 |  |
| subjects affected / exposed | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |  |
| occurrences (all)           | 3                | 0               |  |
| Hypothyroidism              |                  |                 |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 3 / 1820 (0.16%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                               | 3                 | 1                |  |
| Thyroid disorder                                |                   |                  |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                               | 1                 | 0                |  |
| Basedow's disease                               |                   |                  |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%)  | 1 / 608 (0.16%)  |  |
| occurrences (all)                               | 1                 | 1                |  |
| Thyroiditis                                     |                   |                  |  |
| subjects affected / exposed                     | 1 / 1820 (0.05%)  | 0 / 608 (0.00%)  |  |
| occurrences (all)                               | 1                 | 0                |  |
| Musculoskeletal and connective tissue disorders |                   |                  |  |
| Back pain                                       |                   |                  |  |
| subjects affected / exposed                     | 93 / 1820 (5.11%) | 31 / 608 (5.10%) |  |
| occurrences (all)                               | 93                | 31               |  |
| Arthralgia                                      |                   |                  |  |
| subjects affected / exposed                     | 43 / 1820 (2.36%) | 18 / 608 (2.96%) |  |
| occurrences (all)                               | 43                | 18               |  |
| Pain in extremity                               |                   |                  |  |
| subjects affected / exposed                     | 28 / 1820 (1.54%) | 7 / 608 (1.15%)  |  |
| occurrences (all)                               | 28                | 7                |  |
| Myalgia   |                   |                  |  |
| subjects affected / exposed                     | 20 / 1820 (1.10%) | 7 / 608 (1.15%)  |  |
| occurrences (all)                               | 20                | 7                |  |
| Neck pain                                       |                   |                  |  |
| subjects affected / exposed                     | 24 / 1820 (1.32%) | 8 / 608 (1.32%)  |  |
| occurrences (all)                               | 24                | 8                |  |
| Musculoskeletal pain                            |                   |                  |  |
| subjects affected / exposed                     | 23 / 1820 (1.26%) | 8 / 608 (1.32%)  |  |
| occurrences (all)                               | 23                | 8                |  |
| Bursitis  |                   |                  |  |
| subjects affected / exposed                     | 10 / 1820 (0.55%) | 2 / 608 (0.33%)  |  |
| occurrences (all)                               | 10                | 2                |  |
| Muscle spasms                                   |                   |                  |  |

|                             |                   |                 |
|-----------------------------|-------------------|-----------------|
| subjects affected / exposed | 9 / 1820 (0.49%)  | 4 / 608 (0.66%) |
| occurrences (all)           | 9                 | 4               |
| Musculoskeletal chest pain  |                   |                 |
| subjects affected / exposed | 10 / 1820 (0.55%) | 1 / 608 (0.16%) |
| occurrences (all)           | 10                | 1               |
| Musculoskeletal stiffness   |                   |                 |
| subjects affected / exposed | 6 / 1820 (0.33%)  | 3 / 608 (0.49%) |
| occurrences (all)           | 6                 | 3               |
| Joint swelling              |                   |                 |
| subjects affected / exposed | 7 / 1820 (0.38%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 7                 | 1               |
| Tendonitis                  |                   |                 |
| subjects affected / exposed | 11 / 1820 (0.60%) | 2 / 608 (0.33%) |
| occurrences (all)           | 11                | 2               |
| Musculoskeletal discomfort  |                   |                 |
| subjects affected / exposed | 5 / 1820 (0.27%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 5                 | 0               |
| Osteoarthritis              |                   |                 |
| subjects affected / exposed | 7 / 1820 (0.38%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 7                 | 0               |
| Spinal osteoarthritis       |                   |                 |
| subjects affected / exposed | 2 / 1820 (0.11%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 2                 | 1               |
| Arthritis                   |                   |                 |
| subjects affected / exposed | 2 / 1820 (0.11%)  | 2 / 608 (0.33%) |
| occurrences (all)           | 2                 | 2               |
| Bone pain                   |                   |                 |
| subjects affected / exposed | 2 / 1820 (0.11%)  | 1 / 608 (0.16%) |
| occurrences (all)           | 2                 | 1               |
| Coccydynia                  |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Gouty arthritis             |                   |                 |
| subjects affected / exposed | 1 / 1820 (0.05%)  | 0 / 608 (0.00%) |
| occurrences (all)           | 1                 | 0               |
| Groin pain                  |                   |                 |

|                                  |                  |                 |
|----------------------------------|------------------|-----------------|
| subjects affected / exposed      | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                | 1                | 0               |
| Intervertebral disc degeneration |                  |                 |
| subjects affected / exposed      | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                | 1                | 0               |
| Muscular weakness                |                  |                 |
| subjects affected / exposed      | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)                | 1                | 1               |
| Osteopenia                       |                  |                 |
| subjects affected / exposed      | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                | 1                | 0               |
| Pain in jaw                      |                  |                 |
| subjects affected / exposed      | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                | 1                | 0               |
| Rheumatoid arthritis             |                  |                 |
| subjects affected / exposed      | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                | 1                | 0               |
| Sensation of heaviness           |                  |                 |
| subjects affected / exposed      | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)                | 1                | 0               |
| Torticollis                      |                  |                 |
| subjects affected / exposed      | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)                | 3                | 0               |
| Intervertebral disc protrusion   |                  |                 |
| subjects affected / exposed      | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)                | 0                | 1               |
| Plantar fasciitis                |                  |                 |
| subjects affected / exposed      | 0 / 1820 (0.00%) | 3 / 608 (0.49%) |
| occurrences (all)                | 0                | 3               |
| Temporomandibular joint syndrome |                  |                 |
| subjects affected / exposed      | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)                | 1                | 1               |
| Tenosynovitis                    |                  |                 |
| subjects affected / exposed      | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)                | 2                | 0               |
| Cervical spinal stenosis         |                  |                 |

|                                 |                  |                 |
|---------------------------------|------------------|-----------------|
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Chondropathy                    |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Costochondritis                 |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Exostosis                       |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)               | 1                | 1               |
| Flank pain                      |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Joint range of motion decreased |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Pseudarthrosis                  |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Synovial cyst                   |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Systemic lupus erythematosus    |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Toe deformity                   |                  |                 |
| subjects affected / exposed     | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)               | 1                | 0               |
| Fibromyalgia                    |                  |                 |
| subjects affected / exposed     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)               | 0                | 1               |
| Joint stiffness                 |                  |                 |
| subjects affected / exposed     | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)               | 0                | 1               |
| Mixed connective tissue disease |                  |                 |

|   |                            |                           |  |
|---|----------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                      | 0 / 1820 (0.00%)<br>0      | 1 / 608 (0.16%)<br>1      |  |
| myopathy steroid<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 1820 (0.00%)<br>0      | 1 / 608 (0.16%)<br>1      |  |
| Neck mass<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 1820 (0.00%)<br>0      | 1 / 608 (0.16%)<br>1      |  |
| Scleroderma<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 1820 (0.00%)<br>0      | 1 / 608 (0.16%)<br>1      |  |
| Infections and infestations   |                            |                           |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 304 / 1820 (16.70%)<br>304 | 100 / 608 (16.45%)<br>100 |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 59 / 1820 (3.24%)<br>59    | 22 / 608 (3.62%)<br>22    |  |
| Gastrointestinal infection<br>subjects affected / exposed<br>occurrences (all)        | 31 / 1820 (1.70%)<br>31    | 7 / 608 (1.15%)<br>7      |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 29 / 1820 (1.59%)<br>29    | 13 / 608 (2.14%)<br>13    |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 46 / 1820 (2.53%)<br>46    | 13 / 608 (2.14%)<br>13    |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 34 / 1820 (1.87%)<br>34    | 19 / 608 (3.13%)<br>19    |  |
| Vaginal infection<br>subjects affected / exposed<br>occurrences (all)                 | 23 / 1820 (1.26%)<br>23    | 4 / 608 (0.66%)<br>4      |  |
| Pharyngitis   |                            |                           |  |

|                                   |                   |                 |
|-----------------------------------|-------------------|-----------------|
| subjects affected / exposed       | 23 / 1820 (1.26%) | 8 / 608 (1.32%) |
| occurrences (all)                 | 23                | 8               |
| Rhinitis                          |                   |                 |
| subjects affected / exposed       | 19 / 1820 (1.04%) | 7 / 608 (1.15%) |
| occurrences (all)                 | 19                | 7               |
| Tooth infection                   |                   |                 |
| subjects affected / exposed       | 17 / 1820 (0.93%) | 2 / 608 (0.33%) |
| occurrences (all)                 | 17                | 2               |
| Herpes virus infection            |                   |                 |
| subjects affected / exposed       | 13 / 1820 (0.71%) | 1 / 608 (0.16%) |
| occurrences (all)                 | 13                | 1               |
| Influenza                         |                   |                 |
| subjects affected / exposed       | 11 / 1820 (0.60%) | 4 / 608 (0.66%) |
| occurrences (all)                 | 11                | 4               |
| Lower respiratory tract infection |                   |                 |
| subjects affected / exposed       | 9 / 1820 (0.49%)  | 4 / 608 (0.66%) |
| occurrences (all)                 | 9                 | 4               |
| Tonsillitis                       |                   |                 |
| subjects affected / exposed       | 11 / 1820 (0.60%) | 4 / 608 (0.66%) |
| occurrences (all)                 | 11                | 4               |
| Ear infection                     |                   |                 |
| subjects affected / exposed       | 7 / 1820 (0.38%)  | 4 / 608 (0.66%) |
| occurrences (all)                 | 7                 | 4               |
| Fungal infection                  |                   |                 |
| subjects affected / exposed       | 12 / 1820 (0.66%) | 4 / 608 (0.66%) |
| occurrences (all)                 | 12                | 4               |
| Pneumonia                         |                   |                 |
| subjects affected / exposed       | 7 / 1820 (0.38%)  | 3 / 608 (0.49%) |
| occurrences (all)                 | 7                 | 3               |
| Laryngitis                        |                   |                 |
| subjects affected / exposed       | 4 / 1820 (0.22%)  | 2 / 608 (0.33%) |
| occurrences (all)                 | 4                 | 2               |
| Respiratory tract infection       |                   |                 |
| subjects affected / exposed       | 11 / 1820 (0.60%) | 1 / 608 (0.16%) |
| occurrences (all)                 | 11                | 1               |
| Eye infection                     |                   |                 |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 5 / 1820 (0.27%) | 1 / 608 (0.16%) |
| occurrences (all)           | 5                | 1               |
| Localised infection         |                  |                 |
| subjects affected / exposed | 5 / 1820 (0.27%) | 2 / 608 (0.33%) |
| occurrences (all)           | 5                | 2               |
| Abscess limb                |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 1 / 608 (0.16%) |
| occurrences (all)           | 1                | 1               |
| Anal infection              |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Arthritis infective         |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Balanitis candida           |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Cellulitis                  |                  |                 |
| subjects affected / exposed | 8 / 1820 (0.44%) | 1 / 608 (0.16%) |
| occurrences (all)           | 8                | 1               |
| Cystitis                    |                  |                 |
| subjects affected / exposed | 9 / 1820 (0.49%) | 5 / 608 (0.82%) |
| occurrences (all)           | 9                | 5               |
| Erysipelas                  |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Eyelid infection            |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Folliculitis                |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 1 / 608 (0.16%) |
| occurrences (all)           | 3                | 1               |
| Furuncle                    |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| gingival infection          |                  |                 |



|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Herpes zoster               |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)           | 3                | 0               |
| Pyelonephritis              |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Rash pustular               |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Skin infection              |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 1 / 608 (0.16%) |
| occurrences (all)           | 2                | 1               |
| Subcutaneous abscess        |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 1 / 608 (0.16%) |
| occurrences (all)           | 3                | 1               |
| Tinea pedis                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 2 / 608 (0.33%) |
| occurrences (all)           | 1                | 2               |
| Viral infection             |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| adnexitis                   |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Chronic sinusitis           |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Clostridial infection       |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Groin abscess               |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Impetigo                    |                  |                 |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Pilonidal cyst              |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Wound infection             |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Hand fracture               |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 2 / 608 (0.33%) |
| occurrences (all)           | 2                | 2               |
| Onychomycosis               |                  |                 |
| subjects affected / exposed | 4 / 1820 (0.22%) | 0 / 608 (0.00%) |
| occurrences (all)           | 4                | 0               |
| Anogenital warts            |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)           | 3                | 0               |
| Oral candidiasis            |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)           | 3                | 0               |
| Kidney infection            |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Scarlet fever               |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Acute tonsillitis           |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Borrelia infection          |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Chlamydial infection        |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Erythema migrans            |                  |                 |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Gingival abscess            |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Infected cyst               |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Infected insect bite        |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Mastitis                    |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Meningitis bacterial        |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Paronychia                  |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Peritonsillar abscess       |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Pyoderma                    |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Sinusitis fungal            |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Streptococcal infection     |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Tracheobronchitis           |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Urosepsis                   |                  |                 |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed             | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                       | 1                | 0               |  |
| West Nile viral infection               |                  |                 |  |
| subjects affected / exposed             | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                       | 1                | 0               |  |
| Genital herpes                          |                  |                 |  |
| subjects affected / exposed             | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                       | 0                | 1               |  |
| Infected skin ulcer                     |                  |                 |  |
| subjects affected / exposed             | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                       | 0                | 1               |  |
| Liver abscess                           |                  |                 |  |
| subjects affected / exposed             | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                       | 0                | 1               |  |
| Septic shock                            |                  |                 |  |
| subjects affected / exposed             | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                       | 0                | 1               |  |
| Tinea cruris                            |                  |                 |  |
| subjects affected / exposed             | 0 / 1820 (0.00%) | 2 / 608 (0.33%) |  |
| occurrences (all)                       | 0                | 2               |  |
| Tracheitis                              |                  |                 |  |
| subjects affected / exposed             | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)                       | 0                | 1               |  |
| Metabolism and nutrition disorders      |                  |                 |  |
| Dyslipidaemia                           |                  |                 |  |
| subjects affected / exposed             | 5 / 1820 (0.27%) | 3 / 608 (0.49%) |  |
| occurrences (all)                       | 5                | 3               |  |
| Diabetes mellitus                       |                  |                 |  |
| subjects affected / exposed             | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |  |
| occurrences (all)                       | 1                | 0               |  |
| Diabetes mellitus non-insulin-dependent |                  |                 |  |
| subjects affected / exposed             | 2 / 1820 (0.11%) | 1 / 608 (0.16%) |  |
| occurrences (all)                       | 2                | 1               |  |
| Glucose tolerance impaired              |                  |                 |  |

|                             |                  |                 |
|-----------------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Gout                        |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 0 / 608 (0.00%) |
| occurrences (all)           | 3                | 0               |
| Iron deficiency             |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Hypercholesterolaemia       |                  |                 |
| subjects affected / exposed | 3 / 1820 (0.16%) | 2 / 608 (0.33%) |
| occurrences (all)           | 3                | 2               |
| Hypertriglyceridaemia       |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Polydipsia                  |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Hyperuricaemia              |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Vitamin B12 deficiency      |                  |                 |
| subjects affected / exposed | 2 / 1820 (0.11%) | 0 / 608 (0.00%) |
| occurrences (all)           | 2                | 0               |
| Anorexia                    |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Underweight                 |                  |                 |
| subjects affected / exposed | 1 / 1820 (0.05%) | 0 / 608 (0.00%) |
| occurrences (all)           | 1                | 0               |
| Impaired fasting glucose    |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 2 / 608 (0.33%) |
| occurrences (all)           | 0                | 2               |
| Overweight                  |                  |                 |
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |
| occurrences (all)           | 0                | 1               |
| Vitamin C deficiency        |                  |                 |

|                             |                  |                 |  |
|-----------------------------|------------------|-----------------|--|
| subjects affected / exposed | 0 / 1820 (0.00%) | 1 / 608 (0.16%) |  |
| occurrences (all)           | 0                | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 08 February 2007 | Amendment 1 <ul style="list-style-type: none"><li>• Differentiated efficacy and safety objectives and defined a safety endpoint</li><li>• Provided guidance on administration and follow-up for additional dosing with Engerix-B</li><li>• Increased the sample size</li><li>• Adjusted the age range to 18 - 55 years for the United States and Germany</li><li>• Clarified the statistical tests for the efficacy description</li></ul> |
| 29 May 2007      | Amendment 2: <ul style="list-style-type: none"><li>• Added a EudraCT number</li><li>• Removed the United States as a participating country</li><li>• Provided additional details regarding stopping rules and the handling of confidential subject Information</li></ul>  |
| 04 February 2008 | Amendment 3: <ul style="list-style-type: none"><li>• Increased the sample size</li><li>• Updated and clarified the statistical considerations, comparisons, and determination of sample size</li><li>• Clarified the severity grading of AEs</li></ul>  |
| 08 May 2008      | Amendment 4: <ul style="list-style-type: none"><li>• Changed the anti-HBsAg testing assay from AUSAB AxSYM to the Hep B ECi assay</li></ul>   |
| 03 October 2008  | Amendment 5: <ul style="list-style-type: none"><li>• Updated and clarified the objectives, statistical considerations, comparisons, and determination of sample size</li><li>• Defined the end of the trial as the database lock for the study, which was selected due to the delay resulting from the change in the anti-HBsAg assay</li></ul>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported