



## Clinical trial results:

**Ensayo clínico de vacunación fase III, aleatorizado, observador-ciego, controlado con placebo, multicéntrico para evaluar la eficacia profiláctica, seguridad e inmunogenicidad de la vacuna gE/AS01B de GSK Biologicals administrada por vía intramuscular con un esquema de 0, 2 meses en adultos de 70 años y mayores.**

### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2009-015791-94             |
| Trial protocol           | ES FI DE GB SE EE FR IT CZ |
| Global end of trial date | 24 July 2015               |

### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 03 May 2020   |
| First version publication date | 08 August 2016  |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Results have been amended to account for consistency with other registries. |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 113077 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02723773 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 14 January 2016 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 24 July 2015    |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

- Zoster-022 study:  
To evaluate vaccine efficacy (VE) in the prevention of herpes Zoster (HZ) compared to placebo in adults  $\geq 70$  years of age (YOA), as measured by the reduction in HZ risk.
- Zoster-006 and Zoster-022 pooled studies:  
To evaluate VE in the prevention of postherpetic neuralgia (PHN) compared to placebo in subjects  $\geq 70$  YOA across both Phase III studies.  
To consolidate VE estimation in the prevention of HZ compared to placebo in subjects  $\geq 70$  YOA across both Phase III studies.

Protection of trial subjects:

The vaccine/product recipients were to be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccine/product. Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products. Subjects were followed-up for 30 days after the last vaccination/product administration.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 02 August 2010 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | United States: 1879     |
| Country: Number of subjects enrolled | Australia: 309          |
| Country: Number of subjects enrolled | Brazil: 627             |
| Country: Number of subjects enrolled | Canada: 802             |
| Country: Number of subjects enrolled | Czech Republic: 321     |
| Country: Number of subjects enrolled | Estonia: 1015           |
| Country: Number of subjects enrolled | Finland: 1705           |
| Country: Number of subjects enrolled | France: 575             |
| Country: Number of subjects enrolled | Germany: 1202           |
| Country: Number of subjects enrolled | Hong Kong: 180          |
| Country: Number of subjects enrolled | Italy: 109              |
| Country: Number of subjects enrolled | Japan: 511              |
| Country: Number of subjects enrolled | Korea, Republic of: 528 |
| Country: Number of subjects enrolled | Mexico: 453             |

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Spain: 934          |
| Country: Number of subjects enrolled | Sweden: 961         |
| Country: Number of subjects enrolled | Taiwan: 1110        |
| Country: Number of subjects enrolled | United Kingdom: 692 |
| Worldwide total number of subjects   | 13913               |
| EEA total number of subjects         | 7514                |

Notes:

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### Subjects enrolled per age group

|   |       |
|---|-------|
| In utero                                  | 0     |
| Preterm newborn - gestational age < 37 wk | 0     |
| Newborns (0-27 days)                      | 0     |
| Infants and toddlers (28 days-23 months)  | 0     |
| Children (2-11 years)                     | 0     |
| Adolescents (12-17 years)                 | 0     |
| Adults (18-64 years)                      | 13913 |
| From 65 to 84 years                       | 0     |
| 85 years and over                         | 0     |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Only 13900 subjects from the total enrolled number were vaccinated and included in the Total Vaccinated Cohort. In the placebo group, 1 subject had an unknown withdrawal status before the study site closure. This was not identified during database freeze, leading to 1190 subjects in place of 1189 that actually completed the placebo group

### Pre-assignment period milestones

|                              |                      |
|------------------------------|----------------------|
| Number of subjects started   | 14819 <sup>[1]</sup> |
| Number of subjects completed | 13900                |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Eliminated from statistical analysess: 906 |
| Reason: Number of subjects | No vaccination received: 13                |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number started in pre-assignment period are the number of subjects considered for enrollment. However, 906 subjects were excluded for analysis- leading to actual enrolled of 13913, which was considered as the total eligible cohort. This total eligible cohort was considered for further analysis.

### Period 1

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

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes                          |
| <b>Arm title</b>             | Zoster-022 GSK1437173A Group |

Arm description:

Subjects receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.

|  |   |
|--|---|
| Arm type                               | Experimental                                    |
| Investigational medicinal product name | GSK1437173A                                     |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Powder and solvent for suspension for injection |
| Routes of administration               | Intramuscular use                               |

Dosage and administration details:

The study product was administered according to a 0, 2 month schedule.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Zoster-022 Placebo Group |
|------------------|--------------------------|

Arm description:

Subjects receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             | Saline solution        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intramuscular use      |

Dosage and administration details:

The study product was administered according to a 0, 2 month schedule.

| <b>Number of subjects in period 1<sup>[2]</sup></b> | <b>Zoster-022<br/>GSK1437173A<br/>Group</b> | <b>Zoster-022 Placebo<br/>Group</b> |
|---|---|-------------------------------------|
| Started   | 6950  | 6950                                |
| Completed   | 5770  | 5760                                |
| Not completed                                       | 1180  | 1190                                |
| Consent withdrawn by subject                        | 387   | 396                                 |
| Non-Serious Adverse Event                           | 47  | 15                                  |
| No reason from the subject                          | 108   | 102                                 |
| Migrated/moved from study area                      | 51  | 46                                  |
| Suspected HZ Episode                                | 2   | 2                                   |
| Lost to follow-up                                   | 123   | 133                                 |
| Protocol deviation                                  | 6   | 8                                   |
| Serious Adverse Event                               | 456   | 487                                 |
| Unknown completion status                           | -   | 1                                   |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of the 13913 subjects considered for analysis in the trial, 13 were assigned participant codes but did not receive vaccination, hence were excluded from study start.

## Baseline characteristics

### Reporting groups

|   |                              |
|---|------------------------------|
| Reporting group title   | Zoster-022 GSK1437173A Group |
| Reporting group description:<br>Subjects receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule. |                              |
| Reporting group title   | Zoster-022 Placebo Group     |
| Reporting group description:<br>Subjects receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.       |                              |

| Reporting group values             | Zoster-022<br>GSK1437173A<br>Group | Zoster-022 Placebo<br>Group | Total |
|------------------------------------|------------------------------------|-----------------------------|-------|
| Number of subjects                 | 6950                               | 6950                        | 13900 |
| Age categorical<br>Units: Subjects |                                    |                             |       |
| Age continuous                     |                                    |                             |       |
| Age continuous description         |                                    |                             |       |
| Units: years                       |                                    |                             |       |
| arithmetic mean                    | 75.6                               | 75.6                        |       |
| standard deviation                 | ± 4.7                              | ± 4.7                       | -     |
| Gender categorical                 |                                    |                             |       |
| Gender categorical description     |                                    |                             |       |
| Units: Subjects                    |                                    |                             |       |
| Female                             | 3789                               | 3836                        | 7625  |
| Male                               | 3161                               | 3114                        | 6275  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Zoster-022 GSK1437173A Group                     |
| Reporting group description:<br>Subjects receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.  |  |
| Reporting group title  | Zoster-022 Placebo Group                         |
| Reporting group description:<br>Subjects receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.  |  |
| Subject analysis set title   | Zoster-022 GSK1437173A 70-79YOA Group            |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Subjects between 70 and 79 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule. |  |
| Subject analysis set title   | Zoster-022 GSK1437173A >=80YOA Group             |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Subjects above 80 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.          |  |
| Subject analysis set title   | Zoster-022 GSK1437173A >=70YOA Group             |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Subjects above 70 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.          |  |
| Subject analysis set title   | Zoster-022 Placebo 70-79YOA Group                |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Subjects between 70 and 79 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.       |  |
| Subject analysis set title   | Zoster-022 Placebo >=80YOA Group                 |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Subjects above 80 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.                |  |
| Subject analysis set title   | Zoster-022 Placebo >=70YOA Group                 |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Subjects above 70 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.                |  |
| Subject analysis set title   | Zoster-022/006 Pooled GSK1437173A 70-79YOA Group |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Subjects between 70 and 79 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule. |  |
| Subject analysis set title   | Zoster-022/006 Pooled GSK1437173A >=80YOA Group  |
| Subject analysis set type  | Sub-group analysis                               |
| Subject analysis set description:<br>Subjects above 80 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.          |  |
| Subject analysis set title   | Zoster-022/006 Pooled GSK1437173A >=70YOA Group  |
| Subject analysis set type  | Sub-group analysis                               |

Subject analysis set description:

Subjects above 70 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Zoster-022/006 Pooled Placebo 70-79YOA Group |
| Subject analysis set type  | Sub-group analysis                           |

Subject analysis set description:

Subjects between 70 and 79 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group |
| Subject analysis set type  | Sub-group analysis                                |

Subject analysis set description:

Subjects above 80 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group |
| Subject analysis set type  | Sub-group analysis                                |

Subject analysis set description:

Subjects above 70 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled GSK1437173A 50-59 YOA Group |
| Subject analysis set type  | Sub-group analysis                                |

Subject analysis set description:

Subjects between 50 and 59 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled GSK1437173A 60-69 YOA Group |
| Subject analysis set type  | Sub-group analysis                                |

Subject analysis set description:

Subjects between 60 and 69 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled GSK1437173A 70-79 YOA Group |
| Subject analysis set type  | Sub-group analysis                                |

Subject analysis set description:

Subjects between 70 and 79 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled GSK1437173A $\geq 80$ YOA Group |
| Subject analysis set type  | Sub-group analysis                                    |

Subject analysis set description:

Subjects above 80 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled Placebo 50-59 YOA Group |
| Subject analysis set type  | Sub-group analysis                            |

Subject analysis set description:

Subjects between 50 and 59 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled Placebo 60-69 YOA Group |
| Subject analysis set type  | Sub-group analysis                            |

Subject analysis set description:

Subjects between 60 and 69 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled Placebo 70-79 YOA Group |
| Subject analysis set type  | Sub-group analysis                            |

Subject analysis set description:

Subjects between 70 and 79 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group |
| Subject analysis set type  | Sub-group analysis                                |



Subject analysis set description:

Subjects above 80 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Zoster-022/006 Pooled GSK1437173A >=70 YOA Group |
| Subject analysis set type  | Sub-group analysis                               |

Subject analysis set description:

Subjects above 70 years of age (YOA), receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Zoster-022/006 Pooled Placebo >=70 YOA Group |
| Subject analysis set type  | Sub-group analysis                           |

Subject analysis set description:

Subjects above 70 years of age (YOA), receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

### Primary: Number of subjects with any episodes of herpes zoster (HZ)

|                 |  |
|-----------------|--|
| End point title | Number of subjects with any episodes of herpes zoster (HZ) |
|-----------------|--|

End point description:

Confirmed HZ cases during the study in the modified total vaccinated cohort (mTVc). The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values            | Zoster-022<br>GSK1437173A<br>70-79YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=80YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=70YOA<br>Group | Zoster-022<br>Placebo 70-<br>79YOA Group |
|-----------------------------|--|---|---|--|
| Subject group type          | Subject analysis set                           | Subject analysis set                          | Subject analysis set                          | Subject analysis set                     |
| Number of subjects analysed | 5114   | 1427  | 6541  | 5189                                     |
| Units: Subjects             | 17   | 6   | 23  | 169                                      |

| End point values            | Zoster-022<br>Placebo<br>>=80YOA<br>Group | Zoster-022<br>Placebo<br>>=70YOA<br>Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed | 1433                                      | 6622                                      |  |  |
| Units: Subjects             | 54  | 223                                       |  |  |

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Comparison of vaccine efficacy in prevention of Herpes Zoster (HZ) disease between Zoster-022 GSK1437173A 70-79 YOA group and Zoster-022 Placebo 70-79 YOA group.

|                   |  |
|-------------------|--|
| Comparison groups | Zoster-022 GSK1437173A 70-79YOA Group v Zoster-022 |
|-------------------|--|

|   |                        |
|---|------------------------|
|   | Placebo 70-79YOA Group |
| Number of subjects included in analysis | 10303                  |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | other <sup>[1]</sup>   |
| P-value                                 | < 0.0001               |
| Method                                  | Poisson exact test     |
| Parameter estimate                      | Vaccine efficacy       |
| Point estimate                          | 90.02                  |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 83.54                  |
| upper limit                             | 94.32                  |

Notes:

[1] - The efficacy of Herpes Zoster subunit (HZ/su) vaccine against herpes zoster disease was demonstrated if the lower limit (LL) of the two-sided 95% Confidence Interval (CI) of VE was above 10%.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of vaccine efficacy in prevention of Herpes Zoster (HZ) disease between Zoster-022 GSK1437173A  $\geq$ 80YOA Group and Zoster-022 Placebo  $\geq$ 80YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022 Placebo $\geq$ 80YOA Group v Zoster-022 GSK1437173A $\geq$ 80YOA Group |
| Number of subjects included in analysis | 2860  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[2]</sup>  |
| P-value                                 | < 0.0001  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 89.08   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 74.65   |
| upper limit                             | 96.16   |

Notes:

[2] - The efficacy of HZ/su vaccine against herpes zoster disease was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 10%

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of vaccine efficacy in prevention of Herpes Zoster (HZ) disease between Zoster-022 GSK1437173A  $\geq$ 70YOA Group and Zoster-022 Placebo  $\geq$ 70YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022 GSK1437173A $\geq$ 70YOA Group v Zoster-022 Placebo $\geq$ 70YOA Group |
| Number of subjects included in analysis | 13163   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[3]</sup>  |
| P-value                                 | < 0.0001  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 89.79   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 84.29   |
| upper limit         | 93.66   |

Notes:

[3] - The efficacy of HZ/su vaccine against herpes zoster disease was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 10%

**Primary: Outcome measure for the pooled analysis of combined data from studies ZOSTER-006 (NCT01165177) and ZOSTER-022 (NCT01165229): Number of subjects with post-herpetic neuralgia (PHN)**

|                 |  |
|-----------------|--|
| End point title | Outcome measure for the pooled analysis of combined data from studies ZOSTER-006 (NCT01165177) and ZOSTER-022 (NCT01165229): Number of subjects with post-herpetic neuralgia (PHN) |
|-----------------|--|

End point description:

Incidence of PHN calculated using the mTVc during the entire study period in subjects  $\geq 70$  years of age (YOA). The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values            | Zoster-022/006 Pooled GSK1437173A 70-79YOA Group | Zoster-022/006 Pooled GSK1437173A $\geq 80$ YOA Group | Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group | Zoster-022/006 Pooled Placebo 70-79YOA Group |
|-----------------------------|--|---|---|--|
| Subject group type          | Subject analysis set                             | Subject analysis set                                  | Subject analysis set                                  | Subject analysis set                         |
| Number of subjects analysed | 6468   | 1782  | 8250  | 6554   |
| Units: Subjects             | 2  | 2   | 4   | 29   |

| End point values            | Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                              | Subject analysis set                              |  |  |
| Number of subjects analysed | 1792  | 8346  |  |  |
| Units: Subjects             | 7   | 36  |  |  |

**Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Comparison of vaccine efficacy in prevention of Post-Herpetic Neuralgia (PHN) between Zoster-022/006

|   |   |
|---|---|
| Comparison groups                       | Zoster-022/006 Pooled GSK1437173A 70-79YOA Group v Zoster-022/006 Pooled Placebo 70-79YOA Group |
| Number of subjects included in analysis | 13022   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[4]</sup>  |
| P-value                                 | < 0.0001  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 93.04   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 72.47   |
| upper limit                             | 99.19   |

Notes:

[4] - The efficacy of HZ/su vaccine against PHN was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 0%

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Statistical analysis 2  |
| Statistical analysis description:   |   |
| Comparison of vaccine efficacy in prevention of PHN between Zoster-022/006 Pooled GSK1437173A >=80YOA Group and Zoster-022/006 Pooled Placebo >=80YOA Group |   |
| Comparison groups   | Zoster-022/006 Pooled GSK1437173A >=80YOA Group v Zoster-022/006 Pooled Placebo >=80YOA Group |
| Number of subjects included in analysis   | 3574  |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[5]</sup>  |
| P-value   | = 0.1844  |
| Method  | Poisson exact test  |
| Parameter estimate  | Vaccine efficacy  |
| Point estimate  | 71.16   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -51.51  |
| upper limit   | 97.08   |

Notes:

[5] - The efficacy of HZ/su vaccine against PHN was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 0%

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Statistical analysis 3  |
| Statistical analysis description:   |   |
| Comparison of vaccine efficacy in prevention of PHN between Zoster-022/006 Pooled GSK1437173A >=70YOA Group and Zoster-022/006 Pooled Placebo >=70YOA Group |   |
| Comparison groups   | Zoster-022/006 Pooled GSK1437173A >=70YOA Group v Zoster-022/006 Pooled Placebo >=70YOA Group |
| Number of subjects included in analysis   | 16596   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[6]</sup>  |
| P-value   | < 0.0001  |
| Method  | Poisson exact test  |
| Parameter estimate  | Vaccine efficacy  |
| Point estimate  | 88.78   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 68.7    |
| upper limit         | 97.1    |

Notes:

[6] - The efficacy of HZ/su vaccine against PHN was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 0%

**Primary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with confirmed HZ**

|                 |   |
|-----------------|---|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with confirmed HZ |
|-----------------|---|

End point description:

Occurrence of confirmed HZ during the entire study period in subjects  $\geq 70$  YOA. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values            | Zoster-022/006 Pooled GSK1437173A 70-79YOA Group | Zoster-022/006 Pooled GSK1437173A $\geq 80$ YOA Group | Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group | Zoster-022/006 Pooled Placebo 70-79YOA Group |
|-----------------------------|--|---|---|--|
| Subject group type          | Subject analysis set                             | Subject analysis set                                  | Subject analysis set                                  | Subject analysis set                         |
| Number of subjects analysed | 6468   | 1782  | 8250  | 6554   |
| Units: Subjects             | 19   | 6   | 25  | 216  |

| End point values            | Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                              | Subject analysis set                              |  |  |
| Number of subjects analysed | 1792  | 8346  |  |  |
| Units: Subjects             | 68  | 284   |  |  |

**Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Comparison of vaccine efficacy in prevention of herpes zoster disease between Zoster-022/006 Pooled GSK1437173A 70-79YOA Group and Zoster-022/006 Pooled Placebo 70-79YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022/006 Pooled GSK1437173A 70-79YOA Group v Zoster-022/006 Pooled Placebo 70-79YOA Group |
| Number of subjects included in analysis | 13022   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[7]</sup>  |
| P-value                                 | < 0.0001  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 91.27   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 86.04   |
| upper limit                             | 94.85   |

Notes:

[7] - The efficacy of HZ/su vaccine against herpes zoster disease was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 10%

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of vaccine efficacy in prevention of herpes zoster disease between Zoster-022/006 Pooled GSK1437173A  $\geq 80$ YOA Group and Zoster-022/006 Pooled Placebo  $\geq 80$ YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022/006 Pooled GSK1437173A $\geq 80$ YOA Group v Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group |
| Number of subjects included in analysis | 3574  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[8]</sup>  |
| P-value                                 | < 0.0001  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 91.37   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 80.22   |
| upper limit                             | 96.94   |

Notes:

[8] - The efficacy of HZ/su vaccine against herpes zoster disease was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 10%

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of vaccine efficacy in prevention of herpes zoster disease between Zoster-022/006 GSK1437173A  $\geq 70$  YOA Group and Zoster-022/006 Pooled Placebo  $\geq 70$ YOA Group

|                   |   |
|-------------------|---|
| Comparison groups | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group v Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group |
|-------------------|---|

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 16596                |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | other <sup>[9]</sup> |
| P-value                                 | < 0.0001             |
| Method                                  | Poisson exact test   |
| Parameter estimate                      | Vaccine efficacy     |
| Point estimate                          | 91.3                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 86.88                |
| upper limit                             | 94.46                |

Notes:

[9] - The efficacy of HZ/su vaccine against herpes zoster disease was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 10%

### Secondary: Number of subjects with post-herpetic neuralgia (PHN)

|   |   |
|---|---|
| End point title   | Number of subjects with post-herpetic neuralgia (PHN) |
| End point description:  |   |
| PHN cases in the mTVc. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| During the entire study period (3 to 5 year period following Day 0)   |   |

| End point values            | Zoster-022<br>GSK1437173A<br>70-79YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=80YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=70YOA<br>Group | Zoster-022<br>Placebo 70-<br>79YOA Group |
|-----------------------------|--|---|---|--|
| Subject group type          | Subject analysis set                           | Subject analysis set                          | Subject analysis set                          | Subject analysis set                     |
| Number of subjects analysed | 5114   | 1427  | 6541  | 5189                                     |
| Units: Subjects             | 2  | 2   | 4   | 22                                       |

| End point values            | Zoster-022<br>Placebo<br>>=80YOA<br>Group | Zoster-022<br>Placebo<br>>=70YOA<br>Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed | 1433                                      | 6622                                      |  |  |
| Units: Subjects             | 6   | 28  |  |  |

### Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical analysis 1  |
| Statistical analysis description:<br>Comparison of of Vaccine Efficacy (VE) in prevention of PHN between Zoster-022 GSK1437173A 70-79YOA Group and Zoster-022 placebo 70-79YOA Group |   |
| Comparison groups  | Zoster-022 GSK1437173A 70-79YOA Group v Zoster-022 Placebo 70-79YOA Group |
| Number of subjects included in analysis  | 10303   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[10]</sup>   |
| P-value  | < 0.0001  |
| Method   | Poisson exact test  |
| Parameter estimate   | Vaccine efficacy  |
| Point estimate   | 90.8  |
| Confidence interval  |   |
| level  | 90 %  |
| sides  | 2-sided   |
| lower limit  | 62.57   |
| upper limit  | 98.95   |

Notes:

[10] - The efficacy of HZ/su vaccine against PHN was demonstrated if the LL of the two-sided 95% CI of VE was above 0%.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical analysis 2  |
| Statistical analysis description:<br>Comparison of vaccine efficacy in prevention of PHN between Zoster-022 GSK1437173A >=80YOA Group and Zoster-022 Placebo >=80YOA Group |   |
| Comparison groups  | Zoster-022 GSK1437173A >=80YOA Group v Zoster-022 Placebo >=80YOA Group |
| Number of subjects included in analysis  | 2860  |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[11]</sup>   |
| P-value  | = 0.3072  |
| Method   | Poisson exact test  |
| Parameter estimate   | Vaccine efficacy  |
| Point estimate   | 65.76   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -91.58  |
| upper limit  | 96.62   |

Notes:

[11] - The efficacy of HZ/su vaccine against PHN was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 0%

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical analysis 3  |
| Statistical analysis description:<br>Comparison of vaccine efficacy in prevention of PHN between Zoster-022 GSK1437173A >=70YOA Group and Zoster-022 Placebo >=70YOA Group |   |
| Comparison groups  | Zoster-022 GSK1437173A >=70YOA Group v Zoster-022 Placebo >=70YOA Group |



|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 13163                 |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other <sup>[12]</sup> |
| P-value                                 | < 0.0001              |
| Method                                  | Poisson exact test    |
| Parameter estimate                      | Vaccine efficacy      |
| Point estimate                          | 85.49                 |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 58.52                 |
| upper limit                             | 96.3                  |

Notes:

[12] - The efficacy of HZ/su vaccine against PHN was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 0%

### Secondary: Number of days with severe 'worst' HZ-associated pain

|                 |   |
|-----------------|---|
| End point title | Number of days with severe 'worst' HZ-associated pain |
|-----------------|---|

End point description:

Duration of severe 'worst' HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period as measured by the Zoster Brief Pain Inventory (ZBPI) in subjects with confirmed HZ. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values                     | Zoster-022<br>GSK1437173A<br>70-79YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=80YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=70YOA<br>Group | Zoster-022<br>Placebo 70-<br>79YOA Group |
|--------------------------------------|--|---|---|--|
| Subject group type                   | Subject analysis set                           | Subject analysis set                          | Subject analysis set                          | Subject analysis set                     |
| Number of subjects analysed          | 15   | 3   | 18  | 150                                      |
| Units: Days                          |  |   |   |  |
| arithmetic mean (standard deviation) | 21.8 (± 31.41)                                 | 98.7 (± 57.73)                                | 34.6 (± 45.54)                                | 47.9 (± 100.08)                          |

| End point values                     | Zoster-022<br>Placebo<br>>=80YOA<br>Group | Zoster-022<br>Placebo<br>>=70YOA<br>Group |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed          | 48  | 198                                       |  |  |
| Units: Days                          |   |   |  |  |
| arithmetic mean (standard deviation) | 50.4 (± 106.51)                           | 48.5 (± 101.4)                            |  |  |

## Statistical analyses

| Statistical analysis title   | Statistical analysis 1  |
|--|---|
| Statistical analysis description:  |   |
| Comparison of VE in reduction of duration of severe worst HZ associated pain between Zoster-022 GSK1437173A 70-79YOA Group and Zoster-022 Placebo 70-79YOA Group |   |
| Comparison groups  | Zoster-022 Placebo 70-79YOA Group v Zoster-022 GSK1437173A 70-79YOA Group |
| Number of subjects included in analysis  | 165   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[13]</sup>   |
| P-value  | = 0.3749  |
| Method   | Poisson exact test  |
| Parameter estimate   | Vaccine efficacy  |
| Point estimate   | 21.7  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -34.4   |
| upper limit  | 54.39   |

Notes:

[13] - The efficacy of HZ/su vaccine against duration of severe worst HZ associated pain was demonstrated if the LL of the two-sided 95% CI of VE derived from the Hazard ratio was above 0%.

| Statistical analysis title   | Statistical analysis 2  |
|--|---|
| Statistical analysis description:  |   |
| Comparison of VE in reduction of duration of severe worst HZ associated pain between Zoster-022 GSK1437173A ≥80YOA Group and Zoster-022 Placebo ≥80YOA Group |   |
| Comparison groups  | Zoster-022 GSK1437173A ≥80YOA Group v Zoster-022 Placebo ≥80YOA Group |
| Number of subjects included in analysis  | 51  |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[14]</sup>   |
| P-value  | = 0.2466  |
| Method   | Poisson exact test  |
| Parameter estimate   | Vaccine efficacy  |
| Point estimate   | 51.76   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -65.55  |
| upper limit  | 85.95   |

Notes:

[14] - The efficacy of HZ/su vaccine against duration of severe worst HZ associated pain was demonstrated if the LL of the two-sided 95% CI of VE derived from the Hazard ratio was above 0%.

| Statistical analysis title | Statistical analysis 3 |
|----------------------------|------------------------|
|----------------------------|------------------------|

# Statistical analysis description:

Comparison of VE in reduction of duration of severe worst HZ associated pain between Zoster-022 GSK1437173A  $\geq 70$ YOA Group and Zoster-022 Placebo  $\geq 70$ YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022 GSK1437173A $\geq 70$ YOA Group v Zoster-022 Placebo $\geq 70$ YOA Group |
| Number of subjects included in analysis | 216   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[15]</sup>   |
| P-value                                 | = 0.1877  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 28.4  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 17.69   |
| upper limit                             | 56.44   |

## Notes:

[15] - The efficacy of HZ/su vaccine against duration of severe worst HZ associated pain was demonstrated if the LL of the two-sided 95% CI of VE derived from the Hazard ratio was above 0%.

## Secondary: Number of subjects with confirmed HZ episode related mortality and hospitalizations

|                 |   |
|-----------------|---|
| End point title | Number of subjects with confirmed HZ episode related mortality and hospitalizations |
|-----------------|---|

## End point description:

The number of subjects with confirmed HZ related mortality and hospitalizations were tabulated. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

## End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values             | Zoster-022 GSK1437173A 70-79YOA Group | Zoster-022 GSK1437173A $\geq 80$ YOA Group | Zoster-022 GSK1437173A $\geq 70$ YOA Group | Zoster-022 Placebo 70-79YOA Group |
|------------------------------|---------------------------------------|--|--|-----------------------------------|
| Subject group type           | Subject analysis set                  | Subject analysis set                       | Subject analysis set                       | Subject analysis set              |
| Number of subjects analysed  | 5114                                  | 1427                                       | 6541                                       | 5189                              |
| Units: Subjects              |                                       |  |  |                                   |
| Mortality                    | 0                                     | 0  | 0  | 0                                 |
| Hospitalization              | 0                                     | 0  | 0  | 3                                 |
| Mortality or hospitalization | 0                                     | 0  | 0  | 3                                 |

| End point values | Zoster-022 Placebo $\geq 80$ YOA Group | Zoster-022 Placebo $\geq 70$ YOA Group |  |  |
|------------------|--|--|--|--|
|------------------|--|--|--|--|

|                              |                      |                      |  |  |
|------------------------------|----------------------|----------------------|--|--|
| Subject group type           | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed  | 1433                 | 6622                 |  |  |
| Units: Subjects              |                      |                      |  |  |
| Mortality                    | 0                    | 0                    |  |  |
| Hospitalization              | 2                    | 5                    |  |  |
| Mortality or hospitalization | 2                    | 5                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with overall mortality and HZ-related mortality

|                 |  |
|-----------------|--|
| End point title | Number of subjects with overall mortality and HZ-related mortality |
|-----------------|--|

End point description:

The number of subjects with overall mortality and HZ related mortality were tabulated. Evaluation of VE in the reduction of overall and HZ related mortality as per study objective was not performed due to low number of events reported. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values            | Zoster-022<br>GSK1437173A<br>70-79YOA<br>Group | Zoster-022<br>GSK1437173A<br>≥80YOA<br>Group | Zoster-022<br>GSK1437173A<br>≥70YOA<br>Group | Zoster-022<br>Placebo 70-<br>79YOA Group |
|-----------------------------|--|--|--|--|
| Subject group type          | Subject analysis set                           | Subject analysis set                         | Subject analysis set                         | Subject analysis set                     |
| Number of subjects analysed | 5114   | 1427   | 6541   | 5189                                     |
| Units: Subjects             | 0  | 0  | 0  | 0  |

| End point values            | Zoster-022<br>Placebo<br>≥80YOA<br>Group | Zoster-022<br>Placebo<br>≥70YOA<br>Group |  |  |
|-----------------------------|--|--|--|--|
| Subject group type          | Subject analysis set                     | Subject analysis set                     |  |  |
| Number of subjects analysed | 1433                                     | 6622                                     |  |  |
| Units: Subjects             | 0  | 0  |  |  |

## Statistical analyses

**Secondary: Number of subjects with confirmed HZ episode related hospitalizations**

|                 |   |
|-----------------|---|
| End point title | Number of subjects with confirmed HZ episode related hospitalizations |
|-----------------|---|

End point description:

Incidence of overall and HZ-related hospitalizations during the study. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values            | Zoster-022<br>GSK1437173A<br>70-79YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=80YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=70YOA<br>Group | Zoster-022<br>Placebo 70-<br>79YOA Group |
|-----------------------------|--|---|---|--|
| Subject group type          | Subject analysis set                           | Subject analysis set                          | Subject analysis set                          | Subject analysis set                     |
| Number of subjects analysed | 5114   | 1427  | 6541  | 5189                                     |
| Units: Subjects             | 0  | 0   | 0   | 3  |

| End point values            | Zoster-022<br>Placebo<br>>=80YOA<br>Group | Zoster-022<br>Placebo<br>>=70YOA<br>Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed | 1433                                      | 6622                                      |  |  |
| Units: Subjects             | 2   | 5   |  |  |

**Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Comparison of VE in reduction of overall and HZ related hospitalizations between Zoster-022 GSK1437173A 70-79YOA Group and Zoster-022 Placebo 70-79YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022 GSK1437173A 70-79YOA Group v Zoster-022 Placebo 70-79YOA Group |
| Number of subjects included in analysis | 10303   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[16]</sup>   |
| P-value                                 | = 0.2533  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 100   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -144.13 |
| upper limit         | 100     |

Notes:

[16] - Efficacy of the HZ/su vaccine against overall and HZ related hospitalizations was demonstrated if the LL of the two-sided 95% CI of VE was above 0%.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of VE in reduction of overall and HZ related hospitalizations between Zoster-022 GSK1437173A  $\geq$ 80YOA Group and Zoster-022 Placebo  $\geq$ 80YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022 GSK1437173A $\geq$ 80YOA Group v Zoster-022 Placebo $\geq$ 80YOA Group |
| Number of subjects included in analysis | 2860  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[17]</sup>   |
| P-value                                 | = 0.5024  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 100   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -435.14   |
| upper limit                             | 100   |

Notes:

[17] - Efficacy of the HZ/su vaccine against overall and HZ related hospitalizations was demonstrated if the LL of the two-sided 95% CI of VE was above 0%.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of VE in reduction of overall and HZ related hospitalizations between Zoster-022 GSK1437173A  $\geq$ 70YOA Group and Zoster-022 Placebo  $\geq$ 70YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022 GSK1437173A $\geq$ 70YOA Group v Zoster-022 Placebo $\geq$ 70YOA Group |
| Number of subjects included in analysis | 13163   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[18]</sup>   |
| P-value                                 | = 0.0636  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 100   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -9.92   |
| upper limit                             | 100   |

Notes:

[18] - Efficacy of the HZ/su vaccine against overall and HZ related hospitalizations was demonstrated if the LL of the two-sided 95% CI of VE was above 0%.

## Secondary: Number of subjects with HZ related complications

|  |  |
|--|--|
| End point title  | Number of subjects with HZ related complications |
| End point description:   |  |
| Incidence of HZ complications during the study in subjects with confirmed HZ. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| During the entire study period (3 to 5 year period following Day 0)  |  |

| End point values            | Zoster-022<br>GSK1437173A<br>70-79YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=80YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=70YOA<br>Group | Zoster-022<br>Placebo 70-<br>79YOA Group |
|-----------------------------|--|---|---|--|
| Subject group type          | Subject analysis set                           | Subject analysis set                          | Subject analysis set                          | Subject analysis set                     |
| Number of subjects analysed | 17   | 6   | 23  | 169                                      |
| Units: Subjects             |  |   |   |  |
| At least one complication   | 1  | 0   | 1   | 6  |
| HZ vasculitis               | 0  | 0   | 0   | 0  |
| Disseminated Disease        | 0  | 0   | 0   | 0  |
| Ophthalmic Disease          | 1  | 0   | 1   | 4  |
| Neurologic Disease          | 0  | 0   | 0   | 3  |
| Visceral Disease            | 0  | 0   | 0   | 0  |
| Stroke                      | 0  | 0   | 0   | 0  |

| End point values            | Zoster-022<br>Placebo<br>>=80YOA<br>Group | Zoster-022<br>Placebo<br>>=70YOA<br>Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed | 54  | 223                                       |  |  |
| Units: Subjects             |   |   |  |  |
| At least one complication   | 4   | 10  |  |  |
| HZ vasculitis               | 0   | 0   |  |  |
| Disseminated Disease        | 2   | 2   |  |  |
| Ophthalmic Disease          | 2   | 6   |  |  |
| Neurologic Disease          | 0   | 3   |  |  |
| Visceral Disease            | 0   | 0   |  |  |
| Stroke                      | 0   | 0   |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Statistical analysis 1                             |
| Statistical analysis description:   |  |
| Comparison of VE in reduction of HZ related complications between Zoster-022 GSK1437173A 70-79YOA Group and Zoster-022 Placebo 70-79YOA Group |  |
| Comparison groups   | Zoster-022 GSK1437173A 70-79YOA Group v Zoster-022 |

|   |                        |
|---|------------------------|
|   | Placebo 70-79YOA Group |
| Number of subjects included in analysis | 186                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | other <sup>[19]</sup>  |
| P-value                                 | = 0.4947               |
| Method                                  | Poisson exact test     |
| Parameter estimate                      | Vaccine efficacy       |
| Point estimate                          | -65.69                 |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | -827.06                |
| upper limit                             | 73.62                  |

Notes:

[19] - Efficacy of the HZ/su vaccine against HZ related complications was demonstrated if the LL of the VE was above 0%.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Statistical analysis 2  |
| Statistical analysis description:   |   |
| Comparison of VE in reduction of HZ related complications between Zoster-022 GSK1437173A >=80YOA Group and Zoster-022 Placebo >=80YOA Group |   |
| Comparison groups   | Zoster-022 GSK1437173A >=80YOA Group v Zoster-022 Placebo >=80YOA Group |
| Number of subjects included in analysis   | 60  |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[20]</sup>   |
| P-value   | = 1   |
| Method  | Poisson exact test  |
| Parameter estimate  | Vaccine efficacy  |
| Point estimate  | 100   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -558.05   |
| upper limit   | 100   |

Notes:

[20] - Efficacy of the HZ/su vaccine against HZ related complications was demonstrated if the LL of the VE was above 0%

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Statistical analysis 3  |
| Statistical analysis description:   |   |
| Comparison of VE in reduction of HZ related complications between Zoster-022 GSK1437173A >=70YOA Group and Zoster-022 Placebo >=70YOA Group |   |
| Comparison groups   | Zoster-022 GSK1437173A >=70YOA Group v Zoster-022 Placebo >=70YOA Group |
| Number of subjects included in analysis   | 246   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[21]</sup>   |
| P-value   | = 1   |
| Method  | Poisson exact test  |
| Parameter estimate  | Vaccine efficacy  |
| Point estimate  | 0.97  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -433.32 |
| upper limit         | 83.16   |

Notes:

[21] - Efficacy of the HZ/su vaccine against HZ related complications was demonstrated if the LL of the VE was above 0%

### Secondary: Number of subjects receiving pain medication associated with HZ

|                 |   |
|-----------------|---|
| End point title | Number of subjects receiving pain medication associated with HZ |
|-----------------|---|

End point description:

Incidence of use of pain medications throughout the study. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values            | Zoster-022<br>GSK1437173A<br>70-79YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=80YOA<br>Group | Zoster-022<br>GSK1437173A<br>>=70YOA<br>Group | Zoster-022<br>Placebo 70-<br>79YOA Group |
|-----------------------------|--|---|---|--|
| Subject group type          | Subject analysis set                           | Subject analysis set                          | Subject analysis set                          | Subject analysis set                     |
| Number of subjects analysed | 17   | 6   | 23  | 169                                      |
| Units: Subjects             |  |   |   |  |
| At least 1 pain medication  | 7  | 3   | 10  | 123                                      |
| 1 pain medication only      | 5  | 0   | 5   | 43                                       |
| 2 pain medications only     | 0  | 1   | 1   | 30                                       |
| 3 pain medications or more  | 2  | 2   | 4   | 50                                       |

| End point values            | Zoster-022<br>Placebo<br>>=80YOA<br>Group | Zoster-022<br>Placebo<br>>=70YOA<br>Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                      | Subject analysis set                      |  |  |
| Number of subjects analysed | 54  | 223                                       |  |  |
| Units: Subjects             |   |   |  |  |
| At least 1 pain medication  | 37  | 160                                       |  |  |
| 1 pain medication only      | 17  | 60  |  |  |
| 2 pain medications only     | 4   | 34  |  |  |
| 3 pain medications or more  | 16  | 66  |  |  |

### Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical analysis 1  |
| Statistical analysis description:<br>Comparison of VE in reduction in use of pain medication between Zoster-022 GSK1437173A 70-79YOA Group and Zoster-022 Placebo 70-79YOA Group |   |
| Comparison groups  | Zoster-022 GSK1437173A 70-79YOA Group v Zoster-022 Placebo 70-79YOA Group |
| Number of subjects included in analysis  | 186   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[22]</sup>   |
| P-value  | = 0.0112  |
| Method   | Poisson exact test  |
| Parameter estimate   | Vaccine efficacy  |
| Point estimate   | 43.42   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 10.77   |
| upper limit  | 70.53   |

Notes:

[22] - Efficacy of the HZ/su vaccine against use of pain medications was demonstrated if the LL of the two-sided 95% CI of VE was above 0%.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical analysis 2  |
| Statistical analysis description:<br>Comparison of VE in reduction in use of pain medication between Zoster-022 GSK1437173A $\geq$ 80YOA Group and Zoster-022 Placebo $\geq$ 80YOA Group |   |
| Comparison groups  | Zoster-022 GSK1437173A $\geq$ 80YOA Group v Zoster-022 Placebo $\geq$ 80YOA Group |
| Number of subjects included in analysis  | 60  |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[23]</sup>   |
| P-value  | = 0.3903  |
| Method   | Poisson exact test  |
| Parameter estimate   | Vaccine efficacy  |
| Point estimate   | 27.03   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | -26.43  |
| upper limit  | 73.2  |

Notes:

[23] - Efficacy of the HZ/su vaccine against use of pain medications was demonstrated if the LL of the two-sided 95% CI of the VE was above 0%

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical analysis 3  |
| Statistical analysis description:<br>Comparison of VE in reduction in use of pain medication between Zoster-022 GSK1437173A $\geq$ 70YOA group and Zoster-022 Placebo $\geq$ 70YOA Group |   |
| Comparison groups  | Zoster-022 GSK1437173A $\geq$ 70YOA Group v Zoster-022 Placebo $\geq$ 70YOA Group |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 246                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other <sup>[24]</sup> |
| P-value                                 | = 0.0083              |
| Method                                  | Poisson exact test    |
| Parameter estimate                      | Vaccine efficacy      |
| Point estimate                          | 39.6                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 10.79                 |
| upper limit                             | 64.75                 |

Notes:

[24] - Efficacy of the HZ/su vaccine against use of pain medications was demonstrated if the LL of the two-sided 95% CI of VE was above 0%.

### Secondary: Number of days with pain medication associated with HZ

|                 |  |
|-----------------|--|
| End point title | Number of days with pain medication associated with HZ |
|-----------------|--|

End point description:

Incidence of reduction of duration of pain medication associated with HZ throughout the study. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values                     | Zoster-022<br>GSK1437173A<br>70-79YOA<br>Group | Zoster-022<br>GSK1437173A<br>≥80YOA<br>Group | Zoster-022<br>GSK1437173A<br>≥70YOA<br>Group | Zoster-022<br>Placebo 70-<br>79YOA Group |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Subject analysis set                           | Subject analysis set                         | Subject analysis set                         | Subject analysis set                     |
| Number of subjects analysed          | 7  | 3  | 10   | 123                                      |
| Units: Days                          |  |  |  |  |
| arithmetic mean (standard deviation) | 38.7 (± 56.44)                                 | 274.7 (± 337)                                | 109.5 (± 200.88)                             | 218.6 (± 593.8)                          |

| End point values                     | Zoster-022<br>Placebo<br>≥80YOA<br>Group | Zoster-022<br>Placebo<br>≥70YOA<br>Group |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Subject analysis set                     | Subject analysis set                     |  |  |
| Number of subjects analysed          | 37                                       | 160                                      |  |  |
| Units: Days                          |  |  |  |  |
| arithmetic mean (standard deviation) | 135 (± 207.31)                           | 199.3 (± 530.6)                          |  |  |

## Statistical analyses

| Statistical analysis title  | Statistical analysis 1  |
|---|---|
| Statistical analysis description:   |   |
| Comparison of VE in reduction in duration of pain medication associated with HZ between Zoster-022 GSK1437173A 70-79YOA Group and Zoster-022 Placebo 70-79YOA Group |   |
| Comparison groups   | Zoster-022 GSK1437173A 70-79YOA Group v Zoster-022 Placebo 70-79YOA Group |
| Number of subjects included in analysis   | 130   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[25]</sup>   |
| P-value   | = 0.0232  |
| Method  | Poisson exact test  |
| Parameter estimate  | Vaccine efficacy  |
| Point estimate  | 58.94   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 11.45   |
| upper limit   | 80.96   |

Notes:

[25] - Efficacy of the HZ/su vaccine against duration of pain medication associated with HZ was demonstrated if the LL of the two-sided 95% CI of VE derived from the hazard ratio was above 0%.

| Statistical analysis title  | Statistical analysis 2  |
|---|---|
| Statistical analysis description:   |   |
| Comparison of VE in reduction in duration of pain medication associated with HZ between Zoster-022 GSK1437173A ≥80YOA Group and Zoster-022 Placebo ≥80YOA Group |   |
| Comparison groups   | Zoster-022 GSK1437173A ≥80YOA Group v Zoster-022 Placebo ≥80YOA Group |
| Number of subjects included in analysis   | 40  |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[26]</sup>   |
| P-value   | = 0.8324  |
| Method  | Poisson exact test  |
| Parameter estimate  | Vaccine efficacy  |
| Point estimate  | -14.56  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -303.3  |
| upper limit   | 67.46   |

Notes:

[26] - Efficacy of the HZ/su vaccine against duration of pain medication associated with HZ was demonstrated if the LL of the two-sided 95% CI of VE derived from the hazard ratio was above 0%.

| Statistical analysis title | Statistical analysis 3 |
|----------------------------|------------------------|
|----------------------------|------------------------|

## Statistical analysis description:

Comparison of VE in reduction in duration of pain medication associated with HZ between Zoster-022 GSK1437173A  $\geq 70$ YOA Group and Zoster-022 Placebo  $\geq 70$ YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022 GSK1437173A $\geq 70$ YOA Group v Zoster-022 Placebo $\geq 70$ YOA Group |
| Number of subjects included in analysis | 170   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[27]</sup>   |
| P-value                                 | = 0.0404  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 49.25   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 2.92  |
| upper limit                             | 73.47   |

## Notes:

[27] - Efficacy of the HZ/su vaccine against duration of pain medication associated with HZ was demonstrated if the LL of the two-sided 95% CI of VE derived from the hazard ratio was above 0%.

**Secondary: Number of subjects with any and grade 3 solicited local symptoms**

|                 |  |
|-----------------|--|
| End point title | Number of subjects with any and grade 3 solicited local symptoms |
|-----------------|--|

## End point description:

Occurrence, intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset; Assessed solicited local symptoms were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = pain that prevented normal activity. Grade 3 redness/swelling = redness/swelling spreading beyond 100 millimeters (mm) of injection site. The analysis was performed on the total vaccinated cohort – Diary Card, which was a subset of subjects from the total vaccinated cohort, who completed diary cards with any solicited symptoms during the 7 days (Day 0 to Day 6) post vaccination period

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

## End point timeframe:

Within the 7 days (Days 0-6) after each vaccination

| End point values                     | Zoster-022 GSK1437173A Group | Zoster-022 Placebo Group |  |  |
|--------------------------------------|------------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group              | Reporting group          |  |  |
| Number of subjects analysed          | 505                          | 505                      |  |  |
| Units: Subjects                      |                              |                          |  |  |
| Any Pain, Dose 1 (N=502;504)         | 297                          | 26                       |  |  |
| Grade 3 Pain, Dose 1 (N=502;504)     | 12                           | 1                        |  |  |
| Any Redness, Dose 1 (N=502;504)      | 143                          | 3                        |  |  |
| Grade 3 Redness, Dose 1 (N=502;504)  | 9                            | 0                        |  |  |
| Any Swelling, Dose 1 (N=502;504)     | 85                           | 2                        |  |  |
| Grade 3 Swelling, Dose 1 (N=502;504) | 2                            | 0                        |  |  |
| Any Pain, Dose 2 (N=492;491)         | 282                          | 23                       |  |  |
| Grade 3 Pain, Dose 2 (N=492;491)     | 12                           | 0                        |  |  |
| Any Redness, Dose 2 (N=492;491)      | 137                          | 3                        |  |  |
| Grade 3 Redness, Dose 2 (N=492;491)  | 15                           | 0                        |  |  |

|  |     |    |  |  |
|--|-----|----|--|--|
| Any Swelling, Dose 2 (N=492;491)           | 68  | 0  |  |  |
| Grade 3 Swelling, Dose 2 (N=492;491)       | 7   | 0  |  |  |
| Any Pain, Across Doses (N=505;505)         | 347 | 43 |  |  |
| Grade 3 Pain, Across Doses (N=505;505)     | 22  | 1  |  |  |
| Any Redness, Across Doses (N=505;505)      | 198 | 5  |  |  |
| Grade 3 Redness, Across Doses (N=505;505)  | 20  | 0  |  |  |
| Any Swelling, Across Doses (N=505;505)     | 114 | 2  |  |  |
| Grade 3 Swelling, Across Doses (N=505;505) | 8   | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with any, grade 3 and related solicited general symptoms

|                 |   |
|-----------------|---|
| End point title | Number of subjects with any, grade 3 and related solicited general symptoms |
|-----------------|---|

End point description:

Assessed solicited general symptoms were fatigue, gastrointestinal symptoms, headache, myalgia, shivering and fever [defined as axillary temperature equal to or above 37.5 degrees Celsius (°C)]. Any = occurrence of the symptom regardless of intensity grade. Grade 3 symptom = symptom that prevented normal activity. Grade 3 fever = fever > 39.0 °C. Related = symptom assessed by the investigator as related to the vaccination. The analysis was performed on the total vaccinated cohort – Diary Card, which was a subset of subjects from the total vaccinated cohort, who completed diary cards with any solicited symptoms during the 7 days (Day 0 to Day 6) post vaccination period

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

End point timeframe:

Within the 7 days (Days 0-6) post-vaccination period following each dose and across doses

| End point values                             | Zoster-022<br>GSK1437173A<br>Group | Zoster-022<br>Placebo Group |  |  |
|--|------------------------------------|-----------------------------|--|--|
| Subject group type                           | Reporting group                    | Reporting group             |  |  |
| Number of subjects analysed                  | 501                                | 505                         |  |  |
| Units: Subjects                              |                                    |                             |  |  |
| Any Fatigue, Dose 1 (N=501;503)              | 104                                | 56                          |  |  |
| Grade 3 Fatigue, Dose 1 (N=501;503)          | 8                                  | 4                           |  |  |
| Related Fatigue, Dose 1 (N=501;503)          | 85                                 | 34                          |  |  |
| Any Gastrointestinal, Dose 1 (N=501;503)     | 25                                 | 28                          |  |  |
| Grade 3 Gastrointestinal, Dose 1 (N=501;503) | 3                                  | 2                           |  |  |
| Related Gastrointestinal, Dose 1 (N=501;503) | 16                                 | 14                          |  |  |
| Any Headache, Dose 1 (N=501;503)             | 72                                 | 42                          |  |  |
| Grade 3 Headache, Dose 1 (N=501;503)         | 2                                  | 4                           |  |  |

|  |     |    |  |  |
|--|-----|----|--|--|
| Related Headache, Dose 1 (N=501;503)               | 58  | 27 |  |  |
| Any Myalgia, Dose 1 (N=501;503)                    | 106 | 27 |  |  |
| Grade 3 Myalgia, Dose 1 (N=501;503)                | 6   | 2  |  |  |
| Related Myalgia, Dose 1 (N=501;503)                | 91  | 16 |  |  |
| Any Shivering, Dose 1 (N=501;503)                  | 38  | 17 |  |  |
| Grade 3 Shivering, Dose 1 (N=501;503)              | 1   | 1  |  |  |
| Related Shivering, Dose 1 (N=501;503)              | 32  | 12 |  |  |
| Any Temperature, Dose 1 (N=501;503)                | 39  | 9  |  |  |
| Grade 3 Temperature, Dose 1 (N=501;503)            | 0   | 2  |  |  |
| Related Temperature, Dose 1 (N=501;503)            | 31  | 4  |  |  |
| Any Fatigue, Dose 2 (N=492;489)                    | 122 | 39 |  |  |
| Grade 3 Fatigue, Dose 2 (N=492;489)                | 9   | 0  |  |  |
| Related Fatigue, Dose 2 (N=492;489)                | 105 | 30 |  |  |
| Any Gastrointestinal, Dose 2 (N=492;489)           | 37  | 19 |  |  |
| Grade 3 Gastrointestinal, Dose 2 (N=492;489)       | 3   | 1  |  |  |
| Related Gastrointestinal, Dose 2 (N=492;489)       | 26  | 13 |  |  |
| Any Headache, Dose 2 (N=492;489)                   | 76  | 26 |  |  |
| Grade 3 Headache, Dose 2 (N=492;489)               | 4   | 0  |  |  |
| Related Headache, Dose 2 (N=492;489)               | 63  | 20 |  |  |
| Any Myalgia, Dose 2 (N=492;489)                    | 113 | 18 |  |  |
| Grade 3 Myalgia, Dose 2 (N=492;489)                | 7   | 0  |  |  |
| Related Myalgia, Dose 2 (N=492;489)                | 94  | 16 |  |  |
| Any Shivering, Dose 2 (N=492;489)                  | 59  | 11 |  |  |
| Grade 3 Shivering, Dose 2 (N=492;489)              | 5   | 1  |  |  |
| Related Shivering, Dose 2 (N=492;489)              | 47  | 9  |  |  |
| Any Temperature, Dose 2 (N=492;489)                | 38  | 6  |  |  |
| Grade 3 Temperature, Dose 2 (N=492;489)            | 0   | 2  |  |  |
| Related Temperature, Dose 2 (N=492;489)            | 35  | 2  |  |  |
| Any Fatigue, Across Doses (N=504;505)              | 166 | 77 |  |  |
| Grade 3 Fatigue, Across Doses (N=504;505)          | 16  | 4  |  |  |
| Related Fatigue, Across Doses (N=504;505)          | 140 | 52 |  |  |
| Any Gastrointestinal, Across Doses (N=504;505)     | 55  | 40 |  |  |
| Grade 3 Gastrointestinal, Across Doses (N=504;505) | 5   | 2  |  |  |
| Related Gastrointestinal, Across Doses (N=504;505) | 38  | 21 |  |  |
| Any Headache, Across Doses (N=504;505)             | 124 | 55 |  |  |
| Grade 3 Headache, Across Doses (N=504;505)         | 5   | 4  |  |  |
| Related Headache, Across Doses (N=504;505)         | 104 | 37 |  |  |
| Any Myalgia, Across Doses (N=504;505)              | 157 | 41 |  |  |
| Grade 3 Myalgia, Across Doses (N=504;505)          | 12  | 2  |  |  |
| Related Myalgia, Across Doses (N=504;505)          | 137 | 29 |  |  |

|   |    |    |  |  |
|---|----|----|--|--|
| Any Shivering, Across Doses (N=504;505)       | 75 | 22 |  |  |
| Grade 3 Shivering, Across Doses (N=504;505)   | 6  | 2  |  |  |
| Related Shivering, Across Doses (N=504;505)   | 64 | 16 |  |  |
| Any Temperature, Across Doses (N=504;505)     | 62 | 13 |  |  |
| Grade 3 Temperature, Across Doses (N=504;505) | 0  | 2  |  |  |
| Related Temperature, Across Doses (N=504;505) | 54 | 6  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with any, grade 3 and related unsolicited adverse events (AEs)

|                 |   |
|-----------------|---|
| End point title | Number of subjects with any, grade 3 and related unsolicited adverse events (AEs) |
|-----------------|---|

End point description:

Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects. An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to vaccination. Grade 3 AE = an AE which prevented normal, everyday activities. Related = AE assessed by the investigator as related to the vaccination.

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

End point timeframe:

Within the 30 days (Days 0-29) after each vaccination

| End point values            | Zoster-022<br>GSK1437173A<br>Group | Zoster-022<br>Placebo Group |  |  |
|-----------------------------|------------------------------------|-----------------------------|--|--|
| Subject group type          | Reporting group                    | Reporting group             |  |  |
| Number of subjects analysed | 6950                               | 6950                        |  |  |
| Units: Subjects             |                                    |                             |  |  |
| Any AE(s)                   | 3859                               | 2263                        |  |  |
| Grade 3 AE(s)               | 485                                | 265                         |  |  |
| Related AE(s)               | 2853                               | 529                         |  |  |

## Statistical analyses

No statistical analyses for this end point



**Secondary: Number of subjects with any and related serious adverse events (SAEs)**

|   |   |
|---|---|
| End point title   | Number of subjects with any and related serious adverse events (SAEs) |
| End point description:<br>Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity. |   |
| End point type  | Secondary   |
| End point timeframe:<br>From Month 0 to Month 14  |   |

| End point values            | Zoster-022<br>GSK1437173A<br>Group | Zoster-022<br>Placebo Group |  |  |
|-----------------------------|------------------------------------|-----------------------------|--|--|
| Subject group type          | Reporting group                    | Reporting group             |  |  |
| Number of subjects analysed | 6950                               | 6950                        |  |  |
| Units: Subjects             |                                    |                             |  |  |
| Any SAE(s)                  | 891                                | 939                         |  |  |
| Related SAE(s)              | 12                                 | 7                           |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of subjects with any and related potential immune mediated diseases (pIMDs)**

|   |  |
|---|--|
| End point title   | Number of subjects with any and related potential immune mediated diseases (pIMDs) |
| End point description:<br>Occurrence and relationship to vaccination of any potential immune-mediated diseases (pIMDs) during the entire study period in all subjects. This analysis was based on the the total vaccinated cohort, which included all subjects with at least one dose of study vaccine or placebo administered. |  |
| End point type  | Secondary  |
| End point timeframe:<br>During the entire study period (3 to 5 year period following Day 0)   |  |

| End point values            | Zoster-022<br>GSK1437173A<br>Group | Zoster-022<br>Placebo Group |  |  |
|-----------------------------|------------------------------------|-----------------------------|--|--|
| Subject group type          | Reporting group                    | Reporting group             |  |  |
| Number of subjects analysed | 6950                               | 6950                        |  |  |
| Units: Subjects             |                                    |                             |  |  |
| Any pIMD                    | 92                                 | 97                          |  |  |
| Related pIMD(s)             | 8                                  | 6                           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with any and related Medically Attended visits

|                 |   |
|-----------------|---|
| End point title | Number of subjects with any and related Medically Attended visits |
|-----------------|---|

End point description:

Occurrence and relationship to vaccination of medically attended visits other than routine health care visits, from Month 0 to Month 8 in all subjects. Medically attended visits were defined as events for which the subject received medical attention defined as hospitalization, an emergency room visit, or a visit to or from medical personnel (medical doctor) for any reason. Any medically attended visits(s) = Occurrence of any medically attended visits(s) regardless of intensity grade or relation to vaccination. This analysis was based on the the total vaccinated cohort, which included all subjects with at least one dose of study vaccine or placebo administered.

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

End point timeframe:

From Month 0 to Month 8 post-vaccination

| End point values                  | Zoster-022<br>GSK1437173A<br>Group | Zoster-022<br>Placebo Group |  |  |
|-----------------------------------|------------------------------------|-----------------------------|--|--|
| Subject group type                | Reporting group                    | Reporting group             |  |  |
| Number of subjects analysed       | 6950                               | 6950                        |  |  |
| Units: Subjects                   |                                    |                             |  |  |
| Any medically attended visits     | 2882                               | 2911                        |  |  |
| Related medically attended visits | 165                                | 66                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Overall number of subjects with PHN in subjects $\geq 50$ YOA

|                 |  |
|-----------------|--|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Overall number of subjects with PHN in subjects $\geq 50$ YOA |
|-----------------|--|

End point description:

Incidence of PHN calculated using the mTVc during the entire study period in subjects  $\geq 50$  YOA. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| During the entire study period (3 to 5 year period following Day 0) |           |

| End point values            | Zoster-022/006 Pooled GSK1437173A 50-59 YOA Group | Zoster-022/006 Pooled GSK1437173A 60-69 YOA Group | Zoster-022/006 Pooled GSK1437173A 70-79 YOA Group | Zoster-022/006 Pooled GSK1437173A >=80 YOA Group |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set                              | Subject analysis set                              | Subject analysis set                              | Subject analysis set                             |
| Number of subjects analysed | 3491  | 2140  | 6468  | 1782   |
| Units: Subjects             | 0   | 0   | 2   | 2  |

| End point values            | Zoster-022/006 Pooled Placebo 50-59 YOA Group | Zoster-022/006 Pooled Placebo 60-69 YOA Group | Zoster-022/006 Pooled Placebo 70-79 YOA Group | Zoster-022/006 Pooled Placebo >=80 YOA Group |
|-----------------------------|---|---|---|--|
| Subject group type          | Subject analysis set                          | Subject analysis set                          | Subject analysis set                          | Subject analysis set                         |
| Number of subjects analysed | 3523  | 2166  | 6554  | 1792   |
| Units: Subjects             | 8   | 2   | 29  | 7  |

## Statistical analyses

| Statistical analysis title   | Statistical analysis 1  |
|--|---|
| Statistical analysis description:  |   |
| Comparison of vaccine efficacy in prevention of PHN between Zoster-022/006 Pooled GSK1437173A 50-59YOA Group and Zoster-022/006 Pooled Placebo 50-59YOA Group.Comparison of vaccine efficacy for groups 70-79 and above 80 YOA are presented in outcome measure 2. |   |
| Comparison groups  | Zoster-022/006 Pooled GSK1437173A 50-59 YOA Group v Zoster-022/006 Pooled Placebo 50-59 YOA Group |
| Number of subjects included in analysis  | 7014  |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[28]</sup>   |
| P-value  | = 0.0081  |
| Method   | Poisson exact test  |
| Parameter estimate   | Vaccine efficacy  |
| Point estimate   | 100   |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 40.88   |
| upper limit  | 100   |

Notes:

[28] - The efficacy of HZ/su vaccine against PHN was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 0%

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Statistical analysis 2  |
| Statistical analysis description:   |   |
| Comparison of vaccine efficacy in prevention of PHN between Zoster-022/006 Pooled GSK1437173A 60-69YOA Group and Zoster-022/006 Pooled Placebo 60-69YOA Group |   |
| Comparison groups   | Zoster-022/006 Pooled GSK1437173A 60-69 YOA Group v Zoster-022/006 Pooled Placebo 60-69 YOA Group |
| Number of subjects included in analysis   | 4306  |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[29]</sup>   |
| P-value   | = 0.5097  |
| Method  | Poisson exact test  |
| Parameter estimate  | Vaccine efficacy  |
| Point estimate  | 100   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -442.83   |
| upper limit   | 100   |

Notes:

[29] - The efficacy of HZ/su vaccine against PHN was demonstrated if the lower limit of the of the 2-sided 95% CI of VE was above 0%

**Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with a reduction of PHN incidence in subjects  $\geq$  50 YOA with confirmed HZ**

|   |   |
|---|---|
| End point title   | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with a reduction of PHN incidence in subjects $\geq$ 50 YOA with confirmed HZ |
| End point description:<br>Occurrence of PHN during the entire study period in all subjects with confirmed HZ. |   |
| End point type  | Secondary   |
| End point timeframe:<br>During the entire study period (3 to 5 year period following Day 0)                   |   |

| <b>End point values</b>     | Zoster-022/006 Pooled GSK1437173A 50-59 YOA Group | Zoster-022/006 Pooled GSK1437173A 60-69 YOA Group | Zoster-022/006 Pooled GSK1437173A 70-79 YOA Group | Zoster-022/006 Pooled GSK1437173A $\geq$ 80 YOA Group |
|-----------------------------|---|---|---|---|
| Subject group type          | Subject analysis set                              | Subject analysis set                              | Subject analysis set                              | Subject analysis set                                  |
| Number of subjects analysed | 4   | 3   | 19  | 6   |
| Units: Subjects             | 0   | 0   | 2   | 2   |

| <b>End point values</b> | Zoster-022/006 Pooled Placebo 50-59 YOA Group | Zoster-022/006 Pooled Placebo 60-69 YOA Group | Zoster-022/006 Pooled Placebo 70-79 YOA Group | Zoster-022/006 Pooled Placebo $\geq$ 80 YOA Group |
|-------------------------|---|---|---|---|
|-------------------------|---|---|---|---|

|                             |                      |                      |                      |                      |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 103                  | 90                   | 216                  | 68                   |
| Units: Subjects             | 8                    | 2                    | 29                   | 7                    |

## Statistical analyses

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of Vaccine efficacy in reduction of PHN incidence in subjects with confirmed HZ episode in Zoster-022/006 Pooled GSK1437173A 50-59 YOA Group versus Zoster-022/006 Pooled Placebo 50-59 YOA Group

|   |  |
|---|--|
| Comparison groups                       | Zoster-022/006 Pooled GSK1437173A 50-59 YOA Group v<br>Zoster-022/006 Pooled Placebo 50-59 YOA Group |
| Number of subjects included in analysis | 107  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other <sup>[30]</sup>  |
| P-value                                 | = 1  |
| Method                                  | Poisson exact test   |
| Parameter estimate                      | Vaccine efficacy   |
| Point estimate                          | 100  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -649.86  |
| upper limit                             | 100  |

Notes:

[30] - The efficacy of HZ/su vaccine in reduction of PHN in subjects with confirmed HZ episodes was demonstrated if the LL of the two-sided 95% CI of VE was above 0%

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of Vaccine efficacy in reduction of PHN incidence in subjects with confirmed HZ episode in Zoster-022/006 Pooled GSK1437173A 60-69 YOA Group versus Zoster-022/006 Pooled Placebo 60-69 YOA Group

|   |  |
|---|--|
| Comparison groups                       | Zoster-022/006 Pooled GSK1437173A 60-69 YOA Group v<br>Zoster-022/006 Pooled Placebo 60-69 YOA Group |
| Number of subjects included in analysis | 93   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other <sup>[31]</sup>  |
| P-value                                 | = 1  |
| Method                                  | Poisson exact test   |
| Parameter estimate                      | Vaccine efficacy   |
| Point estimate                          | 100  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -3938.7  |
| upper limit                             | 100  |

Notes:

[31] - The efficacy of HZ/su vaccine in reduction of PHN in subjects with confirmed HZ episodes was demonstrated if the LL of the two-sided 95% CI of VE was above 0%

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Statistical analysis 3   |
| Statistical analysis description:  |  |
| Comparison of Vaccine efficacy in reduction of PHN incidence in subjects with confirmed HZ episode in Zoster-022/006 Pooled GSK1437173A 70-79 YOA Group versus Zoster-022/006 Pooled Placebo 70-79 YOA Group |  |
| Comparison groups  | Zoster-022/006 Pooled GSK1437173A 70-79 YOA Group v<br>Zoster-022/006 Pooled Placebo 70-79 YOA Group |
| Number of subjects included in analysis  | 235  |
| Analysis specification   | Pre-specified  |
| Analysis type  | other <sup>[32]</sup>  |
| P-value  | = 1  |
| Method   | Poisson exact test   |
| Parameter estimate   | Vaccine efficacy   |
| Point estimate   | 21.6   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -149.41  |
| upper limit  | 78.91  |

Notes:

[32] - The efficacy of HZ/su vaccine in reduction of PHN in subjects with confirmed HZ episodes was demonstrated if the LL of the two-sided 95% CI of VE was above 0%

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Statistical analysis 4   |
| Statistical analysis description:  |  |
| Comparison of Vaccine efficacy in reduction of PHN incidence in subjects with confirmed HZ episode in Zoster-022/006 Pooled GSK1437173A $\geq 80$ YOA Group versus Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group |  |
| Comparison groups  | Zoster-022/006 Pooled GSK1437173A $\geq 80$ YOA Group v<br>Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group |
| Number of subjects included in analysis  | 74   |
| Analysis specification   | Pre-specified  |
| Analysis type  | other <sup>[33]</sup>  |
| P-value  | = 0.1528   |
| Method   | Poisson exact test   |
| Parameter estimate   | Vaccine efficacy   |
| Point estimate   | -223.81  |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -883.05  |
| upper limit  | 18.84  |

Notes:

[33] - The efficacy of HZ/su vaccine in reduction of PHN in subjects with confirmed HZ episodes was demonstrated if the LL of the two-sided 95% CI of VE was above 0%

**Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with reduction of duration of severe 'worst' HZ-associated pain in subjects  $\geq 70$  YOA with confirmed HZ**

|                 |   |
|-----------------|---|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with reduction of duration of severe 'worst' HZ-associated pain in subjects $\geq 70$ YOA with confirmed HZ |
|-----------------|---|

End point description:

The duration of severe 'worst' HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period was measured by the ZBPI in subjects  $\geq 70$  YOA with confirmed HZ. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values            | Zoster-022/006 Pooled GSK1437173A 70-79 YOA Group | Zoster-022/006 Pooled GSK1437173A $\geq 80$ YOA Group | Zoster-022/006 Pooled Placebo 70-79 YOA Group | Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group |
|-----------------------------|---|---|---|---|
| Subject group type          | Subject analysis set                              | Subject analysis set                                  | Subject analysis set                          | Subject analysis set                              |
| Number of subjects analysed | 19  | 6   | 216   | 68  |
| Units: Subjects             | 17  | 3   | 193   | 61  |

| End point values            | Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                                  | Subject analysis set                              |  |  |
| Number of subjects analysed | 25  | 284   |  |  |
| Units: Subjects             | 20  | 254   |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Comparison of VE in reduction of duration of severe worst HZ associated pain between Zoster-022/006 pooled GSK1437173A 70-79YOA Group and Zoster-022/006 pooled Placebo 70-79YOA Group

|                   |   |
|-------------------|---|
| Comparison groups | Zoster-022/006 Pooled GSK1437173A 70-79 YOA Group v Zoster-022/006 Pooled Placebo 70-79 YOA Group |
|-------------------|---|

|   |     |
|---|-----|
| Number of subjects included in analysis | 235 |
|---|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |                       |
|---------------|-----------------------|
| Analysis type | other <sup>[34]</sup> |
|---------------|-----------------------|

|         |          |
|---------|----------|
| P-value | = 0.2885 |
|---------|----------|

|        |                    |
|--------|--------------------|
| Method | Poisson exact test |
|--------|--------------------|

|                    |                  |
|--------------------|------------------|
| Parameter estimate | Vaccine efficacy |
|--------------------|------------------|

|                |       |
|----------------|-------|
| Point estimate | 23.75 |
|----------------|-------|

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -25.8   |
| upper limit         | 53.78   |

Notes:

[34] - The VE of HZ/su against duration of severe worst pain in subjects with confirmed HZ was demonstrated if the LL of the two-sided 95% CI of VE derived from the Hazard ratio was above 0%.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of VE in reduction of duration of severe worst HZ associated pain between Zoster-022/006 pooled GSK1437173A  $\geq 80$  YOA Group and Zoster-022/006 pooled Placebo  $\geq 80$  YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022/006 Pooled GSK1437173A $\geq 80$ YOA Group v Zoster-022/006 Pooled Placebo $\geq 80$ YOA Group |
| Number of subjects included in analysis | 74  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[35]</sup>   |
| P-value                                 | = 0.194   |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 54.93   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -50.03  |
| upper limit                             | 86.46   |

Notes:

[35] - The VE of HZ/su against duration of severe worst pain in subjects with confirmed HZ was demonstrated if the LL of the two-sided 95% CI of VE derived from the Hazard ratio was above 0%.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Comparison of VE in reduction of duration of severe worst HZ associated pain between Zoster-022/006 pooled GSK1437173A  $\geq 70$  YOA Group and Zoster-022/006 pooled Placebo  $\geq 70$  YOA Group

|   |   |
|---|---|
| Comparison groups                       | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group v Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group |
| Number of subjects included in analysis | 309   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[36]</sup>   |
| P-value                                 | = 0.1243  |
| Method                                  | Poisson exact test  |
| Parameter estimate                      | Vaccine efficacy  |
| Point estimate                          | 30.48   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -10.52  |
| upper limit                             | 56.27   |

Notes:

[36] - The VE of HZ/su against duration of severe worst pain in subjects with confirmed HZ was demonstrated if the LL of the two-sided 95% CI of VE derived from the Hazard ratio was above 0%.

## Secondary: Outcome measure for the pooled analysis of combined data from studies



**Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Duration of severe 'worst' HZ-associated pain in subjects ≥ 70 YOA with confirmed HZ**

|                 |   |
|-----------------|---|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Duration of severe 'worst' HZ-associated pain in subjects ≥ 70 YOA with confirmed HZ |
|-----------------|---|

## End point description:

Duration of severe 'worst' HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period was measured by the ZBPI in subjects ≥ 70 YOA with confirmed HZ. The analysis was based on the modified total vaccinated cohort, which included subjects from the total vaccinated cohort, except those who were not administered with the second vaccination or who developed a confirmed case of Herpes Zoster prior to 1 month after the second vaccination.

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

## End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

| End point values                     | Zoster-022/006 Pooled GSK1437173A 70-79 YOA Group | Zoster-022/006 Pooled GSK1437173A ≥80 YOA Group | Zoster-022/006 Pooled Placebo 70-79 YOA Group | Zoster-022/006 Pooled Placebo ≥80 YOA Group |
|--------------------------------------|---|---|---|---|
| Subject group type                   | Subject analysis set                              | Subject analysis set                            | Subject analysis set                          | Subject analysis set                        |
| Number of subjects analysed          | 17  | 3   | 193   | 61  |
| Units: Days                          |   |   |   |   |
| arithmetic mean (standard deviation) | 20.3 (± 29.71)                                    | 98.7 (± 57.73)                                  | 48.3 (± 96.34)                                | 45.2 (± 95.58)                              |

| End point values                     | Zoster-022/006 Pooled GSK1437173A ≥70 YOA Group | Zoster-022/006 Pooled Placebo ≥70 YOA Group |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Subject analysis set                            | Subject analysis set                        |  |  |
| Number of subjects analysed          | 20  | 254   |  |  |
| Units: Days                          |   |   |  |  |
| arithmetic mean (standard deviation) | 32.1 (± 43.80)                                  | 47.5 (± 95.98)                              |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any and Grade 3 solicited local symptoms**

|                 |   |
|-----------------|---|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any and Grade 3 solicited local symptoms |
|-----------------|---|

**End point description:**

Occurrence, intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination, in subjects  $\geq 70$  YOA. Assessed solicited local symptoms were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = pain that prevented normal activity. Grade 3 redness/swelling = redness/swelling spreading beyond 100 millimeters (mm) of injection site. The analysis was performed on the total vaccinated cohort – Diary Card, which was a subset of subjects from the total vaccinated cohort, who completed diary cards with any solicited symptoms during the 7 days (Day 0 to Day 6) post vaccination period.

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

**End point timeframe:**

Within 7 days (Days 0-6) post-vaccination period following each dose and across doses

| <b>End point values</b>                      | Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group |  |  |
|--|---|---|--|--|
| Subject group type                           | Subject analysis set                                  | Subject analysis set                              |  |  |
| Number of subjects analysed                  | 2258  | 2263  |  |  |
| Units: Subjects                              |   |   |  |  |
| Any Pain, Dose 1 (N=2246;2255)               | 1336  | 128   |  |  |
| Grade 3 Pain, Dose 1 (N=2246;2255)           | 42  | 1   |  |  |
| Any Redness, Dose 1 (N=2246;2255)            | 606   | 17  |  |  |
| Grade 3 Redness, Dose 1 (N=2246;2255)        | 43  | 0   |  |  |
| Any Swelling, Dose 1 (N=2246;2255)           | 355   | 17  |  |  |
| Grade 3 Swelling, Dose 1 (N=2246;2255)       | 17  | 0   |  |  |
| Any Pain, Dose 2 (N=2160;2169)               | 1241  | 107   |  |  |
| Grade 3 Pain, Dose 2 (N=2160;2169)           | 60  | 3   |  |  |
| Any Redness, Dose 2 (N=2160;2169)            | 582   | 14  |  |  |
| Grade 3 Redness, Dose 2 (N=2160;2169)        | 39  | 0   |  |  |
| Any Swelling, Dose 2 (N=2160;2169)           | 344   | 10  |  |  |
| Grade 3 Swelling, Dose 2 (N=2160;2169)       | 15  | 0   |  |  |
| Any Pain, Across Doses (N=2258;2263)         | 1562  | 199   |  |  |
| Grade 3 Pain, Across Doses (N=2258;2263)     | 90  | 4   |  |  |
| Any Redness, Across Doses (N=2258;2263)      | 851   | 27  |  |  |
| Grade 3 Redness, Across Doses (N=2258;2263)  | 70  | 0   |  |  |
| Any Swelling, Across Doses (N=2258;2263)     | 519   | 25  |  |  |
| Grade 3 Swelling, Across Doses (N=2258;2263) | 30  | 0   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any, Grade 3 and related solicited general symptoms**

|                 |  |
|-----------------|--|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any, Grade 3 and related solicited general symptoms |
|-----------------|--|

End point description:

Assessed solicited general symptoms were fatigue, gastrointestinal symptoms, headache, myalgia, shivering and fever [defined as axillary temperature equal to or above 37.5 degrees Celsius (°C)]. Any = occurrence of the symptom regardless of intensity grade. Grade 3 symptom = symptom that prevented normal activity. Grade 3 fever = fever > 39.0 °C. Related = symptom assessed by the investigator as related to the vaccination. The analysis was performed on the total vaccinated cohort – Diary Card, which was a subset of subjects from the total vaccinated cohort, who completed diary cards with any solicited symptoms during the 7 days (Day 0 to Day 6) post vaccination period.

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

End point timeframe:

Within the 7-day (Days 0-6) post-vaccination period following each dose and across doses

| End point values                               | Zoster-022/006<br>Pooled<br>GSK1437173A<br>>=70 YOA<br>Group | Zoster-022/006<br>Pooled Placebo<br>>=70 YOA<br>Group |  |  |
|--|--|---|--|--|
| Subject group type                             | Subject analysis set   | Subject analysis set                                  |  |  |
| Number of subjects analysed                    | 2252   | 2264  |  |  |
| Units: Subjects                                |  |   |  |  |
| Any Fatigue, Dose 1 (N=2237;2256)              | 545  | 231   |  |  |
| Grade 3 Fatigue, Dose 1 (N=2237;2256)          | 31   | 13  |  |  |
| Related Fatigue, Dose 1 (N=2237;2256)          | 441  | 147   |  |  |
| Any Gastrointestinal, Dose 1 (N=2237;2256)     | 170  | 123   |  |  |
| Grade 3 Gastrointestinal, Dose 1 (N=2237;2256) | 15   | 6   |  |  |
| Related Gastrointestinal, Dose 1 (N=2237;2256) | 101  | 67  |  |  |
| Any Headache, Dose 1 (N=2237;2256)             | 380  | 189   |  |  |
| Grade 3 Headache, Dose 1 (N=2237;2256)         | 7  | 8   |  |  |
| Related Headache, Dose 1 (N=2237;2256)         | 293  | 132   |  |  |
| Any Myalgia, Dose 1 (N=2237;2256)              | 530  | 159   |  |  |
| Grade 3 Myalgia, Dose 1 (N=2237;2256)          | 26   | 7   |  |  |
| Related Myalgia, Dose 1 (N=2237;2256)          | 445  | 101   |  |  |
| Any Shivering, Dose 1 (N=2237;2256)            | 206  | 73  |  |  |
| Grade 3 Shivering, Dose 1 (N=2237;2256)        | 15   | 3   |  |  |
| Related Shivering, Dose 1 (N=2237;2256)        | 173  | 50  |  |  |
| Any Temperature, Dose 1 (N=2237;2256)          | 142  | 34  |  |  |
| Grade 3 Temperature, Dose 1 (N=2237;2256)      | 1  | 2   |  |  |

|  |     |     |  |  |
|--|-----|-----|--|--|
| Related Temperature, Dose 1<br>(N=2237;2256)           | 111 | 16  |  |  |
| Any Fatigue, Dose 2 (N=2159;2166)                      | 579 | 169 |  |  |
| Grade 3 Fatigue, Dose 2<br>(N=2159;2166)               | 53  | 4   |  |  |
| Related Fatigue, Dose 2 (N=2159;2166)                  | 495 | 116 |  |  |
| Any Gastrointestinal, Dose 2<br>(N=2159;2166)          | 188 | 75  |  |  |
| Grade 3 Gastrointestinal, Dose 2<br>(N=2159;2166)      | 14  | 5   |  |  |
| Related Gastrointestinal, Dose 2<br>(N=2159;2166)      | 142 | 35  |  |  |
| Any Headache, Dose 2 (N=2159;2166)                     | 455 | 133 |  |  |
| Grade 3 Headache, Dose 2<br>(N=2159;2166)              | 30  | 2   |  |  |
| Related Headache, Dose 2<br>(N=2159;2166)              | 386 | 86  |  |  |
| Any Myalgia, Dose 2 (N=2159;2166)                      | 560 | 112 |  |  |
| Grade 3 Myalgia, Dose 2<br>(N=2159;2166)               | 42  | 4   |  |  |
| Related Myalgia, Dose 2 (N=2159;2166)                  | 484 | 75  |  |  |
| Any Shivering, Dose 2 (N=2159;2166)                    | 334 | 55  |  |  |
| Grade 3 Shivering, Dose 2<br>(N=2159;2166)             | 36  | 4   |  |  |
| Related Shivering, Dose 2<br>(N=2159;2166)             | 292 | 34  |  |  |
| Any Temperature, Dose 2<br>(N=2159;2166)               | 224 | 30  |  |  |
| Grade 3 Temperature, Dose 2<br>(N=2159;2166)           | 2   | 3   |  |  |
| Related Temperature, Dose 2<br>(N=2159;2166)           | 189 | 14  |  |  |
| Any Fatigue, Across Doses<br>(N=2252;2264)             | 825 | 326 |  |  |
| Grade 3 Fatigue, Across Doses<br>(N=2252;2264)         | 79  | 17  |  |  |
| Related Fatigue, Across Doses<br>(N=2252;2264)         | 699 | 220 |  |  |
| Any Gastrointestinal, Across Doses<br>(N=2252;2264)    | 304 | 172 |  |  |
| Grade 3 Gastrointestinal, Across<br>Doses(N=2252;2264) | 26  | 10  |  |  |
| Related Gastrointestinal, Across<br>Doses(N=2252;2264) | 210 | 91  |  |  |
| Any Headache, Across Doses<br>(N=2252;2264)            | 653 | 268 |  |  |
| Grade 3 Headache, Across Doses<br>(N=2252;2264)        | 34  | 10  |  |  |
| Related Headache, Across Doses<br>(N=2252;2264)        | 547 | 185 |  |  |
| Any Myalgia, Across Doses<br>(N=2252;2264)             | 790 | 225 |  |  |
| Grade 3 Myalgia, Across Doses<br>(N=2252;2264)         | 62  | 10  |  |  |
| Related Myalgia, Across Doses<br>(N=2252;2264)         | 689 | 157 |  |  |
| Any Shivering, Across Doses<br>(N=2252;2264)           | 439 | 110 |  |  |
| Grade 3 Shivering, Across Doses<br>(N=2252;2264)       | 49  | 6   |  |  |

|   |     |    |  |  |
|---|-----|----|--|--|
| Related Shivering, Across Doses (N=2252;2264)   | 380 | 75 |  |  |
| Any Temperature, Across Doses (N=2252;2264)     | 323 | 61 |  |  |
| Grade 3 Temperature, Across Doses (N=2252;2264) | 3   | 3  |  |  |
| Related Temperature, Across Doses (N=2252;2264) | 265 | 30 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any, grade 3 and related unsolicited AEs in subjects $\geq 70$ YOA

|                 |   |
|-----------------|---|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any, grade 3 and related unsolicited AEs in subjects $\geq 70$ YOA |
|-----------------|---|

End point description:

Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0-29) after each vaccination, according to the MedDRA classification, in subjects  $\geq 70$  YOA. An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to vaccination. Grade 3 AE = an AE which prevented normal, everyday activities. Related = AE assessed by the investigator as related to the vaccination.

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

End point timeframe:

Within 30 days (Days 0 - 29) after each vaccination

| End point values            | Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                                  | Subject analysis set                              |  |  |
| Number of subjects analysed | 8758  | 8773  |  |  |
| Units: Subjects             |   |   |  |  |
| Any AE(s)                   | 4366  | 2732  |  |  |
| Grade 3 AE(s)               | 553   | 335   |  |  |
| Related AE(s)               | 2961  | 578   |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any and related SAE**

|                 |  |
|-----------------|--|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any and related SAE |
|-----------------|--|

End point description:

Occurrence and relationship to vaccination of all SAEs from Month 0 to Month 14 in subjects  $\geq 70$  YOA. Related SAEs also included any SAEs related to study participation or concurrent GSK medication/vaccine.

|                          |           |
|--------------------------|-----------|
| End point type           | Secondary |
| End point timeframe:     |           |
| From Month 0 to Month 14 |           |

| End point values            | Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                                  | Subject analysis set                              |  |  |
| Number of subjects analysed | 8758  | 8773  |  |  |
| Units: Subjects             |   |   |  |  |
| Any SAEs up to Month 14     | 1117  | 1171  |  |  |
| Related SAEs up to Month 14 | 12  | 7   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any and related pIMDs**

|                 |  |
|-----------------|--|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any and related pIMDs |
|-----------------|--|

End point description:

Occurrence and relationship to vaccination of any pIMDs during the entire study period in subjects  $\geq 70$  YOA. The analysis was based on the total vaccinated cohort, which included all vaccinated subjects with study vaccine or placebo administered.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| During the entire study period (3 to 5 year period following Day 0) |           |

| End point values            | Zoster-022/006<br>Pooled<br>GSK1437173A<br>≥70 YOA<br>Group | Zoster-022/006<br>Pooled Placebo<br>≥70 YOA<br>Group |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Subject analysis set  | Subject analysis set                                 |  |  |
| Number of subjects analysed | 8758  | 8773   |  |  |
| Units: Subjects             |   |  |  |  |
| Any pIMD(s)                 | 110   | 118  |  |  |
| Related pIMD(s)             | 8   | 8  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any and related medically attended visits

|                        |   |
|------------------------|---|
| End point title        | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with any and related medically attended visits  |
| End point description: | Occurrence and relationship to vaccination of medically attended visits (defined as hospitalizations, emergency room visits or visits to or from medical personnel), other than routine health care visits, from Month 0 to Month 8 in subjects ≥ 70 YOA. |
| End point type         | Secondary   |
| End point timeframe:   | From Month 0 to Month 8 post-vaccination  |

| End point values            | Zoster-022/006<br>Pooled<br>GSK1437173A<br>≥70 YOA<br>Group | Zoster-022/006<br>Pooled Placebo<br>≥70 YOA<br>Group |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Subject analysis set  | Subject analysis set                                 |  |  |
| Number of subjects analysed | 8758  | 8773   |  |  |
| Units: Subjects             |   |  |  |  |
| Any MAE(s)                  | 3593  | 3648   |  |  |
| Related MAE(s)              | 180   | 80   |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|  |   |
|--|---|
| End point title  | Number of subjects with fatal serious adverse events (SAEs) |
| End point description:<br>Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity. This analysis was based on the the total vaccinated cohort, which included all subjects with at least one dose of study vaccine or placebo administered. |   |
| End point type   | Secondary   |
| End point timeframe:<br>During the entire study period (3 to 5 year period following Day 0)  |   |

| End point values            | Zoster-022<br>GSK1437173A<br>Group | Zoster-022<br>Placebo Group |  |  |
|-----------------------------|------------------------------------|-----------------------------|--|--|
| Subject group type          | Reporting group                    | Reporting group             |  |  |
| Number of subjects analysed | 6950                               | 6950                        |  |  |
| Units: Participants         |                                    |                             |  |  |
| Fatal SAE(s)                | 426                                | 459                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with SAEs related to study participation or concomitant GSK medication

|   |   |
|---|---|
| End point title   | Number of subjects with SAEs related to study participation or concomitant GSK medication |
| End point description:<br>The number of subjects with SAEs related to study participation or concomitant GSK medication were tabulated. The analysis was based on the total vaccinated cohort, which included all subjects with at least one dose of study vaccine or placebo administered. |   |
| End point type  | Secondary   |
| End point timeframe:<br>During the entire study period (3 to 5 year period following day 0)   |   |

| End point values            | Zoster-022<br>GSK1437173A<br>Group | Zoster-022<br>Placebo Group |  |  |
|-----------------------------|------------------------------------|-----------------------------|--|--|
| Subject group type          | Reporting group                    | Reporting group             |  |  |
| Number of subjects analysed | 6950                               | 6950                        |  |  |
| Units: Participants         | 57                                 | 84                          |  |  |

### Statistical analyses



No statistical analyses for this end point

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**Secondary: Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with fatal SAEs**

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|                 |   |
|-----------------|---|
| End point title | Outcome measure for the pooled analysis of combined data from studies Zoster-006 (NCT01165177) and Zoster-022 (NCT01165229): Number of subjects with fatal SAEs |
|-----------------|---|

End point description:

Fatal SAEs during the entire study period in subjects  $\geq 70$  YOA. The analysis was based on the total vaccinated cohort, which included all vaccinated subjects with study vaccine or placebo administered.

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

End point timeframe:

During the entire study period (3 to 5 year period following Day 0)

---

| End point values            | Zoster-022/006 Pooled GSK1437173A $\geq 70$ YOA Group | Zoster-022/006 Pooled Placebo $\geq 70$ YOA Group |  |  |
|-----------------------------|---|---|--|--|
| Subject group type          | Subject analysis set                                  | Subject analysis set                              |  |  |
| Number of subjects analysed | 8758  | 8773  |  |  |
| Units: Subjects             | 128   | 144   |  |  |

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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:

Solicited symptoms: Within 7 (Days 0-6) days after vaccination; Unsolicited adverse events: within 30 days (Days 0-29) after vaccination; Serious adverse events: during the entire study period (3 to 5 year period following Day 0)

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 10.0   |

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Zoster-022 Placebo Group |
|-----------------------|--------------------------|

Reporting group description:

Subjects receiving saline solution (NaCl solution) as control according to a 0, 2-month schedule.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Zoster-022 GSK1437173A Group |
|-----------------------|------------------------------|

Reporting group description:

Subjects receiving herpes zoster subunit vaccine (gE/AS01B vaccine) according to a 0, 2-month schedule.

| Serious adverse events  | Zoster-022 Placebo Group | Zoster-022 GSK1437173A Group |  |
|---|--------------------------|------------------------------|--|
| Total subjects affected by serious adverse events                   |                          |                              |  |
| subjects affected / exposed   | 1214 / 6950 (17.47%)     | 1153 / 6950 (16.59%)         |  |
| number of deaths (all causes)                                       | 459                      | 426                          |  |
| number of deaths resulting from adverse events                      | 0                        | 1                            |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                          |                              |  |
| Acral lentiginous melanoma  |                          |                              |  |
| subjects affected / exposed   | 1 / 6950 (0.01%)         | 0 / 6950 (0.00%)             |  |
| occurrences causally related to treatment / all                     | 0 / 1                    | 0 / 0                        |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0                        |  |
| Acute monocytic leukaemia   |                          |                              |  |
| subjects affected / exposed   | 1 / 6950 (0.01%)         | 0 / 6950 (0.00%)             |  |
| occurrences causally related to treatment / all                     | 0 / 1                    | 0 / 0                        |  |
| deaths causally related to treatment / all                          | 0 / 1                    | 0 / 0                        |  |
| Acute myeloid leukaemia   |                          |                              |  |
| subjects affected / exposed   | 0 / 6950 (0.00%)         | 2 / 6950 (0.03%)             |  |
| occurrences causally related to treatment / all                     | 0 / 0                    | 1 / 2                        |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 1                        |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Adenocarcinoma                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Adenocarcinoma gastric                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Adenocarcinoma of colon                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Adenocarcinoma pancreas                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Adrenal adenoma                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adrenal gland cancer                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaplastic astrocytoma                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Anaplastic thyroid cancer                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| B precursor type acute leukaemia                |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| B-cell lymphoma                                 |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Basal cell carcinoma                            |                   |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Benign neoplasm of thyroid gland                |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Benign ovarian tumour                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bile duct cancer                                |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2            |  |
| Bladder cancer                                  |                   |                  |  |
| subjects affected / exposed                     | 13 / 6950 (0.19%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1            |  |
| Bladder cancer recurrent                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bladder neoplasm                                |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Bladder papilloma                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder transitional cell carcinoma             |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bladder transitional cell carcinoma recurrent   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Bone cancer                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Bowen's disease                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain neoplasm benign                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Breast cancer metastatic                        |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchial carcinoma                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Carcinoid tumour pulmonary                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Central nervous system neoplasm                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Cholangiocarcinoma                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| Cholesteatoma                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic lymphocytic leukaemia                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Chronic myeloid leukaemia                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Colon adenoma                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colon cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 9 / 6950 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 3            |  |
| Colon cancer metastatic                         |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 3            |  |
| Colon neoplasm                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Diffuse large B-cell lymphoma                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diffuse large B-cell lymphoma stage IV          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Endometrial adenocarcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Fallopian tube cancer                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Follicular thyroid cancer                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gallbladder cancer                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastric cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 4            |  |
| Gastrointestinal carcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Gastrointestinal stromal tumour                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal tract adenoma                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Glioblastoma                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Glioblastoma multiforme                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hepatic cancer                                  |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 2            |  |
| Hepatic cancer metastatic                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hepatic neoplasm                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Hepatocellular carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| Hypergammaglobulinaemia benign monoclonal       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intestinal adenocarcinoma                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Invasive ductal breast carcinoma                |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Invasive lobular breast carcinoma               |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Invasive papillary breast carcinoma             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Large cell lung cancer                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Large intestine benign neoplasm                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal cancer                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lung adenocarcinoma                             |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 0            |  |
| Lung adenocarcinoma metastatic                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| Lung adenocarcinoma stage III                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung cancer metastatic                          |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 6            |  |
| Lung neoplasm                                   |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             |  |
| Lung neoplasm malignant                         |                   |                   |  |
| subjects affected / exposed                     | 13 / 6950 (0.19%) | 22 / 6950 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 22            |  |
| deaths causally related to treatment / all      | 0 / 10            | 0 / 18            |  |
| Lymphoma  |                   |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             |  |
| Malignant fibrous histiocytoma of bone          |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Malignant lymphoma unclassifiable high grade    |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Malignant mast cell neoplasm                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Malignant melanoma                              |                   |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 3 / 6950 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 2             |  |
| Malignant melanoma in situ                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Malignant neoplasm of ampulla of Vater          |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Malignant palate neoplasm                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningioma                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Mesothelioma                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to adrenals                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to bone                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 2            |  |
| Metastases to central nervous system            |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 4            |  |
| Metastases to gastrointestinal tract            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Metastases to liver                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 4            |  |
| Metastases to lung                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastases to lymph nodes                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Metastases to peritoneum                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Metastases to stomach                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Metastasis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Metastatic carcinoma of the bladder             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Metastatic gastric cancer                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| Metastatic malignant melanoma                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| Metastatic neoplasm                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Metastatic renal cell carcinoma                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Metastatic squamous cell carcinoma              |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Myelodysplastic syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Neoplasm malignant                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| Neoplasm prostate                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Non-Hodgkin's lymphoma                          |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Non-small cell lung cancer                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Non-small cell lung cancer stage IV             |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Oesophageal adenocarcinoma                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Oesophageal adenocarcinoma metastatic           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Oesophageal cancer metastatic                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| Oesophageal carcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 5            |  |
| Oesophageal squamous cell carcinoma             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Ovarian cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 4            |  |
| Ovarian cancer recurrent                        |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Ovarian epithelial cancer                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ovarian germ cell teratoma benign               |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pancreatic carcinoma                            |                   |                  |  |
| subjects affected / exposed                     | 10 / 6950 (0.14%) | 7 / 6950 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 10            | 0 / 7            |  |
| Pancreatic carcinoma metastatic                 |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 3            |  |
| Pancreatic neoplasm                             |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2            |  |
| Pancreatic neuroendocrine tumour                |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Papillary thyroid cancer                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Paraganglion neoplasm                           |                   |                  |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Parathyroid tumour benign                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pituitary tumour benign                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Plasma cell myeloma                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Prostate cancer                                 |                   |                   |  |
| subjects affected / exposed                     | 18 / 6950 (0.26%) | 19 / 6950 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 19            |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 3             |  |
| Prostate cancer metastatic                      |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 3 / 6950 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 3             |  |
| Prostate cancer recurrent                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 3 / 6950 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Prostate cancer stage IV                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Prostatic adenoma                               |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal adenocarcinoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3            |  |
| Rectal adenoma                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Rectal cancer recurrent                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal cancer                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Renal cancer metastatic                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Renal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Renal cell carcinoma recurrent                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal oncocytoma                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salivary gland cancer                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Sarcoma   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin cancer                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small cell lung cancer                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Small cell lung cancer metastatic               |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Small intestine adenocarcinoma                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Squamous cell carcinoma                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Squamous cell carcinoma of lung                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Squamous cell carcinoma of skin                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Squamous cell carcinoma of the oral cavity      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sweat gland tumour                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| T-cell lymphoma                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Throat cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Thyroid cancer                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tongue neoplasm malignant stage unspecified     |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Transitional cell carcinoma                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Transitional cell carcinoma metastatic          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Urethral neoplasm                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vulval cancer                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular disorders                              |                  |                  |  |
| Aneurysm  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aneurysm ruptured                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Aortic aneurysm                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| Aortic aneurysm rupture                         |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 4            |  |
| Aortic arteriosclerosis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Aortic dissection                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Aortic occlusion                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Aortic rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Aortic stenosis                                 |                  |                  |  |
| subjects affected / exposed                     | 8 / 6950 (0.12%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Arteriosclerosis                                |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 1            |  |
| Arteriovenous fistula                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood pressure inadequately controlled          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Circulatory collapse                            |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 4            |  |
| Deep vein thrombosis                            |                  |                  |  |
| subjects affected / exposed                     | 9 / 6950 (0.13%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Embolism  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Femoral artery aneurysm                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Femoral artery occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma                                       |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemorrhage                                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Hypertension                                    |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 25 / 6950 (0.36%) | 22 / 6950 (0.32%) |  |
| occurrences causally related to treatment / all | 0 / 25            | 0 / 22            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 3             |  |
| Hypertensive crisis                             |                   |                   |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%)  | 7 / 6950 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertensive emergency                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypotension                                     |                   |                   |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%)  | 6 / 6950 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Inferior vena caval occlusion                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Intermittent claudication                       |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Internal haemorrhage                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Labile hypertension                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Microscopic polyangiitis                        |                   |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Necrosis ischaemic                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orthostatic hypotension                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral arterial occlusive disease           |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Peripheral artery aneurysm                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral artery stenosis                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peripheral vascular disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Shock haemorrhagic                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Temporal arteritis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thromboangiitis obliterans                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombophlebitis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombosis                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Varicose vein                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vasculitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Venous thrombosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Venous thrombosis limb                          |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                          | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                      |                  |                  |  |
| Hospitalisation                                      |                  |                  |  |
| subjects affected / exposed                          | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Rectal polypectomy                                   |                  |                  |  |
| subjects affected / exposed                          | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Accidental death                                     |                  |                  |  |
| subjects affected / exposed                          | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 1            |  |
| Administration site erythema                         |                  |                  |  |
| subjects affected / exposed                          | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Administration site pain                             |                  |                  |  |
| subjects affected / exposed                          | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Adverse drug reaction                                |                  |                  |  |
| subjects affected / exposed                          | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Asthenia   |                  |                  |  |
| subjects affected / exposed                          | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 1            |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Cardiac death                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Chest discomfort                                |                   |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chest pain                                      |                   |                   |  |
| subjects affected / exposed                     | 19 / 6950 (0.27%) | 20 / 6950 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 19            | 0 / 20            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chills  |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cyst  |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Death   |                   |                   |  |
| subjects affected / exposed                     | 29 / 6950 (0.42%) | 17 / 6950 (0.24%) |  |
| occurrences causally related to treatment / all | 0 / 29            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 29            | 0 / 17            |  |
| Device battery issue                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Device deposit issue                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Device dislocation                              |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device leakage                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Device occlusion                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drowning  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| General physical health deterioration           |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Generalised oedema                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ill-defined disorder                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incarcerated hernia                             |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Inflammation                                    |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Malaise   |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Multi-organ failure                             |                   |                  |  |
| subjects affected / exposed                     | 12 / 6950 (0.17%) | 9 / 6950 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 11            | 0 / 9            |  |
| Non-cardiac chest pain                          |                   |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Oedema peripheral                               |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Organ failure                                   |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2            |  |
| Peripheral swelling                             |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pyrexia   |                   |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Sudden cardiac death                            |                  |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 2             |  |
| Sudden death                                    |                  |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 13 / 6950 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 13            |  |
| Systemic inflammatory response syndrome         |                  |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Thrombosis in device                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Immune system disorders                         |                  |                   |  |
| Allergic granulomatous angiitis                 |                  |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Amyloidosis                                     |                  |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Anaphylactic reaction                           |                  |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Drug hypersensitivity                           |                  |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Atrophic vulvovaginitis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign prostatic hyperplasia                    |                  |                  |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%) | 9 / 6950 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast dysplasia                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| 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 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatic obstruction                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatitis                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Prostatomegaly                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectocele                                       |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine polyp                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uterine prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal prolapse                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vaginal ulceration                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Acute pulmonary oedema                          |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Acute respiratory failure                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 2            |  |
| Aspiration                                      |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Asthma  |                   |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atelectasis                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchiectasis                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchitis chronic                              |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchospasm                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chronic obstructive pulmonary disease           |                   |                   |  |
| subjects affected / exposed                     | 18 / 6950 (0.26%) | 21 / 6950 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 21            |  |
| deaths causally related to treatment / all      | 0 / 7             | 0 / 8             |  |
| Diaphragmatic disorder                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspnoea  |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Emphysema                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Epistaxis                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemoptysis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemothorax                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperventilation                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxia   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Interstitial lung disease                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Lung disorder                                   |                  |                  |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| Nasal septum deviation                          |                  |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pleural effusion                                |                  |                   |  |
| subjects affected / exposed                     | 8 / 6950 (0.12%) | 5 / 6950 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2             |  |
| Pleurisy  |                  |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pleuritic pain                                  |                  |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumonia aspiration                            |                  |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 10 / 6950 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 7             |  |
| Pneumothorax                                    |                  |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pulmonary cavitation                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pulmonary congestion                            |                  |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary embolism                              |                   |                   |  |
| subjects affected / exposed                     | 21 / 6950 (0.30%) | 15 / 6950 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 21            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 9             | 0 / 3             |  |
| Pulmonary fibrosis                              |                   |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0             |  |
| Pulmonary mass                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary oedema                                |                   |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 1             |  |
| Respiratory arrest                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 3 / 6950 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 3             |  |
| Respiratory distress                            |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Respiratory failure                             |                   |                   |  |
| subjects affected / exposed                     | 15 / 6950 (0.22%) | 15 / 6950 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 15            |  |
| deaths causally related to treatment / all      | 0 / 11            | 0 / 11            |  |
| Psychiatric disorders                           |                   |                   |  |
| Abnormal behaviour                              |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute psychosis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Affective disorder                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcohol withdrawal syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anxiety disorder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breathing-related sleep disorder                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Completed suicide                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Confusional state                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Delirium  |                  |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                        | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all    | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all         | 0 / 1            | 0 / 0            |  |
| Depressed mood                                     |                  |                  |  |
| subjects affected / exposed                        | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all         | 0 / 0            | 0 / 0            |  |
| Depression   |                  |                  |  |
| subjects affected / exposed                        | 3 / 6950 (0.04%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all    | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all         | 0 / 0            | 0 / 0            |  |
| Disorientation                                     |                  |                  |  |
| subjects affected / exposed                        | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all         | 0 / 0            | 0 / 0            |  |
| Hallucination                                      |                  |                  |  |
| subjects affected / exposed                        | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all    | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all         | 0 / 0            | 0 / 0            |  |
| Major depression                                   |                  |                  |  |
| subjects affected / exposed                        | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all    | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all         | 0 / 0            | 0 / 0            |  |
| Mental disorder                                    |                  |                  |  |
| subjects affected / exposed                        | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all    | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all         | 0 / 0            | 0 / 0            |  |
| Mental disorder due to a general medical condition |                  |                  |  |
| subjects affected / exposed                        | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all    | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all         | 0 / 0            | 0 / 0            |  |
| Mental status changes                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Panic attack                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Panic disorder                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychotic disorder                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Schizoaffective disorder bipolar type           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Schizophrenia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Somatoform disorder                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicidal ideation                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Investigations                                  |                  |                  |  |
| Blood creatine phosphokinase increased          |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood glucose fluctuation                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood pressure increased                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| C-reactive protein increased                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemoglobin decreased                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heart rate decreased                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Liver function test abnormal                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Weight increased                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| 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  |                  |                  |  |
| Accident  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Accidental overdose                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ankle fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Back injury                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone fissure                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carbon monoxide poisoning                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Cervical vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Chest injury                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clavicle fracture                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Compression fracture                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Concussion                                      |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Contusion                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery reocclusion                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery restenosis                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Craniocerebral injury                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Deep vein thrombosis postoperative              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye penetration                                 |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Face injury                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Facial bones fracture                           |                   |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Fall  |                   |                   |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%)  | 8 / 6950 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 2             |  |
| Femoral neck fracture                           |                   |                   |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Femur fracture                                  |                   |                   |  |
| subjects affected / exposed                     | 15 / 6950 (0.22%) | 10 / 6950 (0.14%) |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 10            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Fibula fracture                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Foot fracture                                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Forearm fracture                                |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foreign body                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fractured sacrum                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gun shot wound                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hand fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Head injury                                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Hip fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 7 / 6950 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Humerus fracture                                |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incisional hernia                               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Jaw fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint injury                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Kidney contusion                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laceration                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament sprain                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb crushing injury                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar vertebral fracture                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscus injury                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple fractures                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple injuries                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Muscle rupture                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Overdose  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Patella fracture                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pelvic fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pneumothorax traumatic                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural complication                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Post procedural haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural pulmonary embolism              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound complication                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural intestinal perforation               |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Procedural pain                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pubis fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radius fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory fume inhalation disorder            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Rib fracture                                    |                  |                  |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Road traffic accident                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin wound                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skull fracture                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 3            |  |
| Spinal compression fracture                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal cord injury                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal cord injury cervical                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal fracture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Splenic rupture                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Subdural haematoma                              |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 9 / 6950 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 4            |  |
| Subdural haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Synovial rupture                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (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                     | 4 / 6950 (0.06%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thermal burn                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thoracic vertebral fracture                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tibia fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxicity to various agents                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic fracture                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic intracranial haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Ulna fracture                                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper limb fracture                             |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular graft occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular pseudoaneurysm                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound dehiscence                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound evisceration                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Wound haemorrhage                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wrist fracture                                  |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Congenital, familial and genetic disorders      |                   |                   |  |
| Congenital cystic kidney disease                |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertrophic cardiomyopathy                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Pyloric stenosis                                |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal dysplasia                                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cardiac disorders                               |                   |                   |  |
| Acute coronary syndrome                         |                   |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 3 / 6950 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Acute left ventricular failure                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Acute myocardial infarction                     |                   |                   |  |
| subjects affected / exposed                     | 28 / 6950 (0.40%) | 21 / 6950 (0.30%) |  |
| occurrences causally related to treatment / all | 0 / 28            | 1 / 21            |  |
| deaths causally related to treatment / all      | 0 / 14            | 0 / 10            |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| Angina pectoris                                 |                  |                   |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 13 / 6950 (0.19%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Angina unstable                                 |                  |                   |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%) | 7 / 6950 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Aortic valve disease                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Aortic valve incompetence                       |                  |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Aortic valve stenosis                           |                  |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0             |  |
| Arrhythmia                                      |                  |                   |  |
| subjects affected / exposed                     | 9 / 6950 (0.13%) | 5 / 6950 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 3             |  |
| Arrhythmia supraventricular                     |                  |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Arteriosclerosis coronary artery                |                  |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0             |  |
| Atrial fibrillation                             |                  |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 54 / 6950 (0.78%) | 40 / 6950 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 54            | 0 / 40            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 5             |  |
| Atrial flutter                                  |                   |                   |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%)  | 6 / 6950 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block                          |                   |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block complete                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 4 / 6950 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block first degree             |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Atrioventricular block second degree            |                   |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bradyarrhythmia                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bradycardia                                     |                   |                   |  |
| subjects affected / exposed                     | 8 / 6950 (0.12%)  | 4 / 6950 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac arrest                                  |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 17 / 6950 (0.24%) | 23 / 6950 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 23            |  |
| deaths causally related to treatment / all      | 0 / 17            | 0 / 22            |  |
| Cardiac disorder                                |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Cardiac failure                                 |                   |                   |  |
| subjects affected / exposed                     | 57 / 6950 (0.82%) | 51 / 6950 (0.73%) |  |
| occurrences causally related to treatment / all | 0 / 57            | 0 / 51            |  |
| deaths causally related to treatment / all      | 0 / 38            | 0 / 31            |  |
| Cardiac failure acute                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac failure chronic                         |                   |                   |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%)  | 3 / 6950 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 4             | 0 / 2             |  |
| Cardiac failure congestive                      |                   |                   |  |
| subjects affected / exposed                     | 33 / 6950 (0.47%) | 23 / 6950 (0.33%) |  |
| occurrences causally related to treatment / all | 0 / 33            | 0 / 23            |  |
| deaths causally related to treatment / all      | 0 / 12            | 0 / 9             |  |
| Cardiac tamponade                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cardiac valve disease                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardio-respiratory arrest                       |                   |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 3            |  |
| Cardiogenic shock                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiomegaly                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiomyopathy                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cardiopulmonary failure                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronotropic incompetence                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congestive cardiomyopathy                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Cor pulmonale                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Coronary artery disease                         |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 25 / 6950 (0.36%) | 28 / 6950 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 25            | 0 / 28            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 4             |  |
| Coronary artery insufficiency                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2             |  |
| Coronary artery occlusion                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Coronary artery stenosis                        |                   |                   |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%)  | 3 / 6950 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diastolic dysfunction                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Extrasystoles                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Heart valve incompetence                        |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hypertensive heart disease                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Ischaemic cardiomyopathy                        |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0             |  |
| Left ventricular failure                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Left ventricular hypertrophy                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Mitral valve incompetence                       |                   |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Myocardial infarction                           |                   |                   |  |
| subjects affected / exposed                     | 45 / 6950 (0.65%) | 41 / 6950 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 45            | 0 / 41            |  |
| deaths causally related to treatment / all      | 0 / 26            | 0 / 24            |  |
| Myocardial ischaemia                            |                   |                   |  |
| subjects affected / exposed                     | 16 / 6950 (0.23%) | 5 / 6950 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 1             |  |
| Palpitations                                    |                   |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pericarditis                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Right ventricular failure                       |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Sinus arrest                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus node dysfunction                          |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinus tachycardia                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Supraventricular tachycardia                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachyarrhythmia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tachycardia                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Tricuspid valve incompetence                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular arrhythmia                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular extrasystoles                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular fibrillation                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2            |  |
| Ventricular tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Amnesia   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Amyotrophic lateral sclerosis                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Ataxia  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Balance disorder                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Basal ganglia haemorrhage                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Basilar artery thrombosis                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain injury                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Brain stem infarction                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Brain stem syndrome                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery occlusion                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid artery stenosis                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carotid sinus syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Carpal tunnel syndrome                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Central nervous system lesion                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebellar haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Cerebellar ischaemia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral artery embolism                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral artery thrombosis                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Cerebral atrophy                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 6            | 0 / 5            |  |
| Cerebral infarction                             |                  |                  |  |

|   |                   |                   |
|---|-------------------|-------------------|
| subjects affected / exposed                     | 17 / 6950 (0.24%) | 16 / 6950 (0.23%) |
| occurrences causally related to treatment / all | 1 / 17            | 0 / 16            |
| deaths causally related to treatment / all      | 0 / 6             | 0 / 5             |
| Cerebral ischaemia                              |                   |                   |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 2 / 6950 (0.03%)  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 2             |
| Cerebrospinal fluid leakage                     |                   |                   |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Cerebrovascular accident                        |                   |                   |
| subjects affected / exposed                     | 31 / 6950 (0.45%) | 34 / 6950 (0.49%) |
| occurrences causally related to treatment / all | 1 / 31            | 0 / 34            |
| deaths causally related to treatment / all      | 0 / 17            | 0 / 11            |
| Cerebrovascular disorder                        |                   |                   |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 3 / 6950 (0.04%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 3             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |
| Cervical myelopathy                             |                   |                   |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Cognitive disorder                              |                   |                   |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |
| Coma  |                   |                   |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |
| Dementia  |                   |                   |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| Dementia Alzheimer's type                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dementia with Lewy bodies                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic coma                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Dizziness                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drop attacks                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dural arteriovenous fistula                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dyspraxia                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Epilepsy  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Generalised tonic-clonic seizure                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Guillain-Barre syndrome                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Haemorrhage intracranial                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Haemorrhagic stroke                             |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hemiplegia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hydrocephalus                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertonia                                      |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoaesthesia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxic-ischaemic encephalopathy                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Intracranial aneurysm                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intraventricular haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Ischaemic stroke                                |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 7 / 6950 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 4            |  |
| Lacunar infarction                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Loss of consciousness                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Lumbar radiculopathy                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Memory impairment                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Miller Fisher syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mixed dementia                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Myasthenia gravis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myoclonus                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nerve compression                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuralgia                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuropathy peripheral                           |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paralysis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parkinsonism                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parkinson's disease                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Partial seizures                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polyneuropathy                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post herpetic neuralgia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Presyncope                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Progressive supranuclear palsy                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Radiculopathy                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Restless legs syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sciatica  |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Seizure   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Senile dementia                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Somnolence                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylitic myelopathy                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Status epilepticus                              |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Subarachnoid haemorrhage                        |                   |                   |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%)  | 5 / 6950 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 5             |  |
| Syncope   |                   |                   |  |
| subjects affected / exposed                     | 20 / 6950 (0.29%) | 11 / 6950 (0.16%) |  |
| occurrences causally related to treatment / all | 1 / 20            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Thalamic infarction                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Thalamus haemorrhage                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Thrombotic cerebral infarction                  |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Transient global amnesia                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Transient ischaemic attack                      |                   |                   |  |
| subjects affected / exposed                     | 14 / 6950 (0.20%) | 20 / 6950 (0.29%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 20            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Trigeminal neuralgia                            |                   |                   |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| VIIIth nerve lesion                             |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| VIIth nerve paralysis                           |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vascular dementia                               |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vertebrobasilar insufficiency                   |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Blood and lymphatic system disorders            |                   |                  |  |
| Anaemia   |                   |                  |  |
| subjects affected / exposed                     | 13 / 6950 (0.19%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0            |  |
| Anaemia vitamin B12 deficiency                  |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Coagulopathy                                    |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Disseminated intravascular coagulation          |                   |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Haemorrhagic anaemia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypersplenism                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune thrombocytopenic purpura                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iron deficiency anaemia                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenopathy                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Microcytic anaemia                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrogenic anaemia                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Normochromic normocytic anaemia                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancytopenia                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pernicious anaemia                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Sudden hearing loss                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo   |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo positional                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vestibular disorder                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |
| Age-related macular degeneration                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Amaurosis fugax                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cataract  |                  |                  |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%) | 7 / 6950 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Choroidal effusion                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diplopia  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Glaucoma  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iridocele                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iritis  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ocular hypertension                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ocular vascular disorder                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Optic ischaemic neuropathy                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal degeneration                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal detachment                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinal haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal adhesions                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Abdominal discomfort                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal hernia                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain upper                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal strangulated hernia                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal prolapse                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ascites   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Autoimmune pancreatitis                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Barrett's oesophagus                            |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic gastritis                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ischaemic                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis ulcerative                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Constipation                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Crohn's disease                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diaphragmatic hernia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diaphragmatic hernia, obstructive               |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum                                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum intestinal                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diverticulum intestinal haemorrhagic            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Duodenal ulcer                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Duodenal ulcer haemorrhage                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Duodenal ulcer perforation                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Enteritis                                       |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterovesical fistula                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Faecal incontinence                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric perforation                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer                                   |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastric ulcer haemorrhage                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastric ulcer perforation                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastritis                                       |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastritis haemorrhagic                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal angiodysplasia                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematochezia                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoids                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hiatus hernia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileus   |                  |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 7 / 6950 (0.10%)  | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Incarcerated inguinal hernia                    |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Incarcerated umbilical hernia                   |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Inguinal hernia                                 |                   |                  |  |
| subjects affected / exposed                     | 10 / 6950 (0.14%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 10            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Inguinal hernia strangulated                    |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intestinal haemorrhage                          |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intestinal infarction                           |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 0            |  |
| Intestinal ischaemia                            |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 2            |  |
| Intestinal obstruction                          |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 1            |  |
| Intestinal perforation                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Large intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Large intestine perforation                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Large intestine polyp                           |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mallory-Weiss syndrome                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Melaena   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mesenteric artery embolism                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Mesenteric artery thrombosis                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Mesenteritis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mouth ulceration                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nausea  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal haemorrhage                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal spasm                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal ulcer                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophageal ulcer haemorrhage                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oesophagitis                                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatic disorder                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (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                     | 8 / 6950 (0.12%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pancreatitis acute                              |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 1 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Peptic ulcer haemorrhage                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pharyngo-oesophageal diverticulum               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Proctitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal haemorrhage                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal perforation                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal polyp                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rectal prolapse                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retroperitoneal haemorrhage                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salivary gland calculus                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Small intestinal obstruction                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Subileus  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombosis mesenteric vessel                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Umbilical hernia                                |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper gastrointestinal haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Acute hepatic failure                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Bile duct obstruction                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bile duct stone                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary colic                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Biliary dilatation                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cholangitis                                     |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 5 / 6950 (0.07%)  | 5 / 6950 (0.07%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cholangitis acute                               |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cholecystitis                                   |                   |                   |  |
| subjects affected / exposed                     | 15 / 6950 (0.22%) | 7 / 6950 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cholecystitis acute                             |                   |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 7 / 6950 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cholecystitis chronic                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cholelithiasis                                  |                   |                   |  |
| subjects affected / exposed                     | 14 / 6950 (0.20%) | 14 / 6950 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 14            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Cholestasis                                     |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Chronic hepatic failure                         |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Cirrhosis alcoholic                             |                   |                   |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Drug-induced liver injury                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gallbladder perforation                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hepatic cirrhosis                               |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Hepatic failure                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| Hepatic function abnormal                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis acute                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis alcoholic                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Hyperbilirubinaemia                             |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ischaemic hepatitis                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Jaundice cholestatic                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Actinic keratosis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Angioedema                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Decubitus ulcer                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Dermal cyst                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis allergic                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatitis contact                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermatomyositis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic foot                                   |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Drug eruption                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eczema  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lichen planus                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin necrosis                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin ulcer                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Stasis dermatitis                               |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urticaria                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal and urinary disorders                     |                   |                   |  |
| Acute kidney injury                             |                   |                   |  |
| subjects affected / exposed                     | 19 / 6950 (0.27%) | 18 / 6950 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 19            | 0 / 18            |  |
| deaths causally related to treatment / all      | 0 / 7             | 0 / 8             |  |
| Acute prerenal failure                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bladder neck obstruction                        |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bladder perforation                             |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bladder prolapse                                |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Calculus ureteric                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Chronic kidney disease                          |                   |                   |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 11 / 6950 (0.16%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 0            |  |
| Cystitis haemorrhagic                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Cystitis interstitial                           |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Dysuria   |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Glomerulonephritis                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Haematuria                                      |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Hydronephrosis                                  |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Nephroangiosclerosis                            |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Nephrolithiasis                                 |                   |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 6 / 6950 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Nephropathy toxic                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Neurogenic bladder                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Prerenal failure                                |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal cyst                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal disorder                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal failure                                   |                   |                   |  |
| subjects affected / exposed                     | 11 / 6950 (0.16%) | 11 / 6950 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 7             |  |
| Renal hypertension                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal mass                                      |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tubulointerstitial nephritis                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral haemorrhage                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Urethral meatus stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urethral stenosis                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary incontinence                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Urinary retention                               |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract disorder                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Autoimmune thyroiditis                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cushingoid                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Goitre  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperparathyroidism primary                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperthyroidism                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypothyroidism                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Acquired claw toe                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthralgia                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis                                       |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthrofibrosis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthropathy                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Back pain                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bursitis  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cervical spinal stenosis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chondrocalcinosis                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chondropathy                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foot deformity                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gouty arthritis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intervertebral disc protrusion                  |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint effusion                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lumbar spinal stenosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meniscal degeneration                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mixed connective tissue disease                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscular weakness                               |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Musculoskeletal pain                            |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Myositis  |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteoarthritis                                  |                   |                   |  |
| subjects affected / exposed                     | 17 / 6950 (0.24%) | 26 / 6950 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 26            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteochondritis                                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteoporosis                                    |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteoporotic fracture                           |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pain in extremity                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pathological fracture                           |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polymyalgia rheumatica                          |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Polymyositis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pseudarthrosis                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rhabdomyolysis                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Rheumatoid arthritis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rotator cuff syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sjogren's syndrome                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal column stenosis                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal osteoarthritis                           |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spinal pain                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondyloarthropathy                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Spondylolisthesis                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Still's disease adult onset                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovial cyst                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Systemic lupus erythematosus                    |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tenosynovitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Trigger finger                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Abdominal abscess                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Acarodermatitis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Alcaligenes infection                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal abscess                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal fistula infection                          |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anorectal cellulitis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendiceal abscess                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis                                    |                  |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Appendicitis perforated                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arteriosclerotic gangrene                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis bacterial                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthritis infective                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Atypical pneumonia                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| <b>Bacteraemia</b>                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Bacterial sepsis</b>                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| <b>Biliary tract infection</b>                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Bronchitis</b>                               |                  |                  |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%) | 8 / 6950 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 2            |  |
| <b>Bronchitis bacterial</b>                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Bronchopneumonia</b>                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| <b>Candida infection</b>                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Candida sepsis</b>                           |                  |                  |  |



|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Cavernous sinus thrombosis                      |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cellulitis                                      |                   |                  |  |
| subjects affected / exposed                     | 14 / 6950 (0.20%) | 8 / 6950 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1            |  |
| Cholecystitis infective                         |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Clostridium bacteraemia                         |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Clostridium difficile colitis                   |                   |                  |  |
| subjects affected / exposed                     | 5 / 6950 (0.07%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1            |  |
| Clostridium difficile infection                 |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Colonic abscess                                 |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Cystitis  |                   |                  |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cystitis klebsiella                             |                   |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Device related infection                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Diabetic foot infection                         |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Diverticulitis                                  |                   |                  |  |
| subjects affected / exposed                     | 11 / 6950 (0.16%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Empyema   |                   |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Encephalitis                                    |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Encephalitis viral                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Endocarditis                                    |                   |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Enterocolitis viral                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Epididymitis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Erysipelas                                      |                  |                  |  |
| subjects affected / exposed                     | 7 / 6950 (0.10%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Escherichia infection                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Escherichia sepsis                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Escherichia urinary tract infection             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gangrene  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastroenteritis                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 8 / 6950 (0.12%) | 8 / 6950 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastroenteritis clostridial                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gastroenteritis norovirus                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gastroenteritis salmonella                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis viral                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Graft infection                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haematoma infection                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Helicobacter infection                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes simplex                                  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster disseminated                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster meningitis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes zoster oticus                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Incision site infection                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infected dermal cyst                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infection                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Infectious colitis                              |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                           | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all            | 0 / 0            | 0 / 0            |  |
| Infective exacerbation of chronic obstructive airways |                  |                  |  |
| subjects affected / exposed                           | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all            | 0 / 0            | 0 / 0            |  |
| Influenza   |                  |                  |  |
| subjects affected / exposed                           | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all            | 0 / 1            | 0 / 1            |  |
| Intestinal gangrene                                   |                  |                  |  |
| subjects affected / exposed                           | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all       | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all            | 0 / 0            | 0 / 0            |  |
| Kidney infection                                      |                  |                  |  |
| subjects affected / exposed                           | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all       | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all            | 0 / 0            | 0 / 0            |  |
| Klebsiella bacteraemia                                |                  |                  |  |
| subjects affected / exposed                           | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all            | 0 / 0            | 0 / 0            |  |
| Klebsiella sepsis                                     |                  |                  |  |
| subjects affected / exposed                           | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all            | 0 / 1            | 0 / 0            |  |
| Labyrinthitis   |                  |                  |  |
| subjects affected / exposed                           | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all       | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all            | 0 / 0            | 0 / 0            |  |
| Liver abscess   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lobar pneumonia                                 |                  |                  |  |
| subjects affected / exposed                     | 8 / 6950 (0.12%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 0            |  |
| Localised infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower respiratory tract infection               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung abscess                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lung infection                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Medical device site infection                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nasopharyngitis                                 |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Necrotising fasciitis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Necrotising fasciitis streptococcal             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Neuroborreliosis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenic sepsis                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| Oesophageal candidiasis                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ophthalmic herpes zoster                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orchitis  |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oropharyngeal candidiasis                       |                  |                  |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Osteomyelitis                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1             |  |
| Ovarian abscess                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pancreatic abscess                              |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Peritonitis                                     |                   |                   |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%)  | 4 / 6950 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 2             | 0 / 4             |  |
| Peritonitis bacterial                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngitis                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia                                       |                   |                   |  |
| subjects affected / exposed                     | 81 / 6950 (1.17%) | 70 / 6950 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 81            | 0 / 70            |  |
| deaths causally related to treatment / all      | 0 / 38            | 0 / 24            |  |
| Pneumonia bacterial                             |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pneumonia influenzal                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Pneumonia klebsiella                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Pneumonia pneumococcal                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pneumonia streptococcal                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia viral                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post procedural infection                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Postoperative abscess                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative wound infection                   |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pseudomembranous colitis                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pseudomonas infection                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psittacosis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Psoas abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary tuberculosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Purulence                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis                                  |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 3 / 6950 (0.04%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyelonephritis acute                            |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 4 / 6950 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Rectal abscess                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal abscess                                   |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory moniliasis                          |                   |                   |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory tract infection                     |                   |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Sepsis  |                   |                   |  |
| subjects affected / exposed                     | 17 / 6950 (0.24%) | 26 / 6950 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 17            | 0 / 26            |  |
| deaths causally related to treatment / all      | 0 / 11            | 0 / 16            |  |
| Septic shock                                    |                   |                   |  |
| subjects affected / exposed                     | 14 / 6950 (0.20%) | 11 / 6950 (0.16%) |  |
| occurrences causally related to treatment / all | 0 / 14            | 0 / 11            |  |
| deaths causally related to treatment / all      | 0 / 12            | 0 / 10            |  |
| Sinusitis                                       |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Soft tissue infection                           |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal infection                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 4 / 6950 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Staphylococcal osteomyelitis                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal sepsis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Streptococcal sepsis                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tonsillitis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth abscess                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tuberculosis                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper respiratory tract infection               |                  |                  |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary tract infection                         |                   |                   |  |
| subjects affected / exposed                     | 24 / 6950 (0.35%) | 28 / 6950 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 24            | 0 / 28            |  |
| deaths causally related to treatment / all      | 0 / 6             | 0 / 2             |  |
| Urinary tract infection bacterial               |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urosepsis                                       |                   |                   |  |
| subjects affected / exposed                     | 9 / 6950 (0.13%)  | 7 / 6950 (0.10%)  |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 7             |  |
| deaths causally related to treatment / all      | 0 / 3             | 0 / 1             |  |
| Vestibular neuronitis                           |                   |                   |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%)  | 0 / 6950 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral infection                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 2 / 6950 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Vulvitis  |                   |                   |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%)  | 1 / 6950 (0.01%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Wound infection                                 |                   |                   |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%)  | 3 / 6950 (0.04%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Metabolism and nutrition disorders              |                   |                   |  |
| Cachexia  |                   |                   |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Decreased appetite                              |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dehydration                                     |                  |                  |  |
| subjects affected / exposed                     | 8 / 6950 (0.12%) | 8 / 6950 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Diabetes mellitus                               |                  |                  |  |
| subjects affected / exposed                     | 3 / 6950 (0.04%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetes mellitus inadequate control            |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diabetic ketoacidosis                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Electrolyte imbalance                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Failure to thrive                               |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0            |  |
| Gout  |                  |                  |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypercholesterolaemia                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperglycaemia                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyperkalaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Hyperlipidaemia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypocalcaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 4 / 6950 (0.06%) | 6 / 6950 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypokalaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 7 / 6950 (0.10%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hyponatraemia                                   |                  |                  |  |



|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 5 / 6950 (0.07%) | 2 / 6950 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypophagia                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6950 (0.00%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypovolaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Lactic acidosis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malnutrition                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6950 (0.03%) | 1 / 6950 (0.01%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| Marasmus  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Type 2 diabetes mellitus                        |                  |                  |  |
| subjects affected / exposed                     | 6 / 6950 (0.09%) | 5 / 6950 (0.07%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Uraemic acidosis                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6950 (0.01%) | 0 / 6950 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | <b>Zoster-022 Placebo Group</b> | <b>Zoster-022 GSK1437173A Group</b> |  |
|---|---------------------------------|-------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                 |                                     |  |
| subjects affected / exposed                           | 610 / 6950 (8.78%)              | 3067 / 6950 (44.13%)                |  |
| Nervous system disorders                              |                                 |                                     |  |
| Headache  |                                 |                                     |  |
| subjects affected / exposed                           | 243 / 6950 (3.50%)              | 586 / 6950 (8.43%)                  |  |
| occurrences (all)                                     | 307                             | 717                                 |  |
| General disorders and administration site conditions  |                                 |                                     |  |
| Chills  |                                 |                                     |  |
| subjects affected / exposed                           | 39 / 6950 (0.56%)               | 353 / 6950 (5.08%)                  |  |
| occurrences (all)                                     | 46                              | 415                                 |  |
| Fatigue   |                                 |                                     |  |
| subjects affected / exposed                           | 169 / 6950 (2.43%)              | 474 / 6950 (6.82%)                  |  |
| occurrences (all)                                     | 192                             | 592                                 |  |
| Injection site erythema                               |                                 |                                     |  |
| subjects affected / exposed                           | 27 / 6950 (0.39%)               | 864 / 6950 (12.43%)                 |  |
| occurrences (all)                                     | 29                              | 1150                                |  |
| Injection site pain                                   |                                 |                                     |  |
| subjects affected / exposed                           | 148 / 6950 (2.13%)              | 1975 / 6950 (28.42%)                |  |
| occurrences (all)                                     | 165                             | 2762                                |  |
| Injection site swelling                               |                                 |                                     |  |
| subjects affected / exposed                           | 16 / 6950 (0.23%)               | 613 / 6950 (8.82%)                  |  |
| occurrences (all)                                     | 18                              | 773                                 |  |
| Pain  |                                 |                                     |  |
| subjects affected / exposed                           | 60 / 6950 (0.86%)               | 428 / 6950 (6.16%)                  |  |
| occurrences (all)                                     | 67                              | 669                                 |  |
| Pyrexia   |                                 |                                     |  |
| subjects affected / exposed                           | 52 / 6950 (0.75%)               | 535 / 6950 (7.70%)                  |  |
| occurrences (all)                                     | 56                              | 633                                 |  |
| Musculoskeletal and connective tissue disorders       |                                 |                                     |  |

|                             |                   |                    |  |
|-----------------------------|-------------------|--------------------|--|
| Myalgia                     |                   |                    |  |
| subjects affected / exposed | 99 / 6950 (1.42%) | 378 / 6950 (5.44%) |  |
| occurrences (all)           | 113               | 472                |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported